15 November 2014
EMA/748294/2013
Biosimilar Medicinal Products Working Party (BMWP)

Overview of comments received on 'Draft guideline on similar biological medicinal products' (CHMP/437/04 Rev. 1)

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

Name of organisation or individual
1 Novartis International AG, Switzerland
2 Medicines Evaluation Board, Netherlands (deleted)
3 Amgen Ltd.
4 Pharmaceutical Product Development, LLC (PPD)
5 Boehringer Ingelheim Pharma GmbH & Co. KG
6 AET BioTechnologie GmbH
7 Therapeutic Goods Administration, Australia.
8 European Biosimilars Group (EBG), a Sector Group of the European Generic medicines Association (EGA)
9 Merck Serono
10 vfa bio
11 EuropaBio
12 FARMINDUSTRIA
13 EBE (European Biopharmaceutical Enterprises)
14 Apotex Inc.
15 BioIndustry Association (BIA)
16 Biotechnology Industry Organization (BIO)
17 F. Hoffmann-La Roche Ltd
18 Fundamed
19 The Janssen Pharmaceutical Companies of Johnson & Johnson
20 Merck Sharp & Dohme (MSD)
21 PDA (The Parenteral Drug Association)
22 Pfizer Limited
23 SciencePharma
24 Teva Pharmaceutical Ltd

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
1 1	Novartis appreciates this current revised draft version of the overarching guideline on 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. Please find our detailed comments below.	Comment acknowledged.
3 3	“Biosimilars” is arguably one of the most complex issues in the area of pharmaceuticals. The leadership role of European Commission in introducing the biosimilar concept in EU legislation in June 2003, followed by the setting up of a biosimilar legal pathway by the Union in April 2004 and the pragmatic, but science-based and patient centric approach taken by the EMA/CHMP in the area, should be applauded. It is not by coincidence that the EU “biosimilar approach” has served as a source of inspiration around the globe and at the level of the World Health Organisation (WHO). As the EMA surely knows, Amgen has been a leader in the debate on biosimilars since 10 years ago. We have always supported the EU biosimilar pathway, well before our decision to develop biosimilars. It is from the perspective of a company that discovers, develops, manufactures and delivers innovative human therapeutics and biosimilars that we have a few high level observations to make and welcome the	Comment partly acknowledged. For outcome see detailed comments below.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	opportunity to comment on the Guideline on Similar biological Medicinal Products (CHMP/437/04 Rev 1). <u>High level observations</u> Despite the evolution of science which has improved our ability to better characterize biologics, and of EU regulatory experience with biosimilars, we recommend to maintain the following principles, which are at the essence of the EU biosimilar pathway: • biologics are not chemical drugs • the generic approach is not applicable to any biosimilar, and • biosimilars are not generics, from a legal and scientific/regulatory point of view. A resulting consequence is that any biosimilar application should contain non-clinical and clinical data, whilst acknowledging that the type and amount of such data will vary from product to product. A departure from these principles could decrease in our view the meaningful role that safe and effective biosimilars are currently playing in the European health care system. Whilst we acknowledge and support that authorisation decisions in the EU should be solely based on science, and not on economic considerations, in fact, the two are closely intertwined. The market dynamic of the European biotech sector and medical innovation are dependent upon many factors, including continued	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	adherence to the above principles and the availability of so-called sub-standard biologics on the EU market. It would be short sighted in our view to undermine the vibrant, but fledgling biotech industry, especially during difficult economic times, when the EU is losing jobs to overseas competitors and millions of patients are still waiting for treatment in important disease areas. <u>Amgen's comments</u> In general we consider the proposed guideline follows the framework for the review and approval of biosimilar products which has been modified over the past eight years of biosimilar applications and experience in the EU. We welcome the developments in the areas of the provision for a 'global reference product' and enhanced pharmacovigilance requirements in line with other EU legislation. However we consider that there remains an important opportunity to be clear about the use of ICH Q5E in the biosimilar comparability exercise and in the use and limitations of the principle of PD fingerprinting. It is also key for the guideline to be clear that the Agency has no remit to provide guidance or instruction on switching or interchange. We also have reservations about the change from	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	strength to posology when considering a biosimilar vs its reference product and we consider that the biosimilar product should be formulated to the same strength, meaning the actual measured quantity of active ingredient in a given dose. Finally, as extrapolation of indications is an underlying principle of the biosimilar concept, we consider that it is important to mention it in this guidance and would support the inclusion of a section dedicated to this topic.	
3 4	**Scope** We note the proposed approach consisting in having the "biosimilar" approach applicable to any "biological medicinal product", and not only to biosimilars developed with or by the biotechnological processes listed in the Annex to Regulation 726/2004. As a result, such approach may become applicable to biological medicinal products that are unlikely to fall under the definition of "biotech products", such as (i) vaccines, (ii) immunological medicinal products; (iii) medicinal products derived from human blood and human plasma; and (iv) allergen. These "non-biotech" but "biological medicinal products" may, however not necessarily be able to follow the central authorization procedure, even on optional basis (which is possible for generic medicinal products,	Not accepted. From a legal-regulatory viewpoint, the biosimilar approach can apply to any biologicals. Certain biosimilar applications may be submitted nationally, and this Guideline would apply to such cases. In other places in the guideline it is clarified that more poorly characterisable biologicals would be difficult to target for a biosimilar development.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	including when their reference products has not been authorized centrally). It is also questionable whether the EMA biosimilar guidelines are relevant or applicable for such products and/or whether the CHMP/EMA are the competent authorities to give an opinion on the scientific data to substantiate claims of similarity. We nevertheless believe that solutions may exist to confirm the accessibility of the central authorization procedure, which may include to amend the Annex to Regulation 726/2004.	
3 5	**Change from 'Strength' to 'Posology'** We are aware of historical examples where biosimilar developers have apparently formulated product with a non-trivial bias in strength relative to the reference product. Such an example has been documented in the Scientific Discussion of the EPAR for epoetin zeta, among other examples. When posology is used as the standard for strength raher than the actual measure of the active ingredient, biosimilar sponsors may believe they are formulating their product to the "true" label strength while it was the reference product sponsors that were in error. Unfortunately, this view would disregard the basic tenant that the posology of the reference product (and hence of the biosimilar product) is justified based on the substantial clinical evidence	Partly accepted. The new wording is: • The posology and route of administration of the biosimilar must be the same as those of the reference medicinal product. • Deviations from the reference product as regards strength, pharmaceutical form, formulation, excipients or presentation require justification. If needed, additional data should be provided. Any difference should not compromise safety.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	generated with the historical reference product strength ("erroneous" or not). In this context, we recommend that EMA take necessary measures to minimize the possibility that a biosimilar sponsor introduces a deliberate bias in the strength of a product in an attempt to "correct" a systematic error attributed to the reference product sponsor. The biosimilar product should be formulated to the same strength, meaning the actual measured quantity of active ingredient in a given dose, and it is not sufficient to specify that the products should have the same posology (meaning the nominal dosage for a given indication).	
3 6	**PD fingerprinting** The draft guideline indicates that a comprehensive comparative 'PD fingerprint profile' may be sufficient to allow some products to avoid the need for a comparative clinical efficacy study. Although it is acknowledged that a fingerprint 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. Furthermore, the quantity of biomarkers in a fingerprint should not be used to compensate for limitations in either their mechanistic plausbility or their clinical relevance. As such, we do not consider that this is a useful or	Partly Accepted. Deleted from Overarching guideline. Concept maintained in Overarching (Non)-Clinical Guideline and Product specific guidelines.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	helpful concept for the overriding guideline, as it should only be considered on a case-by-case basis depending upon the number of known, mechanistically plausible PD markers, their clinical relevance, and the complexity of the molecule in question and not as an overarching principle for biosimilarity. Furthermore our understanding is that the FDA have also expressed concerns about inappropriate rigor in identification and qualification of biomarkers and about use of biomarkers that were published in limited settings and not reproduced. Examples of oncology biomarkers that had not held up to scrutiny are available. FDA proposed that biomarkers should receive "community acceptance", based on a published body of literature before being considered for a PD fingerprint. We suggest that the EMA should either omit reference to PD fingerprinting from this guideline or, if it remains in the final guideline, that EMA should add additional discussion explaining the limitations of this concept and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy.	
3 7	**Comparability testing** **Biosimilar comparability changes** – It is welcomed that the draft guideline makes reference to the 'scientific principles' when conducting a biosimilar	Not accepted. The following is taken from the comments on the Biosimilar

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	comparability exercise to those outlined in ICH Q5E. However, it needs to be recognised that ICH Q5E describes a risk assessment process for which several important components can be addressed e.g. only for a sponsor evaluating a change to its own manufacturing process (intra-product changes). Although we are in agreement that some of the principles outlined in ICH Q5E can serve as a source of inspiration for inter-product analytical evaulations, as such ICH Q5E cannot be the basis for an evaluation of a biosimilar product. Also, the objective of ICH Q5E is not to provide guidance for the biosimilarity exercise, but rather when changes are made in the (proprietary) manufacturing process for biologics. This fundamental difference in terms of objective/purpose should be reflected in the final guideline. Therefore, we consider that it is important to be clear in the guideline about the distinction between the intra-product comparability vs the inter-product comparability. The terminology is often mis-applied and there is a mis-conception that intra-product comparability assessment for an innovator product and inter-product analytical assessment within a biosimilarity development context should share the same expectations with regard to content. Indeed as Weise states in 'Biosimilars – why terminology matters', although certain principles are the same for both, the	Quality GL: "The scientific principle for the biosimilar comparability exercise (quality aspects) is the same as the comparability exercise following manufacturing changes. Therefore it is important to maintain the term 'comparability' in both cases. However, in order to be clear within this guideline and in presentation of the data required for a claim of biosimilarity (including quality, non-clinical and clinical data), this is referred to in the revised guideline as the 'biosimilar comparability exercise' or comparability of the biosimilar product with the reference medicinal product, to distinguish it from the intra-comparability as described in ICH Q5E."" Although the principles of ICH Q5E and biosimilar comparability exercise may be the same, the data requirements may differ as outlined in the biosimilar guidelines.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	expectations in terms of data requirements for demonstrating inter-product analytical assessment within a biosimilarity context are higher with a need for non-clinical and clinical studies to support conclusions of comparability. Specifically, the comparability exercise described in ICH Q5E rests on an informed assessment of the specific nature of a process change and its potential to impact product quality, safety and efficacy. The assessment is also framed in the context of the sponsor's cumulative historical experience with the product. This is an exercise most commonly applied for the management of incremental process changes and the criteria are typically satisfied using confirmatory analytical comparisons. Indeed, the guideline makes only cryptic reference to the considerations for additional non-clinical and clinical bridging studies. This is clearly insufficient as a framework for a biosimilar comparison with a reference product. Accordingly ICH Q5E should be referenced, if at all, only with respect to considerations for any changes to the biosimilar manufacturing process during development.	
3 8	**Reference Products** While the concept of a global reference product is welcomed as a scientific matter, we consider that a full bridging package including non-clinical and clinical	Not accepted. The possibility to bridge on analytical data alone cannot be excluded. An actual decision will be taken on a case by case

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	pharmacology data will be necessary to determine comparability between a non-EEA authorised version of the reference product and an EEA authorised version of the reference product. We do not consider that it is sufficient to suggest that it is possible to conclude the establishment of a bridge based on analytical studies alone.	basis based on the specific product and the available scientific evidence.
3 9	**Switching and interchange** It is considered that decisions regarding switching and interchangeability rely on national competent authorities and are outside the remit of the EMA/CHMP.	Comment acknowledged.
4 10	PPD welcomes the opportunity to use a non-EEA authorised comparator in certain clinical studies and, where needed, in vivo non-clinical studies. We appreciate that this will require a clear and robust demonstration that any such comparator is representative of the reference product authorised in the EEA. We believe that the approach suggested will, in such cases where appropriate, reduce unnecessary duplication of clinical trials, and therefore increase the speed with which new products can be brought to Marketing Authorization Application, and where successful, to become available to patients.	Comment acknowledged.
4 11	PPD appreciates the clarification of EMA's position with	Comment acknowledged.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	regard to when in vivo non-clinical studies are required to support biosimilar development. In cases where in vivo non-clinical studies are not required we would anticipate some Clinical Investigator concerns over the lack of in vivo data. Does EMA plan to provide any educational material or opportunities to clinical investigators to help address their concerns in order that unnecessary animal studies are not conducted? A number of formal and informal networks of Clinical Investigators involved in, or interested in, conducting clinical trials with biosimilars exist, including PPD's own Biosimilar Investigator Network. PPD would be happy to work with EMA to facilitate access to Clinical Investigators in Europe included in our Biosimilar Investigator Network in order to ensure efficient dissemination of the biosimilar regulatory framework and increase understanding of this field through workshops, webinars, educational documents or other appropriate materials relevant to biosimilar clinical development.	The Agency is committed to adequately inform HCP and patients about biosimilar medicines through appropriate channels including workshops. For further reading on the topic, please see e.g. recent publication from *van Aerts, L. et al, mAbs 2014* (doi 10.4161/mabs.29848)
4 12	As mentioned above PPD appreciates the clarification of EMA's position with regard to when in vivo non-clinical studies are required to support biosimilar development. In cases where in vivo non-clinical studies are not required we would anticipate some concerns over the lack of in vivo data from members of local ethics	Comment acknowledged. See also comment 11.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	committees. Does EMA plan to provide any educational material or opportunities to ethics committees to help address their concerns in order that unnecessary animal studies are not conducted?	
4 13	As mentioned above PPD appreciates the clarification of EMA's position with regard to when in vivo non-clinical studies are required to support biosimilar development. Does EMA plan to provide any additional guidance or support to national authorities to help address their concerns in order that unnecessary animal studies are not requested by national authorities in response to a Clinical Trial Application?	Comment acknowledged. See also comment 11.
4 14	PPD is in support of EMA's position to minimise unnecessary animal use and therefore appreciates the clarification of EMA's position with regard to the possibilities to refine non-clinical studies and to reduce animal numbers.	Comment acknowledged. See also comment 11.
5 15	Throughout the document the term „comparability" is used, which is generally used when changes to an established protein are made, but not when referring to a comparison of reference product and proposed biosimilar, This leads to confusion.	Not accepted See comment 7. The scientific principle for the biosimilar comparability exercise (quality aspects) is the same as the comparability exercise following manufacturing changes. Therefore it is important to maintain the term 'comparability' in both cases.
5 16	Comment:	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	On page 5 the following statement is given : “Safety and efficacy of biosimilars have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended. General technical and product-class specific provisions for biosimilars are addressed in EMA/CHMP guidelines (see section 2). For situations where product-class specific guidance is not available, applicants are encouraged to seek scientific advice from Regulatory Authorities.” Proposed change : BI feels this sentence is misleading as for a biosimilar efficacy and safety does not to be shown independently, but rather be bridged via comparative analytical, pre-clinical, pharmacokinetic and other clinical data from the reference product to the proposed biosimilar.	Partly accepted. The words ‘or otherwise justified’ have been added.
6 17	The revised version of the 'Guideline on Similar Biological Medicinal Products' is well written and considered to provide additional clarity for companies developing biosimilars.	Comment acknowledged.
6 18	The section 3.2. Choice of Reference Product now specifically enabling the use of a non-EEA authorised comparator in certain clinical and in vivo non-clinical studies under specified conditions is considered to be very helpful.	Comment acknowledged.
7 19	While Similar Biological Medicinal Product (SBMP) is a	Accepted.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	clear description of the products referred to, it is clumsy even in acronym form. While having a greater potential for misinterpretation, I believe the adoption of the widely used term “biosimilar”, as appears to be the case in this guideline, is preferable.	The term biosimilar is introduced in the guideline, as it is not the formal legal term.
8 20	The EBG very much appreciates this revised draft version of the guideline on similar biological medicinal products (CHMP/437/04 Rev.1). The revision is in line with the current thinking of the EU regulators as also laid down in the updated EMA Procedural advice for users of the centralised procedure for similar biological medicinal products’ applications (March2013 EMA/940451/2011). The European regulators again have shaped the regulatory framework for biosimilar products in a pioneering role. We very much welcome that the strong scientific principles contained in this draft revised guideline support the use of representative reference product material sourced in ICH regions outside of the EEA – provided that confirming information on the reference product as well as certain bridging data are submitted. It will allow the use of clinical trials in a more global setting and avoid unnecessary and potentially unethical repetition of clinical trials as well as increasing access to highly-innovative biological treatments. The EU and the US also support this approach in the context of the Transatlantic Trade Investment	Comment acknowledged.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	Partnership (TTIP) which will strengthen the formal acceptance of comparative clinical trials based on reference medicines sourced in the EU or US or inthird counties. With the revision of this guideline the pioneering role of the European regulatory and scientific framework for biosimilars will be further extended and strengthened and will continue to ensure high level public health protection. Please find our detailed comments below.	
9 21	Merck Serono welcomes the completely revised draft Guideline on Similar Biological Medicinal Products. This draft document reflects in summary the comprehensive expertise gained by EMA over the last 8 years of biosimilar development. Especially the clarifications provided on the choice of Reference Product are important to support global biosimilar development and to avoid unnecessary replication of clinical studies.	Comment acknowledged.
10 22	• The current draft guideline is appreciated. Clarification of the term biosimilar is supported to avoid inappropriate use. • Some points should be more detailed to make sure that the achieved high-quality European “state of the art” for biosimilars is maintained. • It should be clarified that a biosimilar product should not be used as a reference product. The	Comment acknowledged. The principle that a biosimilar should not be used as a reference product is already stated in section 1.1.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	reference product is the/an originator product.	
11 23	**Overall Comment** EuropaBio welcomes the revised draft Guideline on Similar Biological Medicinal Products. This draft document reflects in summary the comprehensive expertise gained by EMA over the last 8 years of biosimilar development. We welcome the developments in the areas of the provision for a 'global reference product' and enhanced pharmacovigilance requirements in line with other EU legislation. However, we consider that there is still 'room for improvement' and that key sections on extrapolation and labelling of biosimilars are missing as can be seen in our comments below and in the specific comments section. We have also provided some comments detailing a step-wise approach which could assist the applicant when considering the use of a non-EEA reference product. Finally, we further welcome an approach to propose the development of an ICH guidance on biosimilars in order to facilitate global development of medicinal products.We would very much welcome the opportunity to discuss these comments further with the EMA.	Comment acknowledged. For details see comments below.
11 24	**Extrapolation** We consider that extrapolation between indications is a key underlying principle within the biosimilar framework and that as such it is important to mention it in this	Partly accepted. A statement on extrapolation has been included. Demonstration of similarity between the EEA-reference product/non-EEA

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	guidance. It should be clear that if a reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified for each of the claimed indications. Likewise, the Guideline would benefit from the EMA's opinion on if and how the demonstration of similarity between the EEA-reference product/non-EEA reference product and the biosimilar (three-way approach) could impact potential indication extrapolation for the intended biosimilar product.	authorised comparator product and the biosimilar is not expected to impact the issue of extrapolation of indications.
11 25	**Labelling** 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 (especially comparative clinical data on 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 guidance 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	Not accepted. Labelling/SmPC is not within the scope of this Guideline.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	to labelling, as recently applied for Inflectra and Remsima, for all biosimilar approvals such that the SmPC contains no specific information gathered during the biosimilar development, in practice it will be difficult for all interested stakeholders (including patients and physicians) to make evidence-based decisions on key topics such as switching or interchangeability. As such, 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 as it is more of a regulatory matter, we urge the agency to clarify its position on labelling of biosimillars and develop specific guidance for biosimilars in consultation with all stakeholders.	
11 26	**Principles of establishing biosimilarity - safety** It is agreed that the biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms and that this is an overriding principle in the biosimilar development. Furthermore equivalent efficacy and safety is also a cornerstone of biosimilarity, although it is acknowledged that there will always be uncertainties. However, due to the advancement of analytical techniques in recent years, it may be possible that during analytical comparability	Comment acknowledged.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	studies, differences (perhaps due to the precision of the test or simply its ability to detect a previously unknown) may become apparent, but that this will not automatically change the safety or efficacy profile and this should not automatically infer that it is unlikely that biosimilarity will be established but rather that the applicant will be required to conduct additional testing to ensure that the safety and efficacy seen in the clinic are comparable. Furthermore, through advances in technology, it is plausible that the safety profile of a given biosimilar may be more advantageous: for instance if the biosimilar has lower immunogenicity. In instances where such a reduction in immunogenicity is apparent, it should be noted that a non-inferior immunogenicity profile may be accompanied by a reduced incidence of loss of efficacy and in some cases that could manifest as non-equivalent long-term efficacy on a population basis (as highlighted in the guidance on non-clinical and clinical principles released for comment 10 June). We therefore consider that the biosimilar concept should allow for such improvements subject to the caveat that studies are designed to show equivalent efficacy profile in patients that have not experienced ADA-associated loss of efficacy and provided that the biosimilar remains within the abovementioned limit of being 'highly similar' to the reference medicinal product. For example, such	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	studies could evaluate near term response (before reutralizing ADA effect could manifest). See additional comments and suggested changes at line 153.	
11 27	**Change from 'Strength' to 'Posology'** We are aware of historical examples where biosimilar developers have apparently formulated product with a non-trivial bias in strength relative to the reference product. Such an example has been documented for epoetin zeta, among other examples. When this occurs, the biosimilar sponsors may believe they are formulating their product to the "true" label strength while it was the reference product sponsors that were in error. Unfortunately, this view would disregard the basic tenant that the posology of the reference product (and hence of the biosimilar product) is justified based on the substantial clinical evidence generated with the historical reference product strength ("erroneous" or not). In this context, we recommend that EMA take necessary measures to minimize the possibility that a biosimilar sponsor introduces a deliberate bias in the strength of a product in an attempt to "correct" a systematic error attributed to the reference product sponsor. The biosimilar product should be formulated to the same strength, meaning the actual measured quantity of active ingredient in a given dose, and it is not sufficient to specify that the products should have the same posology (meaning the nominal dosage for a	Comment acknowledged. See comment 5 (also relating to posology)

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	given indication). See additional comments at line 104-106.	
11 28	**The 'Biosimilar' Approach** We consider that the regulatory framework for biosimilars, including the annex to the Directive, requires a submission of both non-clinical and clinical information in module 4 AND module 5 data. This is clearly different to a generic product, where a product may claim generic status based on comparative PK data alone. We consider that this revised guidance provides an opportunity to reaffirm the constant practice of the EMA/CHMP and of the European Commission (EC) for approving biosimilars based on their experience to date, namely to apply the 'biosimilarity approach', as opposed to the 'generic approach'. We acknowledge that 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 but we consider that it is crucial to maintain a clear distinction between the two approaches to enable stakeholder, including the EU institutions, to apply and implement	Partly accepted See comment 35 and comment 152.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	the EU and national regulatory frameworks, which increasingly make such a distinction between generics and biosimilars. Hence we consider that the expectations for biosimilar development and the distrinction between a biosimilar and generic product should be clear in the overarching guidance and therefore urge the EMA to ensure that the overarching guidance is clear in this respect. See additional comments at line 86-90.	
11 29	**PD fingerprinting** The draft guideline indicates that a comprehensive comparative 'PD fingerprint approach' may be sufficient to allow some products to avoid the need for comparative clinical efficacy study. Although it is acknowledged that a fingerprint approach is an extension of the PD concept that is already discussed in detail in published guidances, this concept might not be sufficiently scientifically appropriate for all classes of biologics and their biosimilars. We agree that this approach could work when at least one of the PD markers has shown to be a surrogate one but does not cover the entire expected clinical benefit, this approach will also depend upon the number of known PD markers and the complexity of the molecule in question but even in this case this should be specified on a case by case basis and not as an overarching principle for biosimilarity. As such, we consider that this should not	Partly Accepted. Deleted from Overarching guideline. Concept maintained in Overarching (Non)-Clinical Guideline and Product specific guidelines.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	be within the scope of the overarching guidance or if it is to remain we recommend that wording similar to that in the draft guidance non-clinical and clinical issues be used to describe where such an approach may be applicable. See additional comments at line 167.	
11 30	**Comparability testing** **Biosimilar comparability changes** – It is welcomed that the draft guidance makes reference to the 'scientific principles' when conducting a biosimilar comparability exercise to those outlined in ICH Q5E. However, we consider that it is important to be clear in the guidance about the distinction between the intra-comparability versus the inter-product comparability. The current EMA overarching guideline clearly distinguish in our view between (1) the 'biosimilarity exercise' for establishing biosimilarity between the biosimilar and the chosen reference product and (2) the 'comparability exercise', for aspects concerning quality changes to the manufacturing processes of biotechnological/biological products. It refers to ICH Q5E as a 'complementary guideline', only for the purpose of the above point 2. Although we are in agreement that some of the principles outlined in ICH Q5E can serve as a source of inspiration for the evaluation of biosimilarity but as such ICH Q5E cannot be the basis for an evaluation of a biosimilar product. A detailed review of ICH Q5E has	Not accepted. See comment 5

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	lead to the conclusion that the 'scientific principles' for the biosimilarity exercise are not at all based on these applied or outlined in ICH Q5E which would imply that they are they the same when carrying out changes in the manufacturing process of a biological medicinal product**.** This fundamental difference in terms of scope/objective/purpose should be reflected in the final guidance. We suggest making a clear differentiation between a biosimilarity exercise (scope of this document) and the process followed after manufacturing changes as described in ICH Q5E as it is the case in the current guidance. This would also allow alignment with related documents such as the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)", CHMP/BWP/247713/2012, when stating "*It is acknowledged that the biosimilar will have its own lifecycle. When changes to the manufacturing process (active substance and/or finished product) are introduced during development, a comparability assessment (as described in ICH Q5E) should be performed. For the purposes of clarity, any comparability exercise(s) for process changes introduced during development should be clearly identified in the dossier and addressed separately from the comparability exercise versus the reference*	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	medicinal product" Note also that the U.S. Food and Drug Administration's (FDA) Draft Guideline on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product use the word 'comparability' exclusively according to its original ICH Q5E meaning. FDA draws a distinction between conducting a comparability assessment of an innovator product before and after a manufacturing change versus the assessment for establishing biosimilarity. We suggest ICH members take a common approach to these definitions. See additional comments at line 91-93.	
11 31	**Scope** While we support the principle that the concept of a biosimilar is applicable to any biological medicinal product, the previous version of the guideline clearly explained and excluded vaccines, allergens, and gene, cell and tissue therapies, blood or plasma-derived products and their recombinant alternatives . The overall conclusion still applies and should remain. Furthermore we consider that this guidance should contain details underpinning the concept of biosimilarity, namely that of being able to sufficiently characterise the reference product in order to conduct a biocomparability exercise. See additional comments at line 70-71.	Not accepted. See comment 4.
11 32	**Pharmacovigilance**	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	It is welcomed that the draft guidance makes reference to the need to clearly identify the specific medicinal product given to the patient and to record the brand names and batch number for any biological product. Indeed, the EU institutions have already adopted several important steps towards ensuring better identification and traceability of biological medicinal products. Despite this, we believe that there is 'room for improvement' in terms of pharmacovigilance and thus, the identification and traceability of the biological prescribed, dispensed, and administered in the Union, must be implemented at the levels of each Member State. We also believe that progress should be made in the area of a global framework for naming biosimilars. See additional comments at lines 117-120.	Comment acknowledged.
13 33	EBE welcomes the current opportunity to discuss the revised Guideline on Similar Biological Medicinal Products. Overall, EBE supports the proposed draft and agrees with the main principles and methodologies outlined in this guidance. This draft document reflects in summary the comprehensive expertise gained by EMA over the last 8 years of biosimilar development. We appreciate the further clarifications included on the biosimilar approach, the choice of the reference product and the concept of 'biosimilarity'. The guideline in general is short and to the point in	Partly accepted See comment 35 and comment 152.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	addressing the concepts. Unfortunately, however, this has resulted in omission of some very useful clarification that would help stakeholders understand why e.g. a standard generic approach is not appropriate for biosimilar products. This applies for example to • the second paragraph in the former section 2.1 "*Biological medicinal products are usually more difficult to characterise than …. on the robustness and the monitoring of quality aspects." (see specific comment on lines 75-76)* and to • the last bullet point of that same paragraph: " *It should be recognised that, by definition, similar biological medicinal products are not generic …. pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified." (see specific comment on line 117)* We believe the overarching guideline is a good place to include such clarifications, as it contributes to a good understanding of the general principles.	
13 34	It is suggested to include a high-level paragraph on the subject of SmPCs for biosimilars. Product labelling should be transparent and clear, summarizing clinical data submitted for approval, enabling prescriber and patient to make informed decision on use of product. In order to cater to the	Not accepted. Labelling/SmPC is not within the scope of this Guideline.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	specific nature of biosimilars, the label should contain a combination of information on both the biosimilar and the Reference Product which reflects the development plan of the applicant and provides the prescriber with an easily accessible summary of data generated which can be used in making informed decisions such as switching a patient from one product to an other. We have enclosed EBE's position paper on the labelling of biosimilars, which outlines the need for guidance in the area together with the reasons why disclosure of information on both the biosimilar and the reference product is preferred.	
13 35	**Compliance with current legislation** The draft guideline indicates that a clinical efficacy studies could be 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*	Not accepted. The Directive states that Module 4 and Module 5 data shall be submitted, while at the same time making it clear that the need for such studies shall be required by the Competent Authority. This allows a flexible approach, in which scientific considerations must prevail. It is fully at the discretion of the Competent Authority to decide which data must be submitted.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	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 dossier to be valid and therefore the approach outlined in the draft guideline which indicates that it	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	maybe allowable to waive clinical efficacy and safety trials (in their entirety) is not possible, regardless of the complexity of the molecule.	
13 36	**“Comparability” vs “Similarity”** The final guideline should make a clear differentiation between a biosimilarity exercise (scope of this document) and the process followed after manufacturing changes by the same manufacturer as described in ICH Q5E, i.e. a comparability exercise. It seems that the draft document (CHMP/437/04 Rev 1) conflates the term ‘comparability’ with ‘biosimilarity’. These are distinct exercises. ICH Q5E guidance clearly designates the scope as applying to a manufacturer making changes to its own process. This is appropriate when optimizing an approved process for a product that has undergone significant R&D and a full pre-clinical and clinical regulatory approval process. The assessment of biosimilarity following an attempt to reverse engineer a reference product is necessarily a far more extensive exercise. Comparison of drug substance and drug product at various stages of manufacture is an important part of the comparability exercise. This is not possible as part of a biosimilarity assessment since the manufacturer does not have the extensive manufacturing data and experience of the originator and can only compare their version of the product with the final product of the	Not accepted. See comment 7.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	originator. The biosimilar sponsor is therefore required to produce a far more extensive package of analytical, non-clinical and clinical data to support their pre-MAA assertion of biosimilarity than is called for under ICH Q5E. The draft (CHMP/437/04 Rev1) should therefore make clear that the two exercises are distinct. Note also that the U.S. Food and Drug Administration's (FDA) Draft Guideline on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product use the word 'comparability' exclusively according to its original ICH Q5E meaning. FDA draws a distinction between conducting a comparability assessment of an innovator product before and after a manufacturing change versus the assessment for establishing biosimilarity. We suggest ICH members take a common approach to these definitions. (Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; Draft; February 2012; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf)	
13 37	**Scope** While we support the principle that the concept of a biosimilar is applicable to any biological medicinal product, this has interesting (maybe unintended) consequences. Biotech products fall under the mandatory scope of the centralised procedure are listed	Not accepted. See comment 4

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	in the Annex to Regulation 726/2004, as amended. 'Non biotech' products, but which are nevertheless 'biologics' because their active substance is a 'biological substance' as defined at Section 3.2.1.1 Part 1 of the Annex to Directive 2001/83/EC, as amended), namely several groups of products (e.g. vaccines, immunological medicinal products, medicinal products derived from human blood and human plasma and allergens) are not eligible for the centralised procedure. As a result it is not entirely clear whether or not 'biosimilars' of such 'non biotech products' are eligible for the centralised procedure, even on an optional basis. The centralised procedure should be encouraged to ensure uniformity of regulatory approaches. This would be consistent with the situation for generics, which could benefit from the centralised procedure when their references have not be authorised centrally. It would also be questionable whether the EMA/CHMP guidance documents would be applicable for such 'non-biotech' products. This issue merits further analysis and discussions.	
15 38	We welcome the revision of the overarching biosimilars guideline in view of the experience gained with the development and approval of biosimilar products over the last 8 years in the European Union. The BIA believes that the evaluation of biosimilar medicines should be subject to the same scientifically robust regulatory	Partly accepted. See comments 4, 7, 24 and 25

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	standards that are applied to the innovator product in order to ensure that patient safety is not compromised. We support the comments on this draft revised guideline submitted by our sister organisation EuropaBio, the European Association for Bioindustries. In addition, we wish to highlight on behalf of our members the following key issues for consideration by the Agency when finalising this guideline. 1. **Application of the "biosimilar" approach.** There is a need to maintain a clear distinction between the standard generic approach and the "biosimilar" approach in the revised overarching guideline to provide legal certainty and consistency in assessment of such products by the regulatory authorities, but also to ensure that safe and effective biosimilar medicines are approved for patients. 2. **The biosimilar comparability exercise is <u>not</u> the same as demonstrating product comparability.** The comparability approach described in the ICH guideline Q5E applies to changes made to an established manufacturing process, which is not the case of a biosimilar product. We consider that differences between products from different manufacturers with respect to manufacturing process and formulation may have some significant bearing	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	on clinical safety and efficacy. Currently, innovative companies are putting lots of efforts and incurring large costs to show that changes in the manufacturing process of biological products do not impact on product safety and efficacy. The revised overarching guideline should therefore make a clear distinction between conducting a comparability assessment for manufacturing process changes during development of an innovator product from the comparability exercise to demonstrate similarity with the reference product in the interest of patient safety. 3. **Greater clarity on the products for which the "biosimilar" approach would have to be followed or not.** While we support the statement that in principle the concept of a biosimilar is applicable to any biological product, we are of the view that the revised overarching guideline should provide clarity on the types of products where the "biosimilar" approach would be difficult to apply; for example, vaccines, allergens, gene or cell therapy medicinal products, tissue engineered products, blood or plasma-derived products and their recombinant alternatives. 4. **Facilitation of the global development of**	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	biosimilars. We welcome the statement that acceptability of the approach as regards the choice of reference product and the type of acceptable bridging data will be a case-by-case decision and the onus being placed on the applicant to provide a scientific justification depending on the product. 5. **Relaxation in the comparability requirements for "structurally more simple biological medicinal products".** While we support the need to avoid conducting unnecessary clinical trials, the revised overarching guideline should set out clear conditions when comparative PK/PD studies between the biosimilar and the reference product may be sufficient to demonstrate clinical comparability, while emphasising the need for clinical safety studies regardless of the need for a comparative clinical efficacy study. 6. **The issue of extrapolation of indications should be addressed in the revised overarching guideline.** 7. **We would welcome greater transparency in product labelling on the comparative clinical data submitted for biosimilar approvals.** This will provide meaningful information to healthcare professionals and	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	patients to make informed decisions about switching products. We urge the Agency to clarify its position on labelling of biosimilars and develop specific guidance in consultation with all stakeholders.	
16 39	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 (CHMP/437/04 Rev1)." BIO commends EMA on the update of this Draft Guideline, which provides an important international precedent for the 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. BIO appreciates this opportunity to comment on the revised "Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev1)." We would be pleased to provide further input or clarification of our specific,	Comment acknowledged.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	detailed comments, which follow in Section 2, as needed.	
17 40	Need to clarify that the reference product is the originator product. Should be clear that a biosimilar product should not be used as a reference product.	Not accepted. See comment 22.
18 41	The experts of the “Working Team of Biosimilar Drugs”, representing the heath care sector, express the strict need to perform clinical testing for safety and effectiveness for each of the requested indications for the biosimilar medication. In order to protect the safety guarantees in cases of possible extrapolation of the indications for a biological medication established as a reference for a biosimilar, given that this represents a risk for patient health, and it has been concluded that such extrapolation must not be approved unless there are sufficiently solid medical reasons backed up by sufficient traceability systems, in order to ensure safe and effective clinical use, and this extrapolation must be supported by on-going pharmacovigilance. In order to facilitate pharmacovigilance over the biosimilar product, the product should not be prescribed under a generic name or by active substance, but rather by brand, in a manner that will allow individualised tracking. Possible interchangeability for a biological medication implies that it can be exchanged for another one	Partially accepted. See also comment 9, 24, 25.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	considered equivalent in a specific clinical setting. Such interchangeability should only take place based upon the prescribing physician's criteria and with his or her consent. It is considered a risk to state a priori that biological medications are interchangeable, unless there is existing evidence for equivalence between the biosimilar medication and its reference product in terms of quality, safety, and effectiveness to support safe and effective dose-for-dose interchanging of the two biological products. The possibility of substitution of one biological medication for another represents a disregard for the specialist's need to know which medication will ultimately be provided to the patient. It is concluded that this would be a problematic practice, taking into account the lack of security regarding the results since these may not be the ones indicated for individualised patient treatment, and such a practice may also contravene the provisions of ORDER SCO 2874/2007 (a legal order issued by Spain's Ministry of Health and Consumer Affairs). Therefore, substitution of one biological medication for another at the time of dispensing without prior authorisation from the prescribing physician is a practice that is both illegal and considered to be very harmful for the patient, as established in ORDER SCO	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	2874/2007, which indicates that biological medications cannot be substituted. Overall, from the above considerations, the conclusion is that appropriate management and use of biosimilar medications requires the interaction of physicians, pharmacists, and regulatory entities, as well as the bodies responsible for administrative management of these groups.	
19 42	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 (Draft Guideline).[1] 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 postmarket monitoring of biopharmaceutical products. As we noted last year in our comments on the CHMP's related Concept Paper,[2] Johnson & Johnson supports the EMA's decision to review and revise its over-arching biosimilar	Partly accepted. More details on use non-EEA authorised comparator are provided.

[1] "Draft Guideline on Similar Biological Medicinal Products," CHMP/437/04 Rev 1 (22 May 2013) (Draft Guideline), revising the "Guideline on Similar Biological Medicinal Products," CHMP/437/04 (30 October 2005) (Original Guideline).
[2] *See* Johnson & Johnson's comments (21 February 2012) on the "Concept paper on the revision of the guideline on similar biological medicinal products" (EMA/CHMP/572643/2011) (Concept Paper), at Appendix A.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	guidelines. We appreciate the CHMP's continued engagement with stakeholders as it revises these guidelines and the agency's consideration of these comments. The Draft Guideline contains many important features that promote patient safety, including statements that: continue to explain that the standard generic approach is in principle not appropriate for biological products; indicate that the posology and route of administration of a biosimilar should be the same as that of its reference product; note that products with intentional changes to improve efficacy are not eligible for the biosimilar approach; and provide that any observed difference between a proposed biosimilar and its reference product must be appropriately justified or the biosimilar approach may be inappropriate. We strongly support these positions and continue to urge the CHMP to keep patient well-being its paramount consideration as it finalizes the Draft Guideline. We are concerned about a number of areas related to the Draft Guideline, however, and respectfully request some changes that we believe would promote patient welfare. In particular, we urge the agency to exercise considerable caution when considering whether to permit a biosimilar applicant to rely on comparative data involving a non-EEA authorised comparator. We also think it appropriate for the final guideline to	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	provide a more complete overview of the biosimilar approach, reflecting the learning and experience gained by the agency over the past eight years since the Guideline on Similar Biological Medicinal Products (Original Guideline) took effect. These and other concerns, as well as positions in the Draft Guideline that we support, are discussed below.	
20 43	We appreciate the revision of the Guideline on Similar Biological Medicinal Products and the further clarifications included on the biosimilar approach, the reference product and the concept of 'biosimilarity' The guideline in general is short and to the point in addressing the concepts. Unfortunately, however, this has resulted in omission of some very useful clarification that help understand why e.g. a standard generic approach is not appropriate for biosimilar products. This applies for example to the first paragraph in the former section 2.1 "Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. In addition, there is a spectrum of molecular complexity among the various products (recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy, etc.). Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which	Partially accepted See 35, 152. Also see revised quality guideline EMA/CHMP/BWP/247713/2012

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	may initially be considered to be ‘minor’ in the manufacturing process. Thus, the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects.” and to the last bullet point of that same paragraph: ” It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support *pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.”* We believe the overarching guideline is a good place to include such clarifications, as it contributes to a good understanding of the general principles. The concept of extrapolation is addressed in the guideline dealing with non-clinical and clinical issues. The possibility to extrapolate under certain condition has been implicitly linked to the concept of biosimilarity. Therefore, although we feel that a discussion of efficacy/safety aspects does not need to be covered by the overarching guideline, extrapolation should be a topic for which the approach is explained in the general	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	principles.	
21 44	To enhance clarity and consistency, PDA recommends this guideline make reference to existing directives and annexes in defining a biosimilar medicinal product including the emphasis on the significance of the manufacturing process for the quality of a biosimilar. The 'physicochemical and biological characterisation' as stated e.g. in lines 83/84 and 151 of the current guideline is a much too weak argument for a 'biosimilar'. Reference should be made to the definitions of a 'biological' according to Directive 2001/83/EC, Annex I: "A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control." This is also explicitly stated in the EU 'Guideline on Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005): "Consequently, the similar biological medicinal product is defined by the following two sets of characteristics: i) related to the characteristics of the molecule (including product related substances/ impurities), and ii) related	Not accepted. Due reference to relevant documents has been made.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	to its process (which may affect molecular characteristics and includes process related impurities)." To enhance readability of the guideline, PDA recommends avoiding repetition of information in various parts of the document. Some examples are: (1) Executive Summary, lines 26-29, and chapter 1.2 Scope, lines 48-51: "where it is stated that 'the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency'."	
22 45	**Overall Comments** • We welcome the guideline and consider that in general the guideline strikes the right balance of providing sufficient level of information on the over-arching principles without going into too much detail which would not be appropriate. In places, however, further clarity or context would be helpful. • For example It is stated that the scientific principles of are similar to those of ICH Q5E, however, the guideline should also include that the regulatory context of the assessments are very different since ICH Q5E applies to a manufacturer making changes to their own process. The standard and level of evidence for	Partly accepted. See comment 7,8, 24, 25,152 Immunogenicity is addressed in Overarching (Non)-Clinical Guideline and Product specific guidelines

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	biosimilarity assessment must necessarily be higher since the biosimilar developer has developed their own manufacturing process and does not therefore have access to the full development and manufacturing history which the reference product developer would have. The difference in context and level of regulatory hurdle must be made clear. • On the bridging approach to support global development we welcome the case by case assessment and the onus being placed on the applicant to justify the case depending on the product. We further welcome the flexibility that a three way assessment of PK may not always be required and making this a case specific scientific assessment. • Considering that this guideline is the only place where the subject of bridging to a non European Economic Area (EEA) comparator product is discussed, It may be helpful to provide a little more detail in terms of some general principles which the applicant should consider. We request that the agency considers adding some further explanatory text (see proposal for lines 128-146): • It would also be helpful to uphold the distinction in terms of legal pathway (Article 10.4) and	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	scientific data required for a biosimilar as being different from a generic. This guidance could uphold and strengthen these distinctions by adding reference to the articles (see suggestions below). • There seems to be an intent to widen the scope of biological products which could be developed as biosimilars as theoretically no product categories are ruled out, although in practice the high hurdle of developing a similar product will be practically challenging for certain classes of product. We understand that the agency needs to 'future proof' the guideline to take into account any scientific advances which may allow possibilities in the future; however, we also recommend that the agency continues to encourage access to the centralised procedure for all biosimilars irrespective of the type of biological product as this will ensure consistency in assessment. • The guideline notes that for structurally more simple biological medicinal products a comparative clinical efficacy study may not be necessary. However, it is not mentioned that such cases would be the exception rather than the rule and no mention is made of how assessment of immunogenicity would be made;	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	such assessments would need to address the immunogenicity of process-related impurities and not just the intended drug substance. A similar statement occurs in the monoclonal antibodies (MAbs) guideline and in that case the prerequisites and provisos are clearly stated. It is recommended that the agency either lists a similar set of prerequisites or removes this statement from the guidance. **Labelling** We recognise that mention of labelling policy would be out of scope in this scientific guideline as this is more of a regulatory matter. Nonetheless, we urge the agency to consult with all stakeholders on this topic to discuss whether the current policy of labelling biosimilars as generics by including only information of the reference product meets the needs of patients and prescribers. Furthermore, adopting a generic approach could be interpreted as undermining the clear distinction on legal and scientific grounds that biosimilars are not regulated as generics. Although the draft guideline refers to interchangeability status as being out of scope for the scientific assessment, (lines 59-61), adopting a generic approach to labelling could be misinterpreted by physicians and patients as a strong signal that EMA has concluded that the products are in fact interchangeable, even though this is not expressly stated, since generic	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	products have identical labels to their reference product and are generally considered to be interchangeable with their reference product. Product labelling should be transparent and clear, summarizing clinical data submitted for approval, enabling the prescriber and patient to make informed decisions on the use of the 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 which reflects the development plan of the applicant and provides the prescriber with an easily accessible summary of data generated which can be used in making informed decisions such as switching a patient from one product to another. We would cite the European Biopharmaceutical Enterprises" (EBE's) position paper on the labelling of biosimilars which outlines the need for guidance in the area together with the reasons why disclosure of information on both the biosimilar and the reference product is appropriate. : http://www.ebe-biopharma.eu/documents/59/22/EBE-position-paper-on-Biosimilars-Labelling The product label is the first point of reference for any product so exclusion of information on the development of the biosimilar from the SmPC with the expectation that the physician /patient may find this information in the European Public Assessment Report (EPAR) may not	

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	be helpful, as it means they have to access multiple documents with which they may be unfamiliar. Furthermore, as the information in the labels is not identified as being generated on the reference product, the physician/patient may incorrectly assume that all the information has been generated on the biosimilar and may not realise that additional clinical data has been generated. In order to identify the data generated on the biosimilar and the reference product the patient/prescriber would also need to cross refer to the original EPARs on the reference product as well as the EPAR on the biosimilar. It is also unclear how post approval changes to the label will be handled. For example if the reference product obtains a new indication after approval of the biosimilar how will it be determined if this should be reflected in the biosimilar label? For all of the above reasons we recommend that the agency should consider generating separate guidance on the labelling of biosimilars following consultation with all stakeholders.	
24 46	Since the first European Guideline was published in 2005 a lot of experience was gained on the side of Agencies and stakeholders, and therefore it is very much appreciated to have this new revised draft guideline which provides a lot of clarification with regards to principle of concept and terminology for	Comment acknowledged.

Stakeholder number / comment number	General comment (if any)	Outcome (if applicable)
	similar biological medicinal products (“biosimilars”).	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
25-29	11 47	**Comment:** Please add a reference to Article 10.4 of Directive 2001/83/EC as it this article which specifically allows for biosimilar products. **Proposed change:** Consider amending text as follows: This Guideline outlines the general principles to be applied for similar biological medicinal products (also known as biosimilars) as referred to in **Article 10.4 and** Section 4, Part II, Annex I to Directive 2001/83/EC, as amended, where it is stated that 'the general principles to be applied [*for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency.*	Not accepted. Reference is made in section 1.1
25-29	13 48	**Comment:** Please add a reference to Article 10.4 of Directive 2001/83/EC as it this article, which specifically establishes the regulatory pathway for biosimilar products. **Proposed change:** Consider amending text as follows: "This Guideline outlines the general principles to be applied for similar biological medicinal products (also known as biosimilars) as referred to in Article 10.4 and Section 4, Part	Not accepted See comment 47**.**

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		II, Annex I to Directive 2001/83/EC, as amended, where it is stated that “the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency”.”	
25-29	16 49	**Comment:** BIO recommends adding a reference to Article 10.4 of Directive 2001/83/EC, as it is this article that specifically allows for biosimilar products. **Proposed change:** “This Guideline outlines the general principles to be applied for similar biological medicinal products (also known as biosimilars) as referred to in Article 10.4 and Section 4, Part II, Annex I to Directive 2001/83/EC, as amended, where it is stated that ‘*the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency*’.”	Not accepted See comment 47**.**
25-29	22 50	**Comment:** Please add a reference to Article 10.4 of Directive 2001/83/EC as it is this article which specifically allows for biosimilar products and establishes the regulatory pathway for their approval. **Proposed change:**	Not accepted See comment 47**.**

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Consider amending text as follows: 'This Guideline outlines the general principles to be applied for similar biological medicinal products (also known as biosimilars) as referred to in **Article 10.4 and** Section 4, Part II, Annex I to Directive 2001/83/EC, as amended, where it is stated that 'the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency'.	
34	1 51	**Comment:** The wording "A company may choose to develop a new biological medicinal product claimed to be "similar"" might be misleading. Biosimilars are not "new" biological medicinal products as evidenced by the fact that the determination of similarity, not the *de novo* establishment of safety and efficacy, is the basis for biosimilarity. **Proposed change:** "A company may choose to develop a ~~**new**~~ biological medicinal product claimed to be "similar" to a …"	Accepted
34	8 52	**Comment:** The wording "A company may choose to develop a new biological medicinal product claimed to be "similar" might be misleading. The terminology "new" biological medicinal product implies that it is a biological product with a new	See comment 51.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		active substance never approved before. Biosimilars, however, contain a version of a known biological active substance and are therefore not “new” biological medicinal products as evidenced by the fact that the determination of similarity, not the de novo establishment of safety and efficacy, is the basis for biosimilarity. Please also refer to the below comments on lines 76-79 in which it is pointed out that the definition/description of a similar biological medicinal product should be consistent across guidance documents and therefore the wording “…contains a version of the **known biological** active substance” is proposed. Accordingly, the word “new” to designate a biosimilar product may be misleading and it is therefore proposed that it be deleted. **Proposed change:** “A company may choose to develop a ~~**new**~~ biological medicinal product claimed to be “similar” to a …”	
34	11 53	**Comment:** The wording “A company may choose to develop a new biological medicinal product claimed to be “similar”” might be misleading. Biosimilars are not “new” biological medicinal products as evidenced by the fact that the determination of similarity, not the *de novo* establishment of safety and efficacy, is the basis for biosimilarity.	See comment 51.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider amending the text as follows: A company may choose to develop a ~~**new**~~ biological medicinal product claimed to be “similar” to a …	
34	13 54	**Comment:** The wording “A company may choose to develop a new biological medicinal product claimed to be “similar” might be misleading. Biosimilars are not “new” biological medicinal products as evidenced by the fact that the determination of similarity, not the *de novo* establishment of safety and efficacy, is the basis for biosimilarity. **Proposed change:** “A company may choose to develop a ~~new~~ biological medicinal product claimed to be “similar” to a …”	See comment 51.
34	21 55	**Comment:** A biosimilar medicinal product cannot be a 'new' product in the sense of an innovative 'original' product. This is also addressed in Directive 2001/83/EC as amended, Section 4, Part II: *"When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, <u>which refers to an original medicinal product</u> ..."* It is therefore recommended to delete the word 'new'. **Proposed change:**	See comment 51.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		A company may choose to develop a ~~new~~ biological medicinal product claimed to be "similar" to a reference medicinal product, ...	
34	22 56	**Comment:** The wording "A company may choose to develop a new biological medicinal product claimed to be "similar"" might be misleading. Biosimilars are not "new" biological medicinal products as evidenced by the fact that the determination of similarity, not the *de novo* establishment of safety and efficacy, is the basis for biosimilarity. **Proposed change:** "A company may choose to develop a **~~new~~** biological medicinal product claimed to be "similar" to a ..."	See comment 51.
34-35	10 57	**Comment:** Biosimilars are not "new" biological medicinal products. **Proposed change:** „A company may choose to develop a **~~new~~** biological medicinal product claimed to be "similar" to **the originator medicinal product** ~~a reference medicinal product~~..."	Partly accepted See comment 51.
35	17 58	**Proposed change:** to the originator medicinal product **(reference medicinal product)**, which has been granted a marketing authorisation	Not accepted. Proposal does not add clarity.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
40-42	11 59	**Comment:** Change the term “comparability” to biosimilarity. Comparability is the term referring to post approval changes which the same manufacturer makes to their own product. The biosimilarlity context is broader and more extensive. Reference stepwise development. **Proposed change:** Consider amending the text as follows: **A stepwise approach to biosimilarity** ~~comparability~~ studies ~~are~~ **is** needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the similar biological medicinal product **in comparison with** ~~and~~ the chosen reference medicinal product authorised in the EEA ***since a biosimilar is not the same as a generic.***	Not accepted. See comment 7.
40-42	22 60	**Comment:** Change the term “comparability” to biosimilarity. Comparability is the term referring to post approval changes which the same manufacturer makes to their own product according to ICH Q5E. The biosimilarity context is broader and more extensive. Reference stepwise development. **Proposed change:** " **A stepwise approach to biosimilarity** ~~comparability~~ studies ~~are~~ **is** needed to generate evidence substantiating	Not accepted. See comment 7.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		the similar nature, in terms of quality, safety and efficacy, of the similar biological medicinal product in comparison and the chosen reference medicinal product authorised in the EEA .	
44-47	11 61	**Comment:** Please add a reference to Article 10.4 of Directive 2001/83/EC as it this article which specifically allows for biosimilar products **Proposed change:** Consider amending text as follows: The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity (or biosimilarity) used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product (as defined **by article 10.4 and** in Section 3.2.1.1, Part I, Annex I to Directive 2001/83/EC, as amended).	See comment 47.
44-47	13 62	**Comment:** Please add a reference to Article 10.4 of Directive 2001/83/EC as it this article which specifically establishes the regulatory pathway for biosimilar products **Proposed change:** Consider amending text as follows:	See comment 47.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		"The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity (or biosimilarity) used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product (as defined by article 10.4 and Section 3.2.1.1, Part I, Annex I to Directive 2001/83/EC, as amended)".	
44-47	16 63	**Comment:** BIO recommends adding a reference to Article 10.4 of Directive 2001/83/EC, as it is this article that specifically allows for biosimilar products. **Proposed change:** "The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity (or biosimilarity) used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product (as defined by Article 10.4 and in Section 3.2.1.1, Part I, Annex I to Directive 2001/83/EC, as amended)."	See comment 47.
44-47	22 64	**Comment:** Please add a reference to Article 10.4 of Directive 2001/83/EC as it is this article which specifically allows for biosimilar products and establishes the regulatory pathway for their approval.	See comment 47.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider amending text as follows: 'The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity (or biosimilarity) used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product (as defined **by article 10.4** and Section 3.2.1.1, Part I, Annex I to Directive 2001/83/EC, as amended)'.	
48-51	11 65	**Comment:** Please provide a reference to article 10.4 of Directive 2001/83/EC as it states that 'The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex 1 and the related detailed guidelines. **Proposed change:** Consider amending text as follows: The scope of the guideline is to fulfil the requirement of **article 10.4 and** section 4, Part II, Annex I to Directive 2001/83/EC, as amended, which states that '*the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency*.	See comment 47.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
48-51	13 66	**Comment:** Please provide a reference to article 10.4 of Directive 2001/83/EC as it states that 'The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex 1 and the related detailed guidelines. **Proposed change:** Consider amending text as follows: "The scope of the guideline is to fulfil the requirement of article 10.4 and section 4, Part II, Annex I to Directive 2001/83/EC, as amended, which states that 'the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency".	See comment 47.
48-51	16 67	**Comment:** BIO recommends providing a reference to article 10.4 of Directive 2001/83/EC, as it states that "The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex 1 and the related detailed guidelines." **Proposed change:** "The scope of the guideline is to fulfil the requirement of Article 10.4 and section 4, Part II, Annex I to Directive	See comment 47.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		2001/83/EC, as amended, which states that '*the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency*'."	
48-51	22 68	**Comment:** Please provide a reference to article 10.4 of Directive 2001/83/EC as it states that 'The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex 1 and the related detailed guidelines. **Proposed change:** Consider amending text as follows: 'The scope of ~~the~~ **this** guideline is to fulfil the requirement of **article 10.4 and** section 4, Part II, Annex I to Directive 2001/83/EC, as amended, which states that 'the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency'.	See comment 47.
52-53	14 69	**Comment:** Please clarify if these general principles are for biosimilar development and/or for the registration of the dossier application.	Not accepted. Although the assessment will be done during a marketing authorisation application (MAA) procedure, the

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
			manufacturer will have to apply the principles during development in order to produce an appropriate MAA file.
53-55	11 70	**Comment:** 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:** Consider amending text as follows: CHMP guidelines addressing the planning and conduct of biosimilar comparability studies should always be read in conjunction with relevant scientific guidelines, **administrative procedures** and legislative provisions in force in the Union.	Not accepted. Proposal does not give clarity or provide useful guidance.
53-55	13 71	**Comment:** 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:** Consider amending text as follows: “CHMP guidelines addressing the planning and conduct of biosimilar comparability studies should always be read in conjunction with relevant scientific guidelines, administrate	See Comment 70.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		procedures and legislative provisions in force in the Union."	
53-55	16 72	**Comment:** BIO recommends adding a reference to ensure compliance with the relevant administrative procedures and policies of the EMA and with the current guideline CHMP/437/04. **Proposed change:** "The CHMP guidelines addressing the planning and conduct of biosimilar comparability studies should always be read in conjunction with relevant scientific guidelines, administrative procedures and legislative provisions in force in the Union."	See Comment 70.
53-55	22 73	**Comment:** The concepts 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:** Consider amending text as follows: "....CHMP guidelines addressing the planning and conduct of ~~biosimilar comparability~~ **biosimilarity** studies should always be read in conjunction with relevant scientific guidelines, **administrative procedures** and legislative provisions in force in the Union.	Not accepted. See Comments 7 and 70.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
56	14 74	**Comment:** Please clarify if “Regulatory Authorities” refers to National Regulatory Authorities, the EMA or both.	Not accepted. “Regulatory Authorities” refers to the “Regulatory Authorities” relevant for the specific product.
56 – 58	1 75	**Comment:** The Agency should be open and flexible to new or progressive approaches for the development of biosimilars especially when science advances. Therefore, we suggest adding the proposed wording below. **Proposed change:** “Companies developing biosimilars are invited to contact Regulatory Authorities to obtain further advice on their development, whenever there is a need for more detailed information than provided in the guidelines already available or when an alternate approach to that recommended in a product specific guideline is planned to be pursued.”	Not accepted. Proposal does not add content to message.
56 – 58	8 76	**Comment:** It is welcomed that companies developing biosimilars are invited to contact the Agency for scientific advice requesting information beyond the extent of the specific guidelines. However, we would like to strongly encourage the Agency to be even more open and flexible to new or progressive approaches for the development of biosimilars - especially	See comment 75.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		when scientific advances allowing for alternative development approaches are not (yet) covered by product specific guidelines. Therefore it is proposed to amend the sentence below. **Proposed change:** "Companies developing biosimilars are invited to contact Regulatory Authorities to obtain further advice on their development, whenever there is a need for more detailed information than that provided in the guidelines already available **or when an alternate approach to that recommended in a product specific guideline is planned to be pursued.**	
56–58	11 77	**Comment:** The Agency should be open and flexible to new or progressive approaches for the development of biosimilars especially when science advances. Therefore, we suggest adding the proposed wording below. **Proposed change:** Consider amending the text as follows: Companies developing biosimilars are invited to contact Regulatory Authorities to obtain further advice on their development, whenever there is a need for more detailed information than provided in the guidelines already available **or when an alternate approach to that recommended in**	See comment 75.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		a product specific guideline is planned.	
56–58	13 78	**Comment:** The Agency should be open and flexible to new or progressive approaches for the development of biosimilars especially when science advances. Therefore, we suggest adding the proposed wording below. **Proposed change:** “Companies developing biosimilars are invited to contact Regulatory Authorities to obtain further advice on their development, whenever there is a need for more detailed information than provided in the guidelines already available or when an alternate approach to that recommended in a product specific guideline is planned to be pursued.”	See comment 75.
56–58	22 79	**Comment:** The Agency should be open and flexible to new or progressive approaches for the development of biosimilars especially when science advances. In any case, the criteria for seeking scientific advice include situations where divergence from guidance is proposed. **Proposed change:** “Companies developing biosimilars are invited to contact Regulatory Authorities to obtain further advice on their development, whenever there is a need for more detailed	See comment 75.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		information than provided in the guidelines already available **or when the applicant proposes to justify divergence from the guideline."**	
58	11 80	**Comment:** The previous version of the guideline clearly explained and excluded blood or plasma-derived products and their recombinant alternatives due to their complex and variable physic-chemical, biological and functional characteristics which mean that full characterisation is difficult. The overall conclusion still applies and should remain. **Proposed change:** Consider adding the following text after line 58: **In view of the complex and variable physico-chemical, biological and functional characteristics of blood or plasma derived products and their recombinant alternatives (e.g. immunoglobulins, Factor VIII and IX products) it is unlikely to be acceptable to submit a reduced dossier when claiming similarity to a reference medicinal product. As a result, applications for such similar medicinal products will need to satisfy the safety and efficacy requirements described in the BPWG guidelines for "new products" or show direct head-to head comparative clinical trial.**	Not accepted. See also comment 4.
59	20 81	**Comment:** We appreciate the explicit mention that the Agency's	Not accepted. Currently, evaluations of

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. We do believe, however, that the agency could (and should) have a valuable role in defining the scientific criteria for interchangeability and assessing the studies presented for that purpose in the dossier. This is important to avoid a non-harmonised, country-specific scientific approach of this important topic. We therefore strongly urge EMA to start discussions of the possibility to take on the scientific assessment of the data that are presented in support of interchangeability. A position statement on this fundamental topic in this fundamental overarching guideline would be well-placed from our perspective.	biosimilar medicines for authorisation purposes by the EMA do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Substitution policies are within the remit of the EU member states.
59-61	3 82	**Comment:** In accordance with the EMA Questions and Answers on biosimilar medicines (EMA/83785/2011, 27 September 2012) it is recommended that there is consultation with doctors and pharmacists before switching takes place. **Proposed change:** Consider adding the following text: 'The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be interchangeable with its reference medicine. **Furthermore, it is recommended that there is consultation between patients and their doctors and pharmacists before switching takes place.**'	Not accepted. See also 9, 81 GL does not give guidance for clinical practice

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
59-61	6 83	**Comment:** It is acknowledged that the EMA does not provide recommendations on whether a biosimilar should be used interchangeably with its reference medicine, however, it might be feasible to add text clarifying that the absence of such recommendation does on the other hand not exclude such interchangeability. **Proposed change:** 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**, however, this shall not mean that the data provided does not allow such interchangeability**.	Not accepted. See comment 9, 81
59-61	8 84	**Comment:** The draft guideline states that the agency's evaluation would not include recommendations on whether a biosimilar should be used interchangeably with its reference product medicine. In this context we would like to highlight that the definition of "interchangeability" differs between the US and the EU, which has sometimes led to confusion when this topic has been debated. We therefore would like to bring to the attention of EMA/CHMP the definitions as they have been included and published in the European Commission Consensus Information Paper 2013 "What you need to know	Not accepted. See comment 9, 81

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		about Biosimilar Medicinal Products": Interchangeability: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber. Substitution: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber. Switching: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment. According to these EU-wide accepted definitions it is within the remit of the treating physician to decide whether a biosimilar could be used interchangeably with its reference medicinal product. In order to come to a decision on whether a biosimilar medicinal product can be used interchangeably with its reference medicinal product, the thorough assessment undertaken by the Agency which is published in the EPAR should be consulted. Once a biosimilar has been approved in the EU and biosimilarity between the biosimilar and its reference product has been demonstrated, it is proven that the biosimilar product is highly similar to the reference product in physicochemical and biological terms and that clinically meaningful differences between the biosimilar and the reference medicinal product can be ruled out (which means	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		that the products could be used interchangeably). The reasoning for the biosimilarity designation is based on the thorough and comprehensive assessment conducted by the Agency and described in detail in the EPAR. We are consequently of the opinion that the statement “The agency’s evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine” might be open for misinterpretation. We therefore propose to change the wording in lines 59-61 to denote that all scientific evaluations and assessments on the biosimilarity designations can be found in the EPAR – which should be used and consulted for the decision on whether a biosimilar should be used interchangeably with its reference medicine. Based on the EU experience with biosimilars, we expect the EMA to be more assertive in helping doctors to understand what it means in practice that biosimilarity between the biosimilar and the reference medicine has been demonstrated. **Proposed change:** 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 results of these thorough scientific evaluations as performed by the EMA are described in the EPAR which is published on the Agency’s website upon approval. The publicly**	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		accessible EPAR should be consulted in order to substantiate the decision on whether to use a biosimilar instead of its reference medicine.	
59-61	10 85	**Comment:** We believe that EMA should outline at least the consequences of switching patients from one biological medicinal product to another. We also believe that with regard to patient safety EMA should recommend to prevent automatic substitution. **Proposed change:** 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 decisions on interchangeability and/or substitution rely on national competent authorities/prescribers and are outside the remit of EMA/CHMP. When the treating physician switches between one biological medicinal product to another it must be ensured that this is properly and completely recorded. In the SmPC there should be a notion for requirements and precautions regarding potential switches by the treating physician.** **With regard to patient safety, automatic substitution in pharmacies must not take place.**	Not accepted. See comment 9.
59-61	11 86	**Comment:** The term 'switched' is often used in practice to mean	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		'interchangeability' at national levels. The overarching guidance should be consistent with other EMA documentation such as 'Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications (March 2013 – EMA/940451/2011)', and the Questions and answers on biosimilar medicines (similar biological medicinal products (September 2012 – EMA/837805/2011) which sets out that the decisions on substitution/interchangability rely on national competent authorities and are outside the remit of EMA/CHMP and recommends that there is consultation with doctors and pharmacists before any switching takes place. **Proposed change:** Consider amending the text as follows: The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not ***constitute nor*** include recommendations on whether a biosimilar ~~should~~ ***can*** be **switched from one product to another or** used interchangeably with its reference medicine **as such recommendations are outside the scope of the European Marketing Authorisation. Furthermore, it is recommended that there is consultation with doctors and pharmacists before switching for any patients take place**. **The decisions on interchangeability and/or substitution rely on national competent**	See comment 9, 81, 82

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		authorities/prescribers and are outside the remit of EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions.	
59-61	13 87	**Comment:** We recommend that the language on interchangeability becomes even clearer, indicating that the EMA does not assess if interchangeability could be relevant. We also understand that this text is taken from EMA Q&A on biosimilar medicines (EMA/83785/2011, 27 September 2012) however suggest some modifications for clarity. In accordance with this Q&A it should recommended that there is consultation with doctors and pharmacists before switching takes place. Moreover even if the Agency's evaluations do not include recommendations about interchangeability, this aspect is to be considered in the RMP to be assessed by the Agency. **Proposed change:** "The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not constitute nor include recommendations on whether a biosimilar ~~should~~ can be used interchangeably with its reference product. Decisions on interchangeability and/or substitution are made by national competent authorities/prescribers and are outside the remit of EMA/CHMP. Furthermore, consultation with	Not accepted. See comment 9,81,82

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		doctors and pharmacists is recommended before switching for any patients takes place. Interchangeability and switching aspects should be considered in the Applicant's RMP proposal to be assessed by the Agency."	
59-61	14 88	**Comment:** There is a lack of guidance from the EMA regarding the interchangeability of a biosimilar with its reference medicinal product (RMP). Will the EMA provide their position on biosimilar interchangeability in another guideline, and if, so when will this guideline be published?	Not accepted. See comment 9, 81, 82
59-61	16 89	**Comment:** BIO suggests further clarification regarding interchangeability. **Proposed change:** **"**The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not constitute nor include recommendations on whether a biosimilar ~~should~~ can be used interchangeably with its reference product. The decisions on interchangeability and/or substitution rely on national competent authorities/prescribers and are outside the remit of EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions."	Partly accepted. Also see comment 9, 81, 82

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
59-61	17 90	**Comment:** Having in mind that EMA takes the decision to assess similarity of a biosimilar candidate with the reference product, it is clear that only EMA can be responsible for evaluating product interchangeability based on the totality of the evidence e.g. that switching back and forth a biosimilar product with the reference product or one biosimilar product with another biosimilar product does not have a negative impact for a given patient under a defined treatment. As safety issues cannot be excluded, interchangeability with other similar products is a product property established on the basis of data provided by the biosimilar manufacturer (similar to the establishment of quality, safety and efficacy). These data and conclusions may allow a similar biological product to be used instead of the reference product and vice versa without compromising patient safety and efficacy. Member States may then use this qualification of a biosimilar product to decide if a product can be substituted automatically or not. **Proposed change:** **Add sentence** – EMA's responsibility is to ensure safety of products. In case of automatic substitution the EMA should ensure that a product can be interchangeable. **Add sentence** later on in the document which explains the type of data/studies which would be envisaged in order to make a biosimilar product interchangeable.	Not accepted. See comment 9, 81, 82

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
59-61	19 91	**Comment:** "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." We suggest expressly adding the fundamental principle that biosimilarity does not necessarily mean interchangeability (in other words, that the same therapeutic effect cannot necessarily be expected in any given patient).	Not accepted. See comment 9, 81, 82
59-61	22 92	**Comment:** Recommendations on interchangeability are outside of the scope of the European Marketing Authorisation Application and we recommend that this is expressly stated and that it is stated that this is a national member state responsibility. As per our general comment, inclusion of data on both the biosimilar and the reference product development in the SmPC would provide prescribers with ready access to information in order to make informed decisions on switching and interchangeability (see general comments). **Proposed change:** Consider amending the text as follows: The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not ***constitute or*** include recommendations on whether a biosimilar ~~should~~ ***can*** be used interchangeably with its reference product **as such recommendations are outside the scope of the**	Not accepted. See comment 9. 81, 82

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Community Marketing Authorisation. ***Determinations of interchangeability status rely on policies determined by national competent authorities.***	
59-61	23 93	**Comment:** It is stated that EMA's "evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine". It is acknowledged that decisions on interchangeability are taken on national levels. However, as multiple biosimilar products must be authorised by EMA via centralised procedure, the evaluation of data relating to interchangeability and EMA's recommendations would be of high importance. It is therefore suggested that the guideline presents general requirements to establish interchangeability. More detailed criteria could be presented in 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) currently released for public consultations. It is also suggested to clearly state that the issue of interchangeability (if applicable) should be evaluated according to national provisions when assessing biosimilar dossiers for authorisation purposes by national agencies.	Not accepted. See comment 9. 81, 82
59-61	24 94	**Comment:** The decisions on interchangeability and/or substitution rely	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		on national competent authorities and is outside the remit of EMA/CHMP. After a positive scientific assessment by the Agency it is proven that the biosimilar product is highly similar to the reference product in physicochemical and biological terms. And relevant differences between the biosimilar and the reference medicinal product are excluded. Therefore interchangeability in principle is possible. Although interchangeability will not be in the scope of EMA but needs to be granted by each Member States depending on national rules. We think these lines give room for misinterpretation and would therefore propose to re-phrase these lines 59-61. **Proposed change:** 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 decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of the Agency. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions.	See comment 9. 81, 82
60-61	3 95	**Comment:** The term 'switched' is often used in practice to mean 'interchangeability' at national levels. It is important to ensure that this guideline is consistent with the EU framework and other EMA documentation such as 'Procedural	Not accepted. See comment 9. 81, 82

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications (March 2013 – EMA/940451/2011)' which sets out that "decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of EMA/CHMP", and the Questions and answers on biosimilar medicines (September 2012 – EMA/837805/2011), which set out that the EMA's evaluations do not "include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist." This should be reflected as described below: **Proposed change:** Consider amending text as follows: 'The Agency's evaluations do not include recommendations on whether a biosimilar should be **switched from one product to another or** used interchangeably with its reference medicine.'	
62-73	13 96	**Comment:** The current guideline provides exclusionary language for vaccines & allergens, blood products, and gene or cell therapy products, which should be retained in the revised guideline. **Proposed change:** **"**For highly complex biological medicinal products, such as	Not accepted. See comment 4.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		vaccines, allergen, gene or cell therapy products applicants should take appropriate advice from the EU Regulatory Authorities. In view of the complex and variable physico-chemical, biological and functional characteristics of blood or plasma-derived products, and their recombinant alternatives, it will not be acceptable to submit a reduced clinical dossier when claiming similarity to a reference medicinal product. As a result, applications for such similar products will still need to satisfy the safety and efficacy requirements described in the guidelines for new products." 	
62-73	19 97	**Comment:** "Legal Basis and Relevant Guidelines". We support the proposed removal of the list of names of relevant guidelines and their related URLs. Citing instead the area of the EMA's website where additional biosimilar guidelines can be found enhances the readability and durability of the document.	Comment acknowledged.
65-66	11 98	**Comment:** In addition to being the proper legal basis for biosimilar applications, article 10.4 of Directive 2001/83/EC, as amended, also lays down substantive requirements for requiring results of 'appropriate pre-clinical tests or clinical trials' which should be reflected in this guidance, as outlined below: **Proposed change:** Consider amending text as follows:	Acknowledged, but Art. 10 (4) has been referred to in previous sentence.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		'The data requirements for similar biological medicinal products are found in **article 10.4 and** in Part II, Section 4 of the Annex I of Directive 2001/83/EC, as amended.'	
65-66	13 99	**Comment:** In addition to being the proper legal basis for biosimilar applications, article 10.4 of Directive 2001/83/EC, as amended, also lays down substantive requirements for requiring results of 'appropriate pre-clinical tests or clinical trials' which should be reflected in this guidance, as outlined below: **Proposed change:** Consider amending text as follows: "The data requirements for similar biological medicinal products are found in article 10.4 and in Part II, Section 4 of the Annex of Directive 2001/83/EC, as amended."	See comment 98.
65-66	16 100	**Comment:** In addition to being the proper legal basis for biosimilar applications, article 10.4 of Directive 2001/83/EC, as amended, also lays down substantive requirements for requiring results of 'appropriate pre-clinical tests or clinical trials,' which should be reflected in this guideline. **Proposed change:** "The data requirements for similar biological medicinal products are found in Article 10.4 and Part II, Section 4 of	See comment 98.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		the Annex of Directive 2001/83/EC, as amended."	
68-69	12 101	**Comment:** We would point out that the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance-quality issues (EMA/CHMP/BWP/247713/2012)" is still a draft even though the consultation ended on 30th November 2012	This guideline has recently been finalised.
71-72	13 102	**Comment:** In addition to the 2 general guidelines on Quality and Non-Clinical/Clinical issues, reference should be made to the general guideline on immunogenicity assessment of biotechnology–derived therapeutic proteins, which also apply to biosimilar medicines. **Proposed change:** Add the following reference • Guideline on immunogenicity assessment of biotechnology –derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006)	Not accepted. Guideline on immunogenicity assessment is quoted in EMEA/CHMP/BMWP/42832/2005 Rev.
71-72	22 103	**Comment:** In addition to the 2 general guidelines on Quality and Non-Clinical/Clinical issues, reference should be made to the general guideline on immunogenicity assessment of biotechnology–derived therapeutic proteins and the guidance	Not accepted. See comment 102.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		on immunogenicity of biosimilar monoclonal antibodies. **Proposed change:** Add the following references • **Guideline on immunogenicity assessment of biotechnology –derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006)** • **Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010)**	
72	13 104	**Comment:** The current guideline indicates that the scientific principles described in the guidelines applicable to similar biological medicinal products containing biotechnology-derived proteins, may also be useful when considering non biotechnology-derived biological medicinal products. This information should be retained in the revised guideline. **Proposed change:** "The scientific principles described in the guidelines applicable to similar biological medicinal products containing biotechnology-derived proteins, may also be useful when considering non biotechnology-derived biological medicinal products."	Not accepted. No such statement found in line 72.
72-73	11 105	**Comment:**	Accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Product specific guidelines are frequently issued for active substances to support biosimilar development. Thus providing reference to the EMA website instead of providing a list of guidelines which may quickly become outdated is highly welcome. **Proposed change:** Consider removing reference to individual guidance documents but provide a link to the EMA website which we always contain up-to-date general and class specific guidance documents.	A general link is included in the document.
72-73	22 106	**Comment:** Product specific guidelines are frequently issued for active substances to support biosimilar development. Thus providing reference to the EMA website instead of providing a list of guidelines which may quickly become outdated is highly welcome.	See comment 105.
73-73	9 107	**Comment:** Product specific guidelines are frequently issued for active substances to support biosimilar development. Thus providing reference to the EMA website instead of providing a list of guidelines which may quickly become outdated is highly welcome.	See comment 105.
74-120	11 108	**Comment:** It is suggested to include a high-level statement on pharmacovigilance. **Proposed change:**	Partly accepted Modified wording in section 3.1 In order to support pharmacovigilance

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Consider adding the following text after line 79. **Biosimilar products will be subject to at least the same pharmacovigilance (safety surveillance) and ongoing post-marketing requirements as original biological products.**	monitoring and in accordance with Article 102(e) of Directive 2001/83/EC, as amended, all appropriate measures should be taken to clearly identify any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to its brand name and batch number
74-120	11 109	**Comment:** It is suggested to include a high-level statement on extrapolation. **Proposed change:** Consider adding the following text after line 79. **Extrapolation of clinical data to support other indications approved for the originator product should be scientifically justified and, if necessary, demonstrated in more than one patient population.**	Partly accepted see comment 24, 108
74-120	13 110	**Comment:** The concept of extrapolation is addressed in the guideline dealing with non-clinical and clinical issues. The possibility to	Partly accepted Wording in section 3.1:

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		extrapolate under certain condition has been implicitly linked to the concept of biosimilarity. Therefore, although we feel that a discussion of efficacy/safety aspects does not need to be covered by the overarching guideline, extrapolation should be a topic for which the approach is explained in the general principles. It should be clear that if a 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. **Proposed change:** Add the following bullet point between lines 116 and 117: "In case a 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."	If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification
74-120	22 111	**Comment:** It is suggested to include a high-level statement on pharmacovigilance. **Proposed change: Biosimilar products will be subject to pharmacovigilance (safety surveillance) consistent with the reference product plus any additional requirements arising from the assessment process.**	See comment 108.
74-120	22 112	**Comment:** It is suggested to include a high-level statement on	See comment 24, 110

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		extrapolation. **Proposed change: Extrapolation of clinical data to support other indications approved for the originator product should be scientifically justified and depend on the overall totality of evidence.**	
74-174	19 113	**Comment:** "General Principles". Since October 2005 when the Original Guideline took effect, the agency has reviewed over a dozen applications under Article 10(4) of Directive 2001/83/EC and adopted detailed guidelines for nine product classes, and the European Commission has approved biosimilars representing five types of active ingredients. As the EMA has gained greater experience reviewing applications for and regulating biosimilars, additional common principles have emerged, some of which are not addressed in the Draft Guideline. As *the* foundational biosimilar guideline, and with other countries looking to EMA guidelines as models, we believe that the final guideline should provide an overview of the core principles concerning biosimilar regulation in Europe (both for readers familiar with the CHMP's other guidelines and for those who are not). We therefore suggest that the final guideline also discuss the following fundamental principles: • The biological system in which a protein product is produced, and the nature of its manufacturing process, can significantly affect the product's structure and	Not accepted. These issues are discussed in the guidelines: • Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMA/CHMP/BWP/247713/2012) • Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/4

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		function. Even minor structural differences can significantly affect a protein's safety, purity, and/or potency. Current analytical methods may not be able to detect all relevant structural and functional differences between two proteins. • A biosimilar comparability exercise should demonstrate that the proposed biosimilar and the reference product are highly similar in terms of primary, secondary, and (to the extent possible) tertiary and quaternary (if any) structure, taking into account glycosylation and other post-translational modifications. • Because a biological product's propensity for producing an immune response cannot be meaningfully evaluated except through clinical testing, may be sensitive to a variety of factors (including its unique manufacturing processes, handling and storage, or immediate packaging), and can have a variety of undesirable effects on safety and efficacy, protecting patient welfare always requires some comparative clinical immunogenicity testing in a setting sensitive to the detection of immunogenicity differences. We believe the final guideline should state that biosimilar applicants should provide data from at least one premarket clinical study comparing the immunogenicity profile of the proposed biosimilar with that of the reference product in a setting sensitive to detecting differences in immunogenicity. The setting should include use of a dose, dosing regimen,	2832/2005 Rev. For this reason, these guidelines are explicitly mentioned in section 2 (see also comment 97). It would be superfluous and confusing to further discuss these issues in the overarching guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		route of administration, and duration of therapy that is more likely to induce immunogenicity. It should also include a study population where physical condition, underlying disease, and concomitant medications are not likely to suppress immunogenicity or the detection of differences in immunogenicity. • Postmarket safety surveillance will be always necessary. Biosimilar manufacturers should continually engage in postmarket pharmacovigilance to: monitor for safety signals (in larger and more diverse patient populations) that could not be detected through the premarket programme; and monitor for clinically significant changes in the product that may not be detected prior to batch release, including those caused by manufacturing changes or breakdowns in process.	
75, 89, 94 & 100	6 114	**Comment:** In these lines, the word biosimilar in the term biosimilar approach is given in quotation marks which is considered as an unnecessary “weaking” of the term as such. **Proposed change:** Remove quotation marks	Accepted
75-76	13 115	**Comment:** In section 2.1 of the current guideline useful clarification is provided that help understand why a standard generic approach is not appropriate for biosimilar products. This	See comment 43.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		information should be kept in the revised guideline. **Proposed change:** Add the following paragraph: "*Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. In addition, there is a spectrum of molecular complexity among the various products (recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy, etc.).* *Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be 'minor' in the manufacturing process. Thus, the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects."*	
76	21 116	**Comment:** The definition of 'biosimilar' as provided in the current draft guideline is misleading and contradicts the definition as provided in Directive 2001/83/EC as amended: *"... the similar nature of two biological medicinal products, ..."* , Part II, 4.), whereas a 'biological medicinal product is defined as follows: *"A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its*	Not accepted. Proposal is ambiguous in that it could read "*A substance …that is similar to a product"* New wording is: A biosimilar is a biological

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control." (Annex I, 3.2.1.1) **Proposed change:** *"A biosimilar is a biological medicinal product that contains a ~~version of the active~~ **biological** substance **that is similar to** ~~of~~ an already authorised original biological medicinal product (reference medicinal product)."*	medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA.
76-77	10 117	**Comment:** A biosimilar product not only "contains a version of the active substance [*inserted: i.e. drug substance*] of an already authorised original biological medicinal product" but is as such a copycat product of the reference's drug product. Language should remain consistent with other documents. **Proposed change:** "A biosimilar is a biological medicinal product **which is of similar nature as an already authorized original biological medicinal product** ~~that contains a version of the active substance of an already authorised original biological medicinal product~~ (reference medicinal product)."	Not accepted. Proposed definition does not provide additional clarity.
76-77	22 118	**Comment:** A biosimilar product not only "contains a version of the active substance [*inserted: i.e. drug substance*] of an already	See comment 117.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		authorised original biological medicinal product" but is also similar to the reference drug product since it is the drug product which is administered to patients. It is recommended that the wording below is clarified as suggested and that reference to the stepwise approach and non clinically meaningful differences is also made. **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 (reference medicinal product). **The** biosimilar **medicinal product** demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive, **direct** ~~comparability~~ **biosimilarity** exercise **conducted in stepwise fashion**. **Any minor differences arising will have been deemed to be non clinically meaningful for the product to be approved as a biosimilar.**	
76-79	1 119	**Comment:** We strongly support adhering to this definition in the final guideline. The new wording on the definition of a biosimilar product ("…contains a version of the active substance") is clear and concise and preferable to the wording contained in EMA's	Comment acknowledged.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Q&A on biosimilar products dated 26 September 2012 ("The active substance of a biosimilar and its reference medicine is essentially the same biological substance,…."). From a scientific standpoint the word "version" matches the inherent complexity of biological products very well and is therefore well chosen.	
76-79	8 121	**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 contains a version of a **known biological** active substance of an	Not accepted. Agreed new definition is: A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		already authorised original biological medicinal product (reference medicinal product)."	
76-79	11 122	**Comment:** The draft guideline includes a definition of biosimilars which deviates from the definition by Weise et al *(Nature Biotechnology 29 (8), August 2011)* on one important point. Where Weise et al defines a biosimilar as a version of a medicinal product, the current guideline defines a biosimilar as a biological medicinal product that contains a version of the active substance of the reference medicinal product. While the subsequent text in the guideline mentions the need for the same posology and route of administration, the definition 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. **Proposed change:** Consider amending the text as follows: **"**A biosimilar is a biological medicinal product **highly similar to** ~~that contains a version of the active substance of~~ an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy	Not accepted. Agreed new definition is: A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. For the issue of 'same posology', see comment 5.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		based on a comprehensive, **direct** comparability exercise."	
76-79	11 123	**Comment:** It is considered that this paragraph contradicts the paragraph at lines 167 – 172. As stated in this section and in accordance with Part II, Section 4 of the Annex of Directive 2001/83/EC as amended, 'a biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive exercise.' Whereas, lines 167 – 172 suggest that it may be possible to *deduc*e similar efficacy and safety based on physicochemical characteristics and biological activity/potency and comparative PK data. **Proposed change:** see comment at line 167.	Not accepted. This is a seeming contradiction, since a biosimilar may demonstrate similarity in different ways. Only in specific circumstances, when a confirmatory clinical trial may not be necessary, then efficacy and safety may be deduced from other propensities as written in section 3.3.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
76-79	13 124	**Comment:** The draft guideline includes a definition of biosimilars, which deviates from the definition by Weise et al *(Nature Biotechnology 29 (8), August 2011)* on one important point. Where Weise et al defines a biosimilar as a version of a medicinal product, the current guideline defines a biosimilar as a biological medicinal product that contains a version of the active substance of the reference medicinal product. While the subsequent text in the guideline mentions the need for the same posology and route of administration, the definition 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. **Proposed change:** **"**A biosimilar is a biological medicinal product highly similar to ~~that contains a version of the active substance of~~ an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive, direct comparability exercise."	See comment 122.
76-79	16 125	**Comment:** BIO suggests editing the definition offered for "biosimilar" for	Not accepted. The proposed definition does

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		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)."	not provide additional clarity.
76-79	24 126	**Comment:** To explain what a "Biosimilar" is and that it refer to an already approved medicinal product with a well-known active biological active substance we would like to add the word "known biological". **Proposed change:** A biosimilar is a biological medicinal product that contains a version of the **known biological** active substance of an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.	See comments 121, 122
77-78	21 127	**Comment:** For clarity PDA recommends modifying the wording. A biosimilar cannot demonstrate similarity, but an applicant has to do so.	Partly accepted. The new wording reads: Similarity to the reference medicinal product in terms of quality characteristics,

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Proposed change: *"~~A~~ **B**iosimilar**ity** ~~demonstrates similarity~~ to the reference medicinal product **needs to be demonstrated** in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise."*	biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.
79	13 128	**Comment:** The definition of a biosimilar should make it clear that the amino acid sequence of a biosimilar should be identical to the amino acid sequence of the reference product (with the exception of certain variability at the N- and C-terminus that are not the result of intended sequence changes). **Proposed change:** **"**<u>The amino acid sequence of the active substance of a biosimilar should be identical to that of the reference product (with the exception of certain variability at the N- and C-terminus that are not the result of intended sequence changes)</u>.“	Accepted. Statement added in this guideline and also with more details in the quality guideline
79, 107 and 153-154	11 129	**Comment:** The definition of a biosimilar should make it clear that the amino acid sequence of a biosimilar should be identical to the amino acid sequence of the reference product (with the exception of certain variability at the N- and C-terminus that are not the result of intended sequence changes). **Proposed change:**	See comment 128

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Consider adding the following text: **The amino acid sequence of the active substance of a biosimilar should be identical to that of the reference product (with the exception of certain variability at the N- and C-terminus that are not the result of intended sequence changes).**	
79, 107 and 153-154	22 130	**Comment:** The definition of a biosimilar should make it clear that the amino acid sequence of a biosimilar should be identical to the amino acid sequence of the reference product (with the exception of certain variability at the N- and C-terminus that are not the result of intended sequence changes). **Proposed change: The amino acid sequence of the active substance of a biosimilar should be identical to that of the reference product (with the exception of certain variability at the N- and C-terminus that are not the result of intended sequence changes).**	See comment 128.
79, 89, 164	6 131	**Comment:** In order to differentiate the biosimilar comparability 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.	Accepted where needed.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Proposed change: […] **biosimilar** comparability exercise […]	
80	10 132	**Comment:** This sentence is not contributing to the clarity of this chapter. It is of rather general meaning and may be misunderstood or misinterpreted. **Proposed change:** „~~In principle, the concept of a biosimilar is applicable to any biological medicinal product.~~“	Not accepted. See also comment 4.
80	21 133	**Comment:** To improve clarity, PDA recommends changing the phrase 'concept of a biosimilar'. **Proposed change:** It is recommended to replace as follows *In principle, the concept of ~~a~~ biosimilar**ity** is applicable to any biological medicinal product.*	Accepted.
80-81	16 134	**Comment:** BIO believes that deleting the first sentence of the paragraph that begins on Line 80 will better clarify the intended message. **Proposed change:** “~~In principle, the concept of a biosimilar is applicable to any biological medicinal product. However, i~~In practice, the	See comment 132

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		success of developing a biosimilar..."	
80-82	9 135	**Comment:** The word "copy" in relation to biosimilar development should be strictly avoided to differentiate to sub- standard non-comparable biological copy-products which would not fulfil biosimilar criteria as outlined in this guideline. **Proposed change:** .....on the ability to produce a ~~close~~ ~~copy~~ *product with product characteristics as close as possible* to the reference medicinal product.....	Partly accepted. Sentence was rephrased. Word "copy" is deleted throughout document.
81	10 136	**Comment:** "close copy" is not in line with wording in other biosimilar documents **Proposed change:** "the ability to produce a **medicinal product which is highly similar to** ~~close copy to~~ the reference medicinal product"	See comment 135
81	11 137	**Comment:** "close copy" is not consistent with language in other documentation and should be strictly avoided to differentiate to sub-standard non-comparable biological copy-products which would not fulfil biosimilar criteria as outlined in this guideline. **Proposed change:**	See comment 135

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Consider amending the text as follows: However, in practice, the success of developing a biosimilar will depend on the ability to produce ~~a close copy to the reference~~ **a** medicinal product ~~and demonstrate the similar nature of the concerned~~ **which is highly similar to the reference product.**	
81	13 138	**Comment:** "close copy" is not consistent with language in other documentation. In our opinion, the use of the term "close copy" in an official guidance document should be avoided as it can easily lead to misinterpretation. Public discussions (in Norway, but probably also in other countries) indicate that to prescribers, use of the word copy implies the products are identical=generics. The only appropriate word to use is SIMILAR. Semantics is tremendously important (as acknowledged in the paper by Weise et al *(Nature Biotechnology 2011;29:690–3).* Moreover the word "copy" in relation to biosimilar development should be strictly avoided to differentiate to sub-standard non-comparable biological copy-products which would not fulfil biosimilar criteria as outlined in this guideline. **Proposed change:** "However, in practice, the success of developing a biosimilar will depend on the ability to produce a product that is highly similar ~~close copy~~ to the reference medicinal product ….."	See comment 135

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
81	20 139	**Comment:** In our opinion, the use of the term “close copy” in an official guidance document should be avoided as it can easily lead to misinterpretation. Public discussions (in Norway, but probably also in other countries) indicate that to prescribers, use of the word copy implies the products are identical=generics. The only appropriate word to use is SIMILAR. Semantics is tremendously important (as acknowledged in the paper by Weise et al (Nature Biotechnology 2011;29:690–3) **Proposed change:** “However, in practice, the success of developing a biosimilar will depend on the ability to produce ***a product that is highly similar*** ~~close copy~~ to the reference medicinal product …..”	See comment 135
81	21 140	**Comment:** A 'similar' product cannot be a 'copy' of an original (which assumes to be a 1:1 version of the original); see also comment to line 76. **Proposed change:** *"... to produce a product comparable ~~copy~~ to the reference medicinal product and demonstrate the similar nature of the concerned products."*	See comment 135
81	22 141	**Comment:** “close copy” is not consistent with language in the legislation	See comment 135

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		and other guidelines and should be avoided... **Proposed change:** "…ability to produce ~~a close copy to the reference~~ **a** medicinal product **which is highly similar to the** reference…..."	
81-82	16 142	**Comment:** BIO recommends using consistent nomenclature to describe the nature of biosimilar biological medicinal products. **Proposed change:** "...will depend on the ability to produce a ~~close copy~~ medicinal product that is highly similar to the reference medicinal product..."	See comment 135
82-84	14 143	**Comment:** Will the EMA provide a more detailed guidance on the acceptable differences between a biosimilar and its RMP?	Not accepted. Further guidance is given in the guidelines referred to in section 2. However, it should be kept in mind that it is difficult to provide all-encompassing guidance in this respect.
83-84	1 144	**Comment:** We think that the wording "…requires knowledge on how to interpret any differences between …" needs to be clearer.	Not accepted. Sufficient cross–referencing is already given in section 2.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Proposed change: We suggest cross–referencing to other guidelines as applicable.	Further cross–referencing would hamper readability of the document.
83-84	9 145	**Comment:** To align wording with line 152 …. any observed differences ….. **Proposed change:** …. on how to interpret any *observed* differences between……	Not accepted. Doesn´t add clarity in this place of text.
83-84	11 146	**Comment:** To align wording with line 152 …. any observed differences ….. **Proposed change:** Consider amending the text as follows: …. on how to interpret any **observed** differences between……	See comment 145.
83-84	13 147	**Comment:** To align wording with line 152 …. any observed differences ….. **Proposed change:** "…. on how to interpret any *observed* differences between……"	See comment 145.
83-84	13 148	**Comment:**	See comment 144.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		We think that the wording "…requires knowledge on how to interpret any differences between …" needs to be clearer. **Proposed change:** We suggest cross–referencing to other guidelines as applicable.	
83-84	21 149	**Comment:** The significance of the manufacturing process to the quality of a similar biological medicinal product needs to be considered in the biosimilarity concept (see also 'General Comments' and comment to line 151). **Proposed change:** *"This includes physicochemical and biological characterisation* ***as well as any characteristics related to its manufacturing process*** *and requires knowledge on how to interpret any differences between a biosimilar and its* ***biological*** *reference medicinal product."*	Not accepted. Characteristics related to the manufacturing process are not part of the biosimilar comparability exercise. Mentioning this aspect here will cause unnecessary confusion.
83-84	22 150	**Comment:** Recommend clarifying that the challenge is whether or not the scientific knowledge allows the applicant to interpret whether any differences are clinically meaningful. **Proposed change:** .... on how to interpret any **observed** differences between a biosimilar and its reference medicinal product **as to whether such differences are clinically**	Not accepted. Justification of any observed differences with regard to their potential impact on safety and efficacy is covered in section 3.3

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		meaningful",	
84	11 151	**Comment:** The current version of the guideline explained the complexity of biological medicinal products compared to chemically derived medicinal products and acknowledged the molecular spectrum of products and their complexity. We propose to remain with the paragraph of the current version of the guideline. **Proposed change:** Consider amending the text as follows after line 84: **Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products (recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy, etc.). Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be minor in the manufacturing process. Thus, the safety / efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects.**	See comment 43
86-89	4 152	**Comment:** Please can you clarify the meaning of the phrase "in principle" in the sentence: "The standard generic approach	Partially accepted. The standard "generic approach" is applicable when

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		(demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is <u>in principle</u> not appropriate to biological/biotechnology-derived products due to their complexity." One definition of "in principle" is that although something is theoretically possible, in reality it may not actually happen. Does EMA consider that it may be possible in certain, rare circumstances that a generic approach might be acceptable for a biological/biotechnology-derived product? If EMA considers that such a circumstance may be possible, please can you provide a theoretical example for illustration.	the following conditions are met: ■ Same qualitative and quantitative composition of active substances ■ Same pharmaceutical form ■ Demonstration of bioequivalence. To the extent that a biosimilar could meet these conditions, the "generic approach" could theoretically be acceptable.
86-89	16 153	**Comment:** BIO recommends revising the paragraph to better reflect the internationally-aligned scientific opinion on biological/biotechnology-derived products. **Proposed change:** "The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is ~~in principle~~ not	See comment 152.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		appropriate to biological/biotechnology-derived products due to their complexity."	
86-90	10 154	**Comment:** **Proposed change:** „The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is ~~in principle~~ not appropriate ~~to~~ **for** biological/biotechnology-derived products due to their complexity."	See comment 152.
86-90	11 155	**Comment:** It is important to be clear that the standard generic approach is in no way appropriate for biosimilar products and that demonstration of comparability between a proposed biosimilar and its reference biologic product is one of the current clinical requisites of the similarity exercise. Firstly, the proper legal basis for biosimilars is found in article 10.4 and in Part II, Section 4 of the Annex of Directive 2001/83/EC which clearly states the need for 'appropriate pre-clinical tests or clinical trials'. The addition of the words 'in principle' in this sentence suggest that there may be alternatives which are acceptable, however this would be inconsistency with the approach which has been constantly followed by the EMA/CHMP and the EC and may cause confusion for biosimilar developers and other stakeholders,	See comment 152.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		thus a suggestion is made to reflect that it is a necessary, but not exclusive, step in the similarity exercise **Proposed change:** Consider the amending text as follows: The standard generic approach **(Article 10(2) of Directive 2001/83/EC, as amended)** (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is ~~in principle~~ **scientifically** not ***enough evidence by itself for*** ~~appropriate to~~ biological/biotechnology-derived products due to their complexity. The "biosimilar" approach **(Article 10(4) of the Directive 2001/83/EC, as amended)**, based on a comprehensive comparability exercise, will then have to be followed.	
86-90	13 156	**Comment:** We much appreciate that the distinction between chemical drugs and generics and biological/biotechnology-derived medicinal products and biosimilars that has been established in the EU legislative framework is presented in a clear manner. Such distinction is useful and necessary for the sake of (1) legal certainty and consistency in assessment of such products by the regulatory authorities and (2) ensuring clear and correct functioning of the framework. In order to avoid any ambiguity, it is suggested to add references to the respective articles regulating the generic and the biosimilar	See comment 152.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		pathways. The Guideline states: “The standard generic approach…..is in principle not appropriate to biological / biotechnology-derived products due to their complexity.” We strongly agree that the generic approach to demonstrate bioequivalence with a reference medicinal product by appropriate bioavailability studies for a chemically derived medicinal product would not be appropriate for a biotechnology-derived product. In fact, the balance of this EMA Guideline (and the EMA’s regulatory processes to date) focuses on the unique complexities of the requirements to demonstrate biosimilarity for biological/biotechnology- versus chemically derived products. Therefore, we believe that the statement could be strengthened in alignment with the totality of the Guideline, if the phrase “in principle” were removed. **Proposed change:** “The standard generic approach (Article 10(2) of Directive 2001/83/EC, as amended) - i.e. ~~(~~demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies~~)~~ - which is applicable to most chemically-derived medicinal products is ~~in principle~~ not appropriate to biological/biotechnology-derived products due to their complexity. The “biosimilar” approach (Article 10(4) of the Directive 2001/83/EC, as amended), based on a comprehensive comparability exercise, will then have to be followed.”	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
86-90	19 157	**Comment:** "The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is in principle not appropriate to biological/biotechnology-derived products due to their complexity. The 'biosimilar' approach, based on a comprehensive comparability exercise, will then have to be followed." We strongly support the continued inclusion of this concept in the final guideline. As we explained in our comments on the Concept Paper, we believe authorising even "very simple" biological products on a generic legal basis would not be appropriate. Analytical testing cannot demonstrate that biosimilars are identical to their reference products, due to either testing limitations or (conversely) the fact that improved analytical methods may lead to the identification of even more differences between products. Further, even very well characterized biological products with known quality characteristics and mechanisms of action could display unexpected, clinically significant differences from their reference products due to seemingly inconsequential manufacturing differences that result in, for example, microaggregation or microheterogeneity. A bioequivalence study and quality comparability programme thus could not provide assurance that safety or efficacy differences would not emerge between a biosimilar and its reference product in a clinical setting. Continued use of the biosimilar approach for all biological products with abbreviated dossiers will	See comment 152.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		ensure that the EMA has the flexibility to determine the type and amount of data required on a case-by-case basis.	
86-90	22 158	**Proposed change:** Consider the amending text to cite the legal basis and replace term “comparibility” with “biosimilarity”: ‘The standard generic approach **(Article 10(2) of Directive 2001/83/EC, as amended)** (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is in principle not appropriate to biological/biotechnology-derived products due to their complexity. The “biosimilar” approach **(Article 10(4) of the Directive 2001/83/EC, as amended)**, based on a comprehensive ~~comparability~~ **biosimilarity** exercise, will then have to be followed.’	Not accepted. See comments 7 and 152
91-93	1 159	**Comment:** We strongly support the wording in the revised version of the overarching biosimilar guideline 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 scientifically correct and acknowledges the decade-long experience regulators and companies have gained in the comparative evaluation of biologics.	Comment acknowledged. See also comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		• We agree that the scientific principles for assessing comparability of a biosimilar to a reference product are the same as those applied for the evaluation of changes in the manufacturing process. • We also support the expression “biosimilar comparability exercise” which is stated in this revised draft guideline for the first time.	
91-93	3 160	**Comment:** Whilst is agreed that certain principles required for evaluating changes in a well established biological manufacturing process may serve as a source of inspiration for demonstrating biosimilarity between the biosimilar and its reference product, the amount of data required to substantiate biosimilarity is vastly different. It is also clear that the biosimialr developer generally does not have access to the same information about the reference product than the sponsor/originator. It is therefore recommended that the discussion regarding ICH Q5E is moved to a separate section in the guideline or a separate guidance, where a full explanation of the requirements to confirm biosimilarity can be provided. **Proposed change:** Consider deleting the following sentence: ‘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).’	Not accepted. See comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		And provide detail of establishing biosimilarity in a separate section such as 3.3.	
91-93	8 161	**Comment:** We strongly support the current wording in this revised draft version of the guideline on similar biological medicinal products (CHMP/437/04 Rev.1). It states 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 scientifically correct and acknowledges the decade-long experience regulators and companies have gained in the comparative evaluation of biologics. Also, this is in line with the current thinking of leading EU regulators who have repeatedly stated in publications and presentations given at public conferences that the scientific principles of the comparability exercise between a biosimilar and its reference product and the comparability after manufacturing changes are the same. We also support the new expression “biosimilar comparability exercise” which is stated in this revised draft guideline for the first time. It makes clear that the same scientific principles and methodologies apply as those following manufacturing changes.	Comment acknowledged. See also comment 7
91-93	10 162	**Comment:** We suggest to clearly differentiate between a biosimilarity	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		exercise (scope of this document) and the process followed after manufacturing changes as described in ICH Q5E. The current draft document seems to melt the terms 'comparability' and 'biosimilarity'. However, these are distinct exercises. ICH Q5E guidance is appropriate when optimizing an approved process for a product that has undergone significant R&D and a full pre-clinical and clinical regulatory approval process. The assessment of biosimilarity following an attempt to reverse engineer a reference product is necessarily a far more extensive exercise. The draft guideline should therefore make clear that the two exercises are distinct. **Proposed change:** „**Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product.** ~~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).~~"	See comment 7
91-93	11 163	**Comment:**	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		It is acknowledged that, in order to carry out the 'biosimilarity exercise', the biosimilar sponsor would need to undertake comparability studies and that ICH Q5E may therefore serve as a source of inspiration for substantiation the similar nature, in terms of quality, safety and efficacy, of the biosimilar and its reference product. However the amount of data required to substantiate biosimilarity is vastly different. It is also clear that the biosimilar developer generally does not have access to the same information about the reference product than the sponsor/originator. It is therefore recommended making a clear differentiation between a biosimilarity exercise (scope of this document) and the process followed after manufacturing changes and that the discussion regarding ICH Q5E is moved to a separate section in the guidance where a full explanation of the requirements to confirm biosimilarity can be provided. **Proposed change:** Consider amending the text to include a follows: ~~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).~~ **In order to carry out the 'biosimilarity exercise', the biosimilar sponsor would need to undertake comparability studies and therefore scientific principles of such a biosimilar comparability exercise could use those described in ICH Q5E. However, more**	See comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product. **And provide detail of establishing biosimilarity in a separate section such as 3.3.**	
91-93	11 164	**Comment:** It should clear in which section of the dossier the results from the biosimilar comparability exercise should be added. **Proposed change:** Consider adding that the results of the biosimilar comparability exercise should be added to Module 3, 4 and/or 5.	Not accepted. This issue is not within the scope of this Guideline. Please refer to the Similar-biological-medicine applications: questions and answers document.
91-93	12 165	**Comment:** We would change the following sentence: "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)." **Proposed change:** Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, more data and information will be needed to establish biosimilarity than would be needed to	Not accepted. See comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		establish that a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product.	
91-93	13 166	**Comment:** It is agreed that certain principles required for evaluating changes in a well established biological manufacturing process can apply for demonstrating biosimilarity between the biosimilar and its reference product, however the amount of data required to substantiate biosimilarity is vastly different. In particular, considerable scientific overlap occurs at the level of structural and functional comparisons described in ICH Q5E, albeit with inability to compare relevant process data in the case of the biosimilar. However, the risk-based assessments described in ICH Q5E, including considerations for performing any required non-clinical or clinical bridging studies, are inappropriate and insufficient for the evaluation of biosimilarity. It is also clear that the biosimilar developer generally does not have access to the same information about the reference product than the sponsor/originator. Consequently as in the paper by M. Weise et al. *(Blood 120 (26), Dec. 2012)* an explanation should be added as to why in general the comparability program for a biosimilar will be more extensive. **Proposed change:** "The scientific principles of such a biosimilar comparability exercise are based <u>in part</u> on those principles applied for	Not accepted. See comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E). Since the biosimilar will be produced by a different manufacturer, the data requirements for demonstration of biosimilarity will usually be more extensive than for demonstration of comparability of a given biological medicinal product before and after manufacturing changes by the same manufacturer." 	
91-93	16 167	**Comment:** BIO believes that this bullet point conflates the term 'comparability' with 'biosimilarity'. These are distinct exercises. ICH Q5E guidance is appropriate when optimizing an approved process for a product that has undergone significant R&D and a full pre-clinical and clinical regulatory approval process. The assessment of biosimilarity following an attempt to reverse engineer a reference product is necessarily a far more extensive exercise. Comparison of drug substance and drug product at various stages of manufacture is an important part of the comparability exercise. This is not possible as part of a biosimilarity assessment since the manufacturer does not have the extensive manufacturing data and experience of the originator and can only compare their version of the product with the final product of the originator. The biosimilar Sponsor is therefore required to produce a far more extensive package of analytical, non-clinical and clinical data to support their assertion of biosimilarity than is called for	Not accepted. See comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		under ICH Q5E. CHMP/437/04 Rev1 should therefore make clear that the two exercises are distinct. BIO suggests making a clear differentiation between a biosimilarity exercise (scope of CHMP/437/04 Rev1) and the process followed after manufacturing changes as described in ICH Q5E. **Proposed change:** "While ~~T~~the scientific principles of such a biosimilar comparability exercise are ~~based on~~ related to those applied for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E), in general, more data and information will be needed to establish biosimilarity."	
91-93	19 168	**Comment:** "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)." We recommend making clear that a biosimilar comparability exercise is *not the same as* an exercise discussed in ICH Q5E (designed to evaluate the comparability of a single product after a change made to a single manufacturer's manufacturing process). Unlike changes to a manufacturer's own process, biosimilar development entails (among other things) a different manufacturer, different facilities, and use of different starting materials, without the benefit of detailed	Not accepted. See comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		and proprietary information about the reference product's manufacturing process and process history. Demonstrating similarity of a biosimilar to a reference product thus is more complex and requires more data than assessing changes to a single product's manufacturing process under ICH Q5E.	
91-93	22 169	**Comment:** It is acknowledged that, in order to carry out the 'biosimilarity exercise', the biosimilar sponsor would need to undertake comparisons with the reference product and that ICH Q5E may therefore serve as a source of inspiration for substantiation of the similar nature, in terms of quality, safety and efficacy, between the biosimilar and its reference product. However the amount of data required to substantiate biosimilarity is vastly different. It is also clear that the biosimilar developer generally does not have access to the same information about the reference product as the sponsor/originator and has had to develop their own manufacturing process. Additional text should be added to clarify the different regulatory context. **Proposed change:** Consider amending the text as follows: **In order to carry out the 'biosimilarity exercise', the biosimilar sponsor would need to undertake comparative studies with the reference product and therefore scientific principles of ICH Q5E could be utilised. However, more data and information will be**	Not accepted. See comment 7

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		needed to establish biosimilarity which is determined against another company's reference product, than would be needed to establish that the same manufacturer's post-manufacturing change product is comparable to their pre-manufacturing change product as per the scope of ICH Q5E.	
94	11 170	**Comment:** It is whether a biosimilar approach is *possible* which should determine its development as such rather than its applicability. The EMA should also clarify what is meant by regulatory experiences and how these can impact the applicability of the biosimilar approach or delete this reference **Proposed change:** Consider amending the text as follows: Whether the 'biosimilar' approach would be ~~applicable~~ **possible** for a certain biological medicinal product depends on the state of the art of analytical procedures **where comprehensive characterization of recombinant proteins can be accomplished by multiple orthogonal analytical analyses,** the manufacturing processes employed, as well as clinical ~~and regulatory~~ experiences, e.g. as regards the possibility to identify comparability margins, availability of sensitive clinical endpoints and model conditions etc.	Not accepted. Details on analytical procedures are mentioned in the Quality guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
94-96	9 171	**Comment:** "Whether the biosimilar approach would be applicable [...] depends on [...] regulatory experiences". The EMA should clarify what is meant by regulatory experiences and how these can impact the applicability of the biosimilar approach **Proposed change:** Whether the 'biosimilar' approach would be applicable for a certain biological medicinal product depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical ~~and regulatory~~ experiences....	Partly accepted. Reference to regulatory experience has been deleted.
96-97	14 172	**Comment:** It is not clear how to define "comparability margins". Will these be provided in a guideline? If not, clarification from the EMA is requested.	Accepted. Reference to comparability margins has been deleted.
96-97	23 173	**Comment:** "Possibility to identify comparability margins" is not entirely clear as a condition for use of the biosimilar approach. It is noted that comparability margins are most often difficult to derive and frequently only variability of the reference product batches gives clear indications for allowable margins.	See comment 172
98-103	19 174	**Comment:** "Biosimilar comparability exercises are more likely to be applied to products that are highly purified and can be thoroughly characterised (such as many	See comment 4

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		biotechnology-derived products). The 'biosimilar' approach is more difficult to apply to other types of biological medicinal products, which by their nature are more difficult to characterise, such as biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained." The Original Guideline stated that "parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be 'minor' in the manufacturing process. Thus, the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects."[3] We suggest adding back this information and noting that for these reasons, it is critical to carefully characterise biological products, even those that are capable of thorough characterisation. In addition, we recommend again identifying whole virus vaccines, blood and plasma derived products and cell therapies as examples of biologics for which the "biosimilar" approach is more difficult to apply and thus is not presently being applied.[4] Doing so would provide specific examples of more complex biological products and would helpfully explain how the EMA intends to treat them.	

[3] Original Guideline, at § 2.1.
[4] *See* Original Guideline, at §§ 3.3, 3.4, and 3.5

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
98-99	4 175	**Comment:** It is understood that a biosimilar product needs to be comparable to an appropriate reference product and that a critical part of the comparability exercise involves analytical (structural and functional) characterisation of the putative biosimilar and the reference product. Indeed, the revised guideline states that “Biosimilar comparability exercises are more likely to be applied to products that are highly purified and can be thoroughly characterised (such as many biotechnology-derived medicinal products).” There has been much debate about how similar different product classes and individual biosimilar products should be to their reference products. Does EMA intend to provide any further detail of acceptable analytical ranges, or examples where analytical ranges are considered acceptable or unacceptable, perhaps in revised product class specific guidelines?	Not accepted. See comment 143
100-103	11 176	**Comment:** It is suggested to be clear in the guidance that biosimilars are possible where the reference product is hightly purified and can be thoroughly characterized and not to suggest where it is less likely. **Proposed change:** Consider removing the following text: ~~The ‘biosimilar’ approach is more difficult to apply to other types of biological medicinal products, which by their nature~~	Not accepted. Also see comment 4

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		~~are more difficult to characterize, such as biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained.~~	
102	1 177	**Comment:** We suggest omitting the reference at the end of the sentence: “The ‘biosimilar’ approach is more difficult to apply … and/or those for which little clinical and regulatory experience has been gained.”, as this does not make sense for a biosimilar. Biosimilars are versions of established biological medicines that are marketed for a number of years and therefore have obtained clinical and regulatory experiences during that time. **Proposed change:** The ‘biosimilar’ approach is more difficult to apply to other types of biological medicinal products, which by their nature are more difficult to characterise, such as biological substances arising from extraction from biological sources ~~and/or those for which little clinical and regulatory experience has been gained~~.	See comment 176
104-105	13 178	**Comment:** Please confirm the scope of the term “posology”. We understand that the concepts of “strength” and “pharmaceutical forms” which are defined terms as per EDQM, are included in the posology one. However to avoid any misunderstanding it is proposed as in the current	See comment 5.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		guideline, to explicitly mention them in the text. **Proposed change:** "The posology (including the pharmaceutical form, the strength and the frequency of administration) and route of administration of the biosimilar should be the same as that of the reference medicinal product."	
104-105	14 179	**Comment:** What about the similarity in the composition, presentation, dose concentration and strength of a biosimilar product and the RMP?	See comment 5.
104-105	19 180	**Comment:** "The posology and route of administration of the biosimilar should be the same as that of the reference medicinal product." We strongly support the statement that the posology and route of administration of a biosimilar should be the same as that of the reference product and the proposed elimination of language stating that if these features are not the same, additional data should be provided. As we explained in our comments on the Concept Paper, a biological product that incorporates an intentional difference with regard to dosing regimen, pharmaceutical form, strength, or route of administration is not similar to a reference product and should be authorised only under the standard approval pathway on the basis of a full dossier. Such differences carry with them the potential for undetected — and entirely	See comment 5.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		avoidable — clinical risks that analytical and clinical testing can help control but cannot eliminate. For clarity, we suggest explicitly noting that posology includes a medicine's pharmaceutical form and strength. We also recommend stating that posology and route of administration "must" be the same.	
104-106	3 181	**Comment:** Please confirm the scope of the term 'posology' as it has changed from the terms 'pharmaceutical form and strength' which is clear in the current guideline (and are defined terms as per the EDQM). Limiting the principle to posology without strength, which includes concentration, may provide flexibility to biosimilar sponsors. However, if total content and concentration differ from the reference medicinal product, then the possibility of dosing errors is increased and these should be adequately addressed by the sponsor in its Risk Management Plan. We are aware of historical examples where biosimilar developers have apparently formulated product with a non-trivial bias in strength relative to the reference product. Such an example has been documented in the Scientific Discussion of the EPAR for epoetin zeta, among other examples. When this occurs, the biosimilar sponsors may believe they are formulating their product to the "true" label strength while it was the reference product sponsors that were in error. Unfortunately, this view would disregard the basic tenant that the posology of the reference product (and hence of the biosimilar product) is justified based on the substantial	See comment 5.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		clinical evidence generated with the historical reference product strength ("erroneous" or not). In this context, we recommend that EMA take necessary measures to minimize the possibility that a biosimilar sponsor introduces a deliberate bias in the strength of a product in an attempt to "correct" a systematic error attributed to the reference product sponsor. The biosimilar product should be formulated to the same strength, meaning the actual measured quantity of active ingredient in a given dose, and it is not sufficient to specify that the products should have the same posology (meaning the nominal dosage for a given indication). **Proposed change:** Consider adding the following clarification: 'The posology **(including the pharmaceutical form, the strength and the frequency of administration)** and route of administration of the biosimilar should be the same as that of the reference medicinal product.' **In general, the strength (unit contents and concentration) of the biosimilar should be the same as that of the reference medicinal product. The posology and route of administration must be the same as that used by the reference medicinal product. In circumstances where there may be a difference, then the biosimilar Risk Management Plan must address those differences and the potential for dosing errors.**	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
104-106	6 182	**Comment:** Differences in the pharmaceutical form (i.e. lyophilisate vs. liquid formulation) between the biosimilar and the reference product should be acceptable, provided that the strength of the applied medicinal product remains identical. **Proposed change:** The posology and route of administration of the biosimilar should be the same as that of the reference medicinal product. Deviations from the reference product as regards **pharmaceutical form (e.g. Powder for concentrate for solution for injection vs. Solution for injection),** formulation or excipients require justification or further studies.	See comment 5.
104-106	9 183	**Comment:** Merck Serono supports the restriction introduced by the EMA that posology and route of administration of the biosimilar should be the same as that of the reference medicinal product. This may avoid any mishandling in clinical practice. At the same time, flexibility on pharmaceutical formulation and choice of excipients remains. However, the Company would like to propose a slight different wording for clarification. **Proposed change:** Deviations from the reference product as regards *pharmaceutical* formulation or excipients require *further* justification ~~or further~~ *supported by adequate*	See comment 5.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		studies *(e.g. stress stability and/or PK and/or immunogenicity).*	
104-106	10 184	**Comment:** For further clarification we suggest an amendment. **Proposed change:** "The posology and route of administration of the biosimilar should be the same as that of the reference medicinal product. Deviations from the reference product as regards formulation or excipients require justification or further studies **to show that these deviations do not have any clinically meaningful impact on safety (including immunogenicity) and/or efficacy**."	Not accepted. See comment 5.
104-106	11 185	**Comment:** Please confirm the scope of the term 'posology' as it has changed from the terms 'pharmaceutical form and strength' which is clear in the current guidance (and are defined terms as per the EDQM). Limiting the principle to posology without strength, which includes concentration, may provide flexibility to biosimilar sponsors. However, if total content and concentration differ from the reference medicinal product, then the possibility of dosing errors is increased and these should be adequately addressed by the sponsor in its Risk Management Plan. **Proposed change:**	See comment 5.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Consider adding the following clarification: The posology **(including the pharmaceutical form, the strength and the frequency of administration)** and route of administration of the biosimilar should be the same as that of the reference medicinal product. **In general, the strength (unit contents and concentration) of the biosimilar should be the same as that of the reference medicinal product. The posology and route of admustration must be the same as that used by the reference medicinal product. In circumstances where there may be a difference, then the biosimilar Risk Management Plan must address those differences and the potential for dosing errors.**	
104-106	13 186	**Comment:** Limiting the principle to posology without strength, which includes concentration, may provide flexibility to biosimilar sponsors. However, if total content and concentration differ from the reference medicinal product, then the possibility of dosing errors is increased and these should be adequately addressed by the sponsor in its Risk Management Plan. We are aware of historical examples where biosimilar developers have apparently formulated product with a non-trivial bias in strength relative to the reference product. Such an example has been documented for epoetin zeta, among other examples. When this occurs, it may be the case that different sponsors may apply different coefficients or	See comment 5

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		procedures for control of product quantity, and that the biosimilar sponsor may believe the observed bias is due to an error on the part of the reference product manufacturer “error”. Unfortunately, this view would disregard the basic tenant that the posology of the reference product (and hence of the biosimilar product) is justified based on the substantial clinical evidence generated with the historical reference product strength ("erroneous" or not). In this context, we recommend that EMA take necessary measures to minimize the possibility that a biosimilar sponsor introduces a bias in the strength of a product in an attempt to "correct" a systematic “error” attributed to the reference product sponsor. The biosimilar product should be formulated to the same strength, meaning the actual measured quantity of active ingredient in a given dose, and it is not sufficient to specify that the products should have the same posology (meaning the nominal dosage for a given indication) **Proposed change:** Consider adding the following clarification: “In general, the strength (unit contents and concentration) of the biosimilar should be the same as that of the reference medicinal product. The posology and route of administration must be the same as that used by the reference medicinal product. In circumstances where there may be a difference, then the biosimilar Risk Management Plan must address those differences and the potential for dosing errors.”	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
104-106	16 187	**Comment:** BIO agrees with the premise of this paragraph and believes it would benefit from more specifics on the scope of the "justification or further studies." **Proposed change:** "The posology and route of administration of the biosimilar should be the same as that of the reference medicinal product. Deviations from the reference product as regards formulation or excipients require justification ~~or~~ and further studies to show these deviations do not have any clinically meaningful impact on safety (including immunogenicity) and/or efficacy."	See comment 5.
104-106	22 188	**Comment:** It is recommended that in accordance with other global guidance (WHO, US) the term "strength" replaces the term"posology". **Proposed change:** Consider adding the following clarification: "The ~~posology~~ **strength** and route of administration of the biosimilar should be the same as that of the reference medicinal product."	See comment 5.
104-116	18 189	**Comment:** In relation to their molecular characteristics and production processes, the biosimilar medications are by definition products that are "similar to" but not equal to the	Not accepted. See comment 24

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		reference products, which means that their levels of effectiveness and safety can vary. For this reason it's considered strict need to perform clinical testing for safety and effectiveness for each of the requested indications for the biosimilar medication. It is essential for clear evidence to exist for equivalency between the biosimilar medication and the reference medication in terms of their quality, safety, and effectiveness. In order for a biosimilar to be considered as the therapeutic equivalent of the reference product, there must also be data demonstrating dose-for-dose interchangeability of products with each other in terms of safety and effectiveness.	
105-106	13 190	**Comment**: The guideline should also recommend that deviations from the reference product as regards presentation should be justified. **Proposed change:** "Deviations from the reference product as regards pharmaceutical formulation, ~~or~~ excipients or presentation require justification or further studies.	Accepted Also see comment 5
105-106	19 191	**Comment:** "Deviations from the reference product as regards formulation or excipients require justification or further studies." We encourage the agency to indicate that it will exercise caution when a biosimilar applicant seeks authorisation of a	Not accepted. The message regarding the required caution is well-taken and is the reason that deviations regarding

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		product with a different formulation than that of the reference product. Seemingly minor differences in formulation may have profound clinical consequences. They may lead to differences in stability, pharmacology, and bioavailability. They also may, for example, affect the formation (or prevention of formation) of aggregates or affect the product substance's adherence to plastic or glass. Experience has also demonstrated that changes in formulation have the potential to increase a product's immunogenicity, as Johnson & Johnson's experience with epoetin alfa sold under the brand name EPREX® demonstrates. We also suggest that the agency indicate that such differences should be avoided or minimized as feasible. – this should be strongly discouraged or not permitted. We believe the final guideline should state that, in general, differences in formulation will not be permitted. If any such difference is permitted, it should be minor, not reasonably avoidable, and supported by a robust scientific justification demonstrating that it does not result in clinically meaningful differences between the products. As noted above, any intentional difference between the products carries some risk of introducing a clinically significant difference. Thus, avoidable differences between a proposed biosimilar and an innovator product creates avoidable risks. We further recommend that the final guideline state that if there are formulation differences, the "further studies" that may be	formulation or excipients require justification or further studies. There is no overriding scientific reason to state that, in general, differences in formulation will not be permitted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		warranted may include clinical studies evaluating the immunogenicity profile and pharmacokinetics of the proposed biosimilar in its final formulation.	
106	1 192	**Comment:** The default position should be to require further studies if there is a change in route of administration.	Not accepted. It is stated that the route of administration must be the same.
106	11 193	**Comment:** Deviations from the reference product as regards formulation or excipients require justification or further studies. The same applies for deviations in strength, posology or treatment intervals. A biosimilar product can be available in a different or additional strength, defined as the absolute amount of active substance in the presentation (perhaps to allow greater flexibility in dose prescribing and/or less wastage in dosing). We would appreciate clarification in the guideline which deviations in terms of strength and presentation would be acceptable. **Proposed change:** Consider amending the text as follows: Deviations from the reference product as regards formulation or excipients require justification or further studies. **Different or additional strengths of the biosimilar**	Partially accepted. The new wording mentions: Deviations from the reference product as regards strength, pharmaceutical form, formulation, excipients or presentation require justification. If needed, additional data should be provided. Any difference should not compromise safety. See also comment 5.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		product are allowed provided clinical data are presented showing that there is no impact on comparability to the reference product in terms of efficacy and safety.	
107	1 194	**Comment:** We agree that “Intended changes to improve efficacy are not compatible with the biosimilarity approach.”	Comment acknowledged.
107	4 195	**Comment:** Line 107 of the draft guideline revision states that “Intended changes to improve efficacy are not compatible with the biosimilarity approach.” **Proposed change:** We would suggest not limiting such changes to intended changes only. We also understand that there may be small changes in efficacy endpoints which are sufficiently small to be of no clinical significance. We therefore suggest changing the wording of the bullet point on Line 107 to “Changes which lead to clinically significant improvements in efficacy are not compatible with the biosimilarity approach.”	Partly accepted It is acknowledged that clinically significant improvements in efficacy are not compatible with the biosimilarity approach. However, the guideline focuses on intended changes to improve efficacy (e.g. glycooptimisation).
107	7 196	**Comment:** Intended changes to improve efficacy are not compatible with the biosimilarity approach. **Proposed change:**	Not accepted. Change is no improvement.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Products with changes intended to improve efficacy are not compatible with the biosimilarity approach.	
107	10 197	**Comment:** We agree that “intended changes to improve efficacy are not compatible with the biosimilarity approach.“ **Proposed change:** None	Comment acknowledged
107	11 198	**Comment:** While we agree that intended changes to improve efficacy are not compatible with the biosimilarity approach, the term ‘intended changes’ could imply that unintended changes to improve efficacy are acceptable. It must be clear in the guidance that only products which demonstrate comparability between the biosimilar and the reference medicinal product in terms of quality, safety and efficacy fall within the definition of biosimilar. **Proposed change:** Consider amending the text as follows: ~~Intended c~~**C**hanges to improve efficacy are not compatible with the biosimilarity approach.	See comment 195.
107	13 199	**Comment:** We agree that intended changes to improve efficacy are not compatible with the biosimilarity approach. The term ‘intended changes’ could imply that unintended changes to	See comment 195.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		improve efficacy are acceptable. It must be clear in the guidance that only products which demonstrate comparability between the biosimilar and the reference medicinal product in terms of quality, safety and efficacy fall within the definition of biosimilar. **Proposed change:** Consider amending the text as follows: "~~Intended~~ changes ~~to~~ that improve efficacy are not compatible with the biosimilarity approach."	
107	14 200	**Comment:** Please provide some clarification as to what would be considered an "intended change".	Accepted. Example provided.
107	14 201	**Comment:** What if improvement in the efficacy was caused by unintended changed. For example, higher purity of the biosimilar compared to the RMP - Would the product still be considered a biosimilar?	Comment acknowledged. This is a theoretical concern. Slight differences in impurities levels are addressed in (Non)-clinical GL
107	19 202	**Comment:** "Intended changes to improve efficacy are not compatible with the biosimilarity approach." We firmly agree that a product with intentional "improvements" in efficacy — like other intentional differences — cannot be eligible for approval under the biosimilar approach. A "superior" clinical outcome violates	Comment acknowledged. See also comment 195, 201

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		the fundamental principle that "[a] biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms."[5] And every difference between a proposed biosimilar and its reference product carries with it the risk of other (undetected) clinically meaningful differences. Intentional and avoidable differences with respect to efficacy introduce additional and unnecessary risk.	
107	22 203	**Comment:** Recommend adding additional clarification that these products would not be regulated as biosimilars but as stand alone products. **Proposed change:** Consider amending the text as follows: 'Intended changes to improve efficacy are not compatible with the biosimilarity approach. **Such products are more accurately termed new biological products and are regulated as new medicinal products which do not not benefit from an abbreviated tailored route and are not considered as biosimilars.'**	Not accepted. Wording doesn´t add clarity.
108-111	1 204	**Comment:** We agree that the "… technical requirements of the European Pharmacopoeia…" should be followed. We suggest expanding	Not accepted. If the biosimilar intends to be approved in the EU, then it

.[5] Draft Guideline, at § 3.3. *See also id*. at § 3.1 (lines 77-79) ("[a] biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy…."); Original Guideline, at § 1.1.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		the sentence by inclusion of other compendia (JP and USP). The reference product may itself not use the EP. **Proposed change:** The biosimilar shall, with regard to the quality data, fulfill all requirements for Module 3 as defined in Annex I to Directive 2001/83/EC, as amended and satisfy the technical requirements of the European Pharmacopoeia or of the compendia of Japan or the United States or any additional requirements, such as defined in relevant CHMP and ICH guidelines.	must comply with the European Pharmacopoeia. This is a legal requirement.
108-111	11 205	**Comment:** We agree that the technical requirements laid down in the monographs of the European Pharmacopoeia should be followed where applicable. We suggest expanding the sentence by inclusion of other compendia (JP and USP). The reference product may itself not use the EP. It should also be noted that compliance with the technical requirements of the monographs of the European Pharmacopoeia (or of other pharmacopeia) only is not sufficient to establish all aspects pertinent to the biosimilar evaluation. **Proposed change:** Consider amending the text as follows: The biosimilar shall, with regard to the quality data, fulfill all	See comment 204.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		requirements for Module 3 as defined in Annex I to Directive 2001/83/EC, as amended and satisfy the technical requirements of the **monographs of the** European Pharmacopoeia **or of the compendia of Japan or the United States and all** ~~any~~ additional requirements, such as defined in relevant CHMP and ICH guidelines.	
108-111	13 206	**Comment:** We agree that the "… technical requirements of the European Pharmacopoeia…" should be followed. We suggest expanding the sentence by inclusion of other compendia (JP and USP). The reference product may itself not use the EP. **Proposed change:** "The biosimilar shall, with regard to the quality data, fulfill all requirements for Module 3 as defined in Annex I to Directive 2001/83/EC, as amended and satisfy the technical requirements of the European Pharmacopoeia or of the compendia of Japan or the United States or any additional requirements, such as defined in relevant CHMP and ICH guidelines."	See comment 204.
108-111	13 207	**Comment:** It is well established that compliance with the technical requirements of the European Pharmacopoeia (or of other pharmacopeia) is not sufficient to establish all aspects pertinent to the biosimilar evaluation.	Not accepted. Same meaning.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider amending the text as follows: "The biosimilar shall, with regard to the quality data fulfil all requirements for module 3 as defined in Annex I to Directive 2001/83/EC, as amended and satisfy the technical requirements of the European Pharmacopoeia and ~~any~~ <u>all</u> additional requirements, such as defined in relevant CHMP and ICH guidelines."	
108-116	19 208	**Comment:** "The biosimilar shall, with regard to the quality data, fulfill all requirements for Module 3…." and "Safety and efficacy of biosimilars have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended. General technical and product-class specific provision for biosimilars are addressed in EMA/CHMP guidelines…." For organizational reasons we suggest moving the statements about Module 3 requirements, safety and efficacy requirements, and relevant guidelines to section 3.3 of the final guideline ("Principles of Establishing Biosimilarity"). These statements directly concern how to demonstrate biosimilarity.	Not accepted. This statement does not reflect Quality requirements regarding demonstration of biosimilarity; but affirms that a complete Module 3 should be submitted.
112	5 209	**Comment:** On page 5 the following statement is given : "Safety and efficacy of biosimilars have to be demonstrated in accordance with the data requirements laid down in	Partly accepted. Safety and efficacy should be demonstrated for a biosimilar; however, safety

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Directive 2001/83/EC, as amended. General technical and product-class specific provisions for biosimilars are addressed in EMA/CHMP guidelines (see section 2). For situations where product-class specific guidance is not available, applicants are encouraged to seek scientific advice from Regulatory Authorities." **Proposed change:** BI feels this sentence is misleading as for a biosimilar efficacy and safety does not to be shown independently, but rather be bridged via comparative analytical, pre-clinical, pharmacokinetic and other clinical data from the reference product to the proposed biosimilar.	and efficacy are mainly demonstrated through a comparability exercise. The text has been modified for better clarity: Comparable safety and efficacy of a biosimilar to its reference product has to be demonstrated or otherwise justified in accordance with …
112-113	11 210	**Comment:** Suggest editing to accurately reflect the nature and scope of the similarity exercise **Proposed change:** Consider amending the text as follows: **Comparative** safety and efficacy of biosimilars **with their reference products** have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended	See comment 209
112-113	12 211	**Comment:** We would propose to add "comparative" at the beginning of	See comment 209

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		the sentence **Proposed change:** Comparative safety and efficacy of biosimilars have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended.	
112-113	13 212	**Comment:** Suggest editing to accurately reflect the nature and scope of the similarity exercise **Proposed change:** "Comparative ssafety and efficacy of biosimilars with their reference product have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended"	See comment 209
112-113	16 213	**Comment:** BIO recommends revising to more accurately reflect the nature and scope of the similarity exercise. **Proposed change:** "Comparative safety and efficacy of biosimilars with their reference products have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended."	See comment 209.
116	10 214	**Comment:**	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Add additional bullet point on label transparency. **Proposed change:** "A biosimilar label should be transparent and should clearly state that the product is a biosimilar medicinal product to a reference biological product. The label should describe the preclinical and clinical data used to determine similarity and clarify which indications were extrapolated."	Labelling/SmPC is not within the scope of this Guideline. See also comment 25.
116	17 215	**Proposed change:** Add bullet on label transparency after line 116 • A biosimilar label should be transparent and clearly state that the product is a biosimilar to the reference biological product. The label should describe the pre-clinical and clinical data used to determine similarity and clarify which indications were extrapolated.	Not accepted. Labelling/SmPC is not within the scope of this Guideline. See also comment 25.
117	13 216	**Comment:** As in the current guideline it should be explained that in the context of biosimilarity some differences with the reference medicine may only become apparent post-authorisation especially for rare adverse events. Additionally, Article 102(e) of Directive 2001/83/EC, as amended refers to the need to identify any biological medicinal products in order to support traceability and pharmacovigilance monitoring of these products. To take into account possible	Not accepted. Unlikely scenario for Biosimilar.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		interchangeability and switching practices the concept of traceability should be added. **Proposed change:** "Some differences with the reference medicine may only become apparent post-authorisation especially for rare adverse events. In order to support pharmacovigilance monitoring and product traceability, the specific biological medicinal product given to the patient should be clearly identified in accordance with Article 102(e) of Directive 2001/83/EC, as amended."	
117	20 217	We welcome the referral to the need for clear identification as expressed in this last bullet point, with which we fully agree. We would like to point out, however, 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 which are required by law to prescribe by INN or in situations where the name consists of INN plus company name. We believe this could cause loss of traceability, in particular since a biosimilar product may be approved by the EMA/EC using the same INN as the reference product, unless the applicant applies for a different INN. Therefore, additional safeguards will be needed to ensure traceability from prescription through ADR reporting.	Not accepted. Brand name and batch number are required as indicated in Art. 102 (e).
117 – 120	1 218	**Comment:** We strongly recommend that this language remains	Comment acknowledged.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		unchanged in the final guideline. A clear identification of the concerned product is appropriate and necessary to support pharmacovigilance monitoring, namely the product/brand name of the medicinal product and the batch number. These two elements provide the most sensitive/important information allowing the unambiguous identification of the finished drug product which is on the market in an EU Member State. Identifying the product by the INN alone would not provide sufficient information in case of adverse event reporting.	See also comment 217
117 – 120	8 219	**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 INN is not requested because identifying the product by INN only 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	Comment acknowledged. See also comment 217

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		more details 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.	
117 – 120	8 220	**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. 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	Not accepted. This issue (prescriptions) is not within the scope of this Guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		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 bullet point after line 120: • **In order to support clear identification of prescribed and dispensed biological medicinal products, brand names should be used for biological medicines in accordance with Commission Implementing Directive 2012/50/EU laying down measures to facilitate the recognition of medical prescriptions issues in another Member State.**	
117-120	10 221	**Comment:** We agree that the brand name and batch number should be recorded for any biological medicinal product. **Proposed change:** None	Comment acknowledged. See also comment 217.
117-120	11 222	**Comment:**	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		A clear identification of the concerned product is appropriate and necessary to support pharmacovigilance monitoring, namely the product/brand name of the medicinal product and the batch number. These two elements provide important information allowing the unambiguous identification of the finished drug product which is on the market in an EU Member State. Identifying the product by the INN alone would not provide sufficient information in case of adverse event reporting. Article 102(e) of Directive 2001/83/EC, as amended refers to the need to identify and biological medicinal products in order to support traceability and pharmacovigilance monitoring of these products. **Proposed change:** Consider amending the text as follows or ensure consistency with the Guideline on similar biological medicinal products containing biotechnology-dervided proteins as active substance: non-clinica and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1) In order to support pharmacovigilance monitoring, **and product traceability all appropriate measures should be taken to identify clearly** the specific **biological** medicinal product given to the patient **and** should be clearly identified in accordance with Article 102(e) of Directive 2001/83/EC, as amended	Addition does not add clarity. See comment 217.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
117-120	13 223	**Comment:** It is assumed that the guidance refers to the information recorded at time of an adverse event. If this is not indeed the case, the guidance should be clarified in this regard. If the intention of this statement is to record at the time of dispensing, there may be practical difficulties in linking records for products that are dispensed by a pharmacy directly to the patient (may be more challenging to document for a non-hospital product). Other challenges may be expected as an HCP may not be able to recall if a biological product is a biosimilar or not for recording purposes. These practicalities should be further discussed before including in guidance. This comment is raised since the the EPAR of Remicade has been updated recently to add a statement in Section 4.4 of the SmPC to increase the **traceability of** a **specific batch** and also to enable **distinguishing between the use of biosimilars and the original product** when assessing spontaneous adverse event reports: “In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file”. The draft guidance “Guideline on the similar biological medicinal products containing biotechnology-derived proteins as active substance: non clinical and clinical issues” (comments due Nov 2013) line 406 states: all appropriate	Accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		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. It is proposed that the two guidelines be consistent in their language. **Proposed change:** "~~In particular, brand name and batch number should be recorded for any biological medicinal product.~~" Should be changed to: "<u>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</u>."	
117-120	16 224	**Comment:** 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,	Partly accepted. See comment 217

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		reliable pharmacovigilance monitoring.	
117-120	18 225	**Comment:** In order to facilitate pharmacovigilance over the biosimilar product, the product should not be prescribed under a generic name or by active substance, but rather by brand, in a manner that will allow individualised tracking. In this regard, all biosimilar medications must have a name that clearly identifies them for accurate prescription and dispensing, as well as for safe use during their entire life cycle. This is why giving biological products and reference products the same scientific name or INN would represent a hindrance to pharmacovigilance, since in the event that adverse effects are detected it would be difficult to determine which medication was involved.	Not accepted. See 217
117-120	19 226	**Comment:** "In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified in accordance with Article 102(e) of Directive 2001/83/EC, as amended. In particular, brand name and batch number should be recorded for any biological medicinal product." We support the continued inclusion of the recommendation that the specific product given to a patient should be clearly identified. We suggest adding back the Original Guideline's related statement that "by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences	Not accepted. See comment 217

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established."[6] This sentence explains one of the reasons why traceability is critical for biological products and underscores the importance of always identifying the specific biological product dispensed to a patient. The final guideline could also note that traceability is important to enable the detection of adverse clinical effects that may result from changes in one product over time that are not detected in batch release and that lead to clinically meaningful differences between the products.	
117-120	22 227	**Comment:** A clear identification of the concerned product is appropriate and necessary to support pharmacovigilance monitoring, namely the product/brand name of the medicinal product and the batch number. These two elements provide the most sensitive/important information allowing the unambiguous identification of the finished drug product which is on the market in an EU Member State. Identifying the product by the INN alone would not provide sufficient information in case of adverse event reporting. Article 102(e) of Directive 2001/83/EC, as amended refers to the need to identify and biological medicinal products in order to support traceability and pharmacovigilance	Not accepted. See comment 222

[6] Original Guideline, at § 2.1.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		monitoring of these products. **Proposed change:** Consider amending the text as follows: 'In order to support pharmacovigilance monitoring, **and product traceability** all appropriate measures should be taken to identify clearly the specific **biological** medicinal product given to the patient should be clearly identified in accordance with Article 102(e) of Directive 2001/83/EC, as amended'	
119-120	13 228	**Comment:** We agree that brand name and batch number should be recorded for any biological medicinal product. We welcome the referral to the need for clear identification as expressed in this last bullet point, with which we fully agree. We would like to point out, however, 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 which are required by law to prescribe by INN or in situations where the name consists of INN plus company name. We believe this could cause loss of traceability, in particular since a biosimilar product may be approved by the EMA/EC using the same INN as the reference product, unless the applicant applies for a different INN. Therefore, additional safeguards will be needed to ensure traceability from prescription through ADR reporting. The ongoing discussions on the	Not accepted See comment 217

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		revision of the INN policy for biotherapeutics by the WHO INN Expert Group or the policies adopted by other Health Authorities (e.g. PMDA, TGA) on local non-proprietary names for biosimilars, may provide useful experience for addressing these issues.	
120	10 229	**Comment:** Add a sentence. **Proposed change:** “Biological medicinal products including biosimilars should be prescribed by brand name. In order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file.”	Not accepted. Prescription guidance is outside the scope of this Guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
120	17 230	**Comment:** Caution should be taken to avoid switching. Unless interchangeably has been addressed by adequate clinical data and evaluated by EMA then switching should not be allowed to ensure appropriate pharmacovigilance monitoring. **Proposed change:** Add a sentence: Biological product, including biosimilars should be prescribed by brand name. In order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file. A global unique INN could be an alternative	Not accepted. See comments 9 and 217
121-146	19 231	**Comment:** "Choice of Reference Product" We support the CHMP's proposed removal of the statement that a proposed biosimilar containing interferon alfa-2a should not refer to a reference product containing interferon alfa-2b.[7] As we noted in our comments on the Concept Paper, the interferon alfa example could be viewed as inappropriately suggesting that all biological products with the same non-proprietary name necessarily have the same identity for purposes of establishing biosimilarity and/or	Comment acknowledged.

[7] *See* Original Guideline, at § 2.2.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		interchangeability.	
122-123	14 232	**Comment:** What is the basis for this requirement? Considering that most of the RMPs are authorised in the EU and the US at the same time, can both of these products be used interchangeably during the development process?	Not accepted. This requirement is based on Directive 2001/83/EU, as amended, article 10.2(a): *'reference medicinal product' shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;* A non-EEA authorised product is referred to as comparator and not as reference medicinal product. The use of both is explained in this chapter.
122-131	13 233	**Comment:** As outlined in line 131, a "non-EEA authorised comparator" may be used for certain clinical/non-clinical studies. More clarity about the scope/definition of " non-EEA comparator" would be helpful. The current EU legislation requires the Reference Product for Biosimilar should be 1) authorized in EU through full dossier (i.e. another biosimilar cannot be a reference product) 2) sourced from within EEA (i.e. batch	Not accepted. See comment 22.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		release site in EEA) . In the draft guideline, the “non-EEA comparator” is described as “ a non-EEA authorised version of the reference medicinal product”. It should be clarified that a biosimilar cannot be used as a reference product for another biosimilar product. **Proposed change:** Add an additional line to line 123: “The reference medicinal product must be a medicinal product authorised in the EEA, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. A biosimilar cannot be used as a reference for another biosimilar product”.	
123	17 234	**Comment:** Should be clear that an approved biosimilar product should not be used as a reference product. **Proposed change:** The reference medicinal product must be a medicinal product authorised in the EEA, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. **This excludes similar biological medicinal products to be used as a reference.**	Not accepted. See comment 22.
124 – 146	8 235	**Comment:** The biosimilar concept is applied on a case-by-case basis,	Partly accepted. Language in guideline has

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		and as such the comparability programme consisting of quality, non-clinical and clinical studies is specifically adapted for each biosimilar development in order to adequately demonstrate similar quality, safety and efficacy between the biosimilar and the reference product. In specific circumstances clinical efficacy and safety studies may not necessarily be part of the clinical comparability programme (see comments below for lines 167-172 on structurally more simple biological medicinal products). Concerning the bridging assessment between EU and non-EU sourced reference products it is fully agreed that conducting PK/PD bridging studies should not be mandated by default. Therefore, we would like to propose slightly changed wording to address the fact that clinical safety and efficacy studies may not be mandatory in all cases. **Proposed change:** A**s a general principle a** single reference product, defined on the basis of its marketing authorisation in the EEA, should be used as the comparator throughout the comparability programme for quality, ~~**safety and efficacy**~~ **non-clinical and clinical** studies during the development of a biosimilar in order to allow the generation of coherent data and conclusions **on similar quality, safety and efficacy**. (...) As a scientific matter, the type of bridging data needed will	been adjusted for more clarity.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		typically include data from analytical **and *in vitro* non-clinical** studies (e.g. structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and, **if further supportive data are needed, in certain cases, the bridging assessment** may also include clinical PK and/or PD bridging studies data for all three products.	
124-132	19 236	**Comment:** "A single reference medicinal product, defined on the basis of its marketing authorisation in the EEA, should be used as the comparator throughout the comparability programme for quality, safety and efficacy studies during the development of a biosimilar in order to allow the generation of coherent data and conclusions. However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator…." We urge particular caution when considering allowing a biosimilar applicant to rely on comparative data involving a non-EEA authorised comparator. We believe this reliance could pose unnecessary risks to patients. Every comparison involves a confidence interval of uncertainty, and this confidence interval is often relatively wide in comparative clinical studies. Allowing biosimilarity to be demonstrated based in part on comparative data involving a non-EEA	Not accepted. The approach as explained in guideline is not posing unnecessary risks to patients.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		authorised comparator will add uncertainty about the similarity of the non-EEA authorised comparator and the EEA-authorised reference product to the uncertainty about the similarity of the proposed biosimilar and the reference product. This compounding of uncertainty increases the possibility that meaningful differences will go undetected. Additional uncertainty stems from the fact that the EMA does not have direct experience with the non-EEA authorised comparator (or the information that supported its authorisation abroad) and that product is not subject to the agency's postmarket oversight. We therefore believe that comparative data involving a non-EEA authorised comparator generally should be used only in a supportive role, if permitted at all. This approach reflects sound science and is in the best interest of patients.	
128 – 146	1 237	**Comment:** We fully agree with this statement and strongly recommend that it remains unchanged in the final guideline, i.e. that a non-EU reference product is acceptable. On the surface, this seems inconsistent with Line 122 which states that the reference product must be authorized in the EEA. We consider the new wording allowing the use of a representative reference product lots sourced outside of the EEA for certain non-/clinical studies highly appropriate from the scientific, patient access and ethical perspectives: • From a scientific viewpoint it has been shown that the	Comment acknowledged.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		reference products from one manufacturer and sourced from different (ICH) jurisdictions are not distinguishable. Therefore it is justified to show the representativeness of the non-EEA authorised comparator on physico-chemical and biological grounds only. Bridging studies and the conduct of appropriate PK/PD studies should only be requested, if the results from previous studies or from other available data are not conclusive. The conduct of PK/PD bridging studies should not be mandated by default. • In addition, the development program for biosimilars, albeit tailored, still requires extensive non-clinical and clinical studies demonstrating full comparability of the biosimilar to its reference product. The development program for biosimilars is very costly and highly time-consuming. Duplicating such comprehensive clinical studies for approval in each major region is not only cost prohibitive, but also not ethical. Furthermore, it has the potential to discourage biosimilar development overall, thereby depriving patients from access to less pricy alternative biotherapeutic treatment in the EU. Taken together, apart from being fully supported by scientific principles, the ability to use non-EEA sourced reference product in biosimilar development programs ensures that such development programs will be financially justifiable, thereby improving overall access to biologics in the EEA.	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
128 – 146	8 238	**Comment:** We consider the new wording allowing the use of representative reference product lots sourced outside of the EEA for certain non-clinical and/or clinical studies as highly appropriate from the scientific, patient access and ethical perspectives. From a scientific viewpoint it has been shown that the reference products from one manufacturer and sourced from different (ICH) jurisdictions are not distinguishable and therefore it is justified to show the representativeness of the non-EEA reference product on physicochemical and biological grounds only. The bridging studies should require such physicochemical and biological bridging studies, as analytics are much more sensitive in detecting potential differences than animal or human studies. The conduct of comparative PK/PD studies should only be requested if the results from the previous studies or the information available from documents are not conclusive. The conduct of PK/PD bridging studies should not be mandated by default. The rapporteurs and the CHMP are perfectly capable determining representativeness on a case-by-case basis and do not need to be restricted by pre-imposed criteria. In addition, the development programme for biosimilars, albeit tailored, still requires extensive non-clinical and clinical studies demonstrating full comparability of the biosimilar to its reference product. These studies come at a high cost and take years to complete, rendering an applicant's investment	Partly acknowledged. Language in guideline has been adjusted for more clarity.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		in biosimilar development in terms of both, time and money, closer to that of originator reference biological products rather than of generic products. A development programme for biosimilars is estimated to cost 100 to 250 million EUR. A requirement to repeat studies to use a different reference product in the EU and the US would increase the total cost for launching a biosimilar product just in these regions by approximately 100 and 150 million EUR, with the purchase of the comparator reference biological product representing a large share of this cost. Each development programme can take as long as 7-8 years with double the costs of just developing the manufacturing process of a proposed biosimilar compared to the costs of developing a novel compound due to the need to achieve comparability to the originator product. Duplicating such comprehensive clinical studies for approval in each major region is not only cost prohibitive, but has the potential to discourage biosimilar development overall, thereby leaving the originator biopharmaceutical market free from competition and thus rendering the significant benefits of improved patient access to these essential biotherapeutics unachievable in the EU. Therefore, apart from being fully supported by scientific principles, the ability to use non-EEA sourced reference products in biosimilar development programmes ensures that such development programmes will be financially justifiable, thereby improving overall access to biologics in the EEA and	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		ensuring high level public health protection. From a legal perspective, the European Commission legal services have confirmed that the proposed revision regarding the choice of reference product is possible on the basis of the existing legislation. The EMA has announced this new interpretation in the updated EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications (March2013 EMA/940451/2011). We consequently fully agree with this statement and strongly recommend that it remains unchanged in the final guideline.	
128-132	4 239	**Comment:** Where a non-EEA authorised comparator is used in an in vivo non-clinical toxicology study does the EMA envisage that an EEA authorised comparator should also be included in the same toxicology study in all circumstances, or is it anticipated that with sufficient comparative analytical data (e.g., structural and functional data) that it may not be necessary to show comparative toxicology for the EEA authorised and non-EEA authorised comparator?	Not accepted. Only in exceptional cases a comparative in vivo toxicology study would be considered meaningful, even in cases where only an EEA authorised comparator is employed. See also comment 11. There is no need to show comparative toxicology for EEA authorized reference medicinal product and non-EEA authorised comparator.
128-132	19 240	**Comment:** “However, with the aim of facilitating the global	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator…." If in the final guideline the CHMP continues to permit some reliance on data comparing the proposed biosimilar to a non-EEA authorised comparator, we recommend that the final guideline elaborate on the types of "clinical studies and in vivo non-clinical studies" that might be allowed to include a non-EEA authorised comparator. We strongly believe it would not be appropriate to rely on pivotal clinical (efficacy and safety) data involving a non-EEA authorised comparator. We also believe that, as a scientific matter, at least one clinical study must directly compare the immunogenicity of the proposed biosimilar with that of the reference product. Product immunogenicity is specific and sensitive to features that may differ between the non-EEA authorised comparator and the reference product such as manufacturing processes, formulation, and primary packaging. It is therefore critical that the immunogenicity profile of the proposed biosimilar be evaluated against that of the EEA-authorised reference product — the product for which analytical similarity has been extensively evaluated and with which the EMA has direct experience. A direct comparison of immunogenicity of the proposed biosimilar and the reference product is also important because these are the	The approach as explained in guideline is not posing unnecessary risks to patients.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		products between which patients potentially could be switched — without the advance knowledge of the prescribing physician — under the laws and practices in some Member States.	
128-132; 135-138	13 241	**Comment:** The current wording is not clear enough regarding which clinical studies may use a non-EEA approved reference biologic product (emphasis added): "However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar ***in certain clinical studies*** and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator (i.e. a non-EEA authorised version of the reference medicinal product) which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA (i.e. ICH countries)." Suggest adding explicitly which clinical studies are amenable to use of a non-EEA approved reference biologic product, which would provide more clarity to the different stakeholders. This would also impact Lines 135-138 (emphasis added): "***If certain studies*** of the development programme are performed with only the non-EEA authorised comparator, the Applicant should provide adequate data or information to scientifically justify the relevance of these comparative data and establish an acceptable bridge to the EEA-authorised	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		reference product"	
128-134	11 242	**Comment:** Ensure it is clear that the choice of non-EEA authorised comparator should be restricted to those with standards similar to those imposed by ICH, and not only ICH countries. **Proposed change:** Consider amending the text as follows: However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator (i.e. a non-EEA authorised version of the reference medicinal product) which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA ~~(i.e. ICH countries)~~	Accepted. i.e has been changed to e.g.
128-134	16 243	**Comment:** BIO recommends clarifying that the choice of non-EEA authorised comparator is restricted to ICH countries. **Proposed change:** "However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		studies (where needed) with a non-EEA authorised comparator (i.e. a non-EEA authorised version of the reference medicinal product) which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA (i.e. ICH countries only)."	
128-146	7 244	**Comment:** It is stated a non-EEA authorised reference may be used in certain clinical studies and in vivo non-clinical studies. What are these "certain" clinical studies? Does this mean that the bridging comparability study will be a full study according to ICH Q5E or an abbreviated one?	The comment is not understood as ICH Q5E is a Quality guideline and therefore does not describe (full or abbreviated) clinical studies.
128-146	10 245	**Comment:** We believe that in the case of a comparison with a non-EEA comparator, the agency needs to provide a clear list of acceptable non-EEA regulatory authorities or to restrict the applicability to ICH countries. **Proposed change:** see comment	Not accepted.
128-146	11 246	**Comment:** When a rigorous scientific bridge between a non-EEA reference product and the EEA reference product formally identified in a marketing application has been established, data comparing a proposed biosimilar with such a non-EEA reference product may be used to support a finding of biosimilarity in clinical trials. A stepwise approach that could	Partly accepted. Comment 1: not always possible. Comment 2, and 3: partly accepted. Possibility of

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		be followed to establish such a bridge are as follows: 1. Investigate what is known in the public domain on sites of manufacture for the non EEA comparator and the EEA approved reference product and the relationships between companies holding the respective product licenses 2. Assuming step one indicates that the products may be bridgeable conduct in depth comparative analytical characterisation between the products together with comparative functional assays and any other appropriate studies to address any differences in formulation or primary packaging. 3. PK/PD assessment with respect to bridging then 3 way comparative PK/PD assessment should be undertaken. However, this step may not always be necessary. We would recommend that if bridging is established it means that the comparator may be sourced locally in a multi-national trial, and the data from both may be pooled as a single comparator data set. In addition it is necessary to clarify that the applicant has the burden of proof in establishing biosimilarity between a non-EEA authorised comparator and an EEA comparator and the way this needs to be demonstrated. **Proposed change:** Consider the amending the text as follows: However, with the aim of facilitating the global development	stepwise approach is mentioned in the guideline : “As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator…” Further proposal: The comment on pooling is a true implication of the guideline text but too detailed to be spelled out.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in ~~certain~~ clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator….. In addition, it will be the Applicant's responsibility to establish that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA **which will be demonstrated through scientific bridging studies**. **The provision to allow** ~~If~~ certain studies of the development programme **to be** ~~are~~ performed only with the non EEA authorised comparator **depends on** the Applicant**'s ability to confirm that a satisfactory bridge can be created on a scientific basis to** ~~should provide adequate data or information to scientifically~~ justify the relevance of these comparative data **such that they can be considered representative of** ~~and establish an acceptable bridge to~~ the EEA authorised reference product. **If bridging has been successfully established it also justifies an approach wherein the pivotal efficacy study the non EEA comparator may be used to supply ex-EEA clinical sites and the EEA comparator may be used to supply EEA sites and data from both these sources may be pooled as a single comparator data set.**	
128-146	22 247	**Comment:** When a rigorous scientific bridge between a non-EEA reference product and the EEA reference product formally identified in a marketing application has been	See comment 246

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		established, data comparing a proposed biosimilar with such a non-EEA reference product may be used to help support a finding of biosimilarity in clinical trials. Further we would recommend that if bridging is established it means in practice that the comparator may be sourced locally in a multi-national trial, i.e. the EEA product may be used to supply EEA sites and the non EEA product can be used to supply non EEA sites and the data from both may be pooled as a single comparator data set. In addition it is necessary to clarify that the applicant has the burden of proof in establishing biosimilarity between a non-EEA authorised comparator and an EEA comparator. As this guidance is the only guidance which mentions bridging some additional detail would be beneficial for applicants. **Proposed change:** Consider the amending the text as follows: However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in vivo non-clinical studies (where needed) with a non-EEA authorised comparator….. In addition, it will be the Applicant's responsibility to establish that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA **and this will be demonstrated**	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		through scientific bridging studies. **The provision to allow** certain studies of the development programme **to be** performed only with the non EEA authorised comparator **depends on** the applicant's **ability to confirm that a satisfactory bridge can be created on a scientific basis** to justify the relevance of these comparative data **such that they can be considered representative of** the EEA authorised reference product. • **Typically the applicant should follow a stepwise approach when considering bridging:** o **1. Investigate what is known in the public domain on sites of manufacture for the non EEA comparator and the EEA approved reference product and the relationships between companies holding the respective product licenses** o **2. Assuming step one indicates that the products may be bridgeable conduct in depth comparative analytical characterisation between the products together with comparative functional assays and any other appropriate studies to address any differences in formulation or primary packaging.**	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		3. If step 2 reveals that there is still residual uncertainty with respect to bridging then a 3 way comparative PK/PD clinical assessment should be undertaken. **If bridging has been successfully established it means that in the pivotal efficacy study the non EEA comparator may be used to supply ex-EEA clinical sites and the EEA comparator may be used to supply EEA sites and data from both these sources may be pooled as a single comparator data set.**	
128-146	24 248	**Comment:** The possibility to use a representative reference product from a non-EEA source (ICH countries) and make it possible for the applicant to have a global development of biosimilars medicinal products without repetition of clinical trials is very much appreciated.	Comment acknowledged.
132-134	14 249	**Comment:** Please define the expectations of “representative of the RMP”. For example, is it in terms of same presentation, composition, concentration, same manufacturing facility, or all of the above?	Not accepted. There are no prior restrictions. The applicant should demonstrate the comparability of the non EEA comparator and the EEA reference medicinal product.
132-143	19 250	**Comment:** “In addition, it will be the Applicant’s responsibility to establish that the comparator authorised	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		outside the EEA is representative of the reference product authorised in the EEA. If certain studies of the development programme are performed with only the non-EEA authorised comparator, the Applicant should provide adequate data or information to scientifically justify the relevance of these comparative data and establish an acceptable bridge to the EEA-authorised reference product. As a scientific matter, the type of bridging data needed will typically include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and may also include clinical PK and/or PD bridging studies data for all three products. ...." If in the final guideline the CHMP continues to permit some reliance on data comparing the proposed biosimilar to a non-EEA authorised comparator, we also suggest providing additional details about establishing "an acceptable bridge to the EEA-authorised reference product." We believe that, at a minimum, a sufficiently robust PK and/or PD study (in addition to analytical studies) must compare the three products. In addition, immunogenicity of the non-EEA authorised comparator should be compared to that of the EEA-authorised reference product. If the non-EEA authorised comparator has higher immunogenicity, it should be deemed inappropriate for use as a comparator product because its pharmacokinetics, safety, and efficacy could differ significantly from those of the EEA-authorised reference product and could lead to an inappropriate determination	Facilitating the global development of biosimilars to avoid unnecessary repetition of clinical trials is possible as explained in this guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		that the proposed biosimilar is biosimilar to the EEA-authorised reference product. The final guideline should further note that additional data may be necessary — for example, if the non-EEA authorised comparator has a different strength, pharmaceutical form, or route of administration than the proposed biosimilar and the reference product. In addition, we understand that the clinical bridging data that compare the three products will be obtained from two or more trials comparing two of the three products. The final guideline therefore should state that if an applicant seeks to rely on comparative data involving a non-EEA authorised comparator, the confidence interval employed should be tighter to compensate for the additional potential for error introduced by reliance on this additional comparative exercise. This is needed because showing similarity (within ranges) to a product that is not *identical* to the reference product increases the likelihood that larger differences between the proposed biosimilar and the reference product may go undetected. In addition to providing data that bridges to the reference product, we believe that a biosimilar applicant should be required to explain the relationship between the manufacturer of the non-EEA authorised comparator and the manufacturer of the EEA-authorised reference product, including whether the non-EEA authorised comparator is manufactured in the same facility(ies) as the reference	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		product. We believe that the final guideline should state that if the manufacturer of the non-EEA authorised comparator is not the same as (or is not closely related to, and sharing the same manufacturing and testing processes as) the manufacturer of the reference product, use of data involving the non-EEA authorised comparator generally will not be appropriate. Also, in our view, reliance on comparative data involving a non-EEA authorised comparator is not appropriate for relatively complex biological products. The analytical similarity of complex biological products is more difficult to assess, they often have multiple and less well defined mechanisms of action, and the clinically significant differences between products may be more difficult to detect. Monoclonal antibodies, for example, may have mechanisms of action that are not well understood and have several functional domains within a single molecule, each potentially influencing different clinical outcomes. We believe the risk of introducing even greater uncertainty by relying on data evaluating a product other than the reference product is great and cannot be justified.	
133	21 251	**Comment:** In order to avoid uncertainty about the exact expectations of an applicant to 'establish' that a 'non-EU-comparator product' is a representative of the reference product, it is recommended to revise the sentence by exchanging the verb 'establish' by 'demonstrate'. Consistent with the biosimilar	Accepted

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		approach, scientific data must 'demonstrate' that comparator material authorised outside the EEA is representative of the reference product authorised in the EEA." **Proposed change:** *"In addition, it will be the Applicant's responsibility to ~~establish~~ **demonstrate** that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA."*	
135	13 252	**Comment:** It is mentioned that if certain studies are performed with "only" the non-EEA comparator, the applicant should provide scientific justification. This requirement should not be limited to the case where "only" the non-EEA comparator is used. It should apply to any case where non-EEA comparator is used in a study either partially or in totality. It would be interesting to obtain clarity as to whether the establishment of a bridge between an EEA-authorized reference product and a non EEA-authorized comparator, would provide support for data from a global trial utilizing both products to be combined in an integrated analysis that serves as a pivotal analysis for efficacy and safety. **Proposed change:** "If certain studies of the development programme are performed with ~~only~~ the non-EEA authorised comparator, the Applicant should provide ....."	Accepted

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
138-141	3 253	**Comment:** It is considered that all bridging data between a non-EEA authorised comparator product and an EEA authorised comparator product will include clinical PK and/or PD bridging studies between all three products. For example, in approving a new indication for cetuximab in 2011, the FDA noted that the US sourced product had a higher bioavailability than the EU sourced product, and that this was taken into consideration when evaluating clinical data generated with the EU-sourced product (Erbitux US Prescribers Information, Updated 2011). This difference in PK may not have been predictable from analytical bridging studies. **Proposed change:** Consider amending the text as follows: 'As a scientific matter, the type of bridging data needed will typically include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), ~~and may also~~ and **must** include clinical PK and/or PD bridging studies data for all three products **to establish that the biosimilar candidate is similar to each of the EEA-authorised reference product and the non EEA-authorised comparator as well as to establish that the EEA- and non EEA-sourced products are equivalent to each**	Not accepted. Clinical PK bridging data are not always needed. It is noted that any 'real' difference in clinical (including bioavailability) properties between a EU product and a US product must have a root cause in the quality of the products, which can be determined by analytical studies. If such analytical differences have not been found, then either the analytical bridging studies were incomplete or the different bioavailability was a chance finding which would not be repeatable.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		<u>other.</u>	
138-141	9 254	**Comment:** Merck Serono supports the statement that bridging data should include analytical data but only “may” include clinical PK and/or PD bridging studies. If full representativeness of non-EEA-authorised to EEA-authorised comparator can be demonstrated by 3-way analytical comparison including comprehensive physicochemical and bio-analytical testing *in vitro*, 3-way PK/PD data may not be warranted and thus unethical exposure of subjects in clinical trials could be avoided.	Comment acknowledged.
138-141	11 255	**Comment:** It is considered that all bridging data between a non-EEA authorised comparator product and an EEA authorised comparator product should include clinical PK and/or PD bridging studies between all three products, unless suitably justified. It would be helpful if the EMA could provide some minimum necessary characteristics regard the nature of the subjects to be studied in the PK and/or PD studies. **Proposed change:** Consider amending the text as follows: As a scientific matter, the type of bridging data needed will typically include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and ~~may also~~ **should** include clinical PK and/or PD bridging studies data for	Not accepted. If analytical data at first are not convincing it is obvious that additional data are needed.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		all three products, **unless justified**.	
138-141	14 256	**Comment:** Please clarify when it would be necessary to conduct clinical PK and/or PD bridging studies in addition to the analytical similarity studies?	See comment 255.
138-142	13 257	**Comment:** The Guideline would benefit from at least some minimum necessary characteristics regarding the nature of the subjects to be studied in PK and/or PD studies, addressing key issues such as using the most sensitive clinical model (e.g. healthy volunteers vs. patients; non-immunosuppressed vs immunosuppressed patients, etc.). It must be acknowledged though that this is at last partially addressed in Lines 164-166: “The ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, population, endpoints and conduct to detect such differences” Also it would benefit from more specifics if no clinically relevant PD marker is available (Lines 143-146 are a welcome addition to set the right expectations for relevant stakeholders, but still leaves much uncertainty on how to specifically move forward following this approach) Likewise, the Guideline would benefit from the EMA’s opinion on how this three-way approach could impact potential	Not accepted. Too specific for overarching concepts.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		indication extrapolation for the intended biosimilar product	
138-143	16 258	**Comment:** BIO believes that clinical PK and/or PD bridging studies are necessary additions to three-way, head-to-head comparative analytical exercises between EEA-approved, non-EEA approved reference biologic products and intended biosimilars. **Proposed change:** "As a scientific matter, the type of bridging data needed will typically include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and ~~may~~ <u>will</u> also include clinical PK and/or PD bridging studies data for all three products. All comparisons should meet the target acceptance criteria for analytical and PK/PD similarity which will be determined on a case-by-case/product-type basis."	Not accepted. See comment 253 and 255.
141-143	9 259	**Comment:** Merck Serono also welcomes the statement that acceptance criteria for comparability testing should be determined on a case-by-case/product-type basis. This is very important as for biosimilar development, considering the complexity of the molecules; a "one fits all" approach is not adequate.	Comment acknowledged.
147	13 260	**Comment:** This paragraph in fact explains the principles of establishing	Partly accepted. We do not see the distinction

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		biosimilarity for registration purposes (in contrast to para 3.1, which addresses the scientific principles behind biosimilarity and the type of data needed). To avoid confusion and make immediately clear from the title what the differences are, the term “regulatory” should be added. It would also be appropriate, as it is a general principle, to include in this section that the biosimilarity comparison is only performed once, at the time of approval, and that there will not be a repeat biosimilarity evaluation when either biosimilar or reference product (or both) undergoes manufacturing changes. Each manufacturing change for the biosimilar product post approval will be evaluated through a comparability exercise as outlined in ICHQ5E i.e. post approval a biosimilar follows its own life cycle as per novel biologics.	between scientific and regulatory principles in this guideline. As regards the regulatory requirements to repeat the demonstration of biosimilarity a statement has been added to section 3.1.
147	20 261	**Comment:** This paragraph in fact explains the principles of establishing biosimilarity for registration purposes (in contrast to para 3.1, which addresses the scientific principles behind biosimilarity and the type of data needed). To avoid confusion and make immediately clear from the title what the differences are, the term regulatory should be added. It would also be appropriate, as it is a general principle, to include in this section that the biosimilarity comparison is only performed once, at the time of approval, and that there will not be a repeat biosimilarity evaluation when either biosimilar or reference product (or both) undergoes manufacturing changes. Each manufacturing change will only	See comment 260

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		be evaluated through a comparability exercise as outlined in ICHQ5E.	
148-150	10 262	**Comment:** The wording is vague and allows for different interpretation. **Proposed change:** "The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the reference product ~~by the best possible means,~~ ensuring that ~~the previously proven~~ safety and efficacy proven for ~~of~~ the reference medicinal product also applies to the biosimilar."	Not accepted. State of the art methods should be used. No clarity added by suggestion.
148-150	14 263	**Comment:** Please provide an explanation as to the "best possible means" requirement.	See comment 262
148-150	16 264	**Comment:** BIO recommends revising the sentence to avoid misinterpretation. **Proposed change:** "The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the reference product ~~by the best possible means~~, ensuring that the ~~previously proven~~ safety and efficacy proven for ~~of~~ the reference medicinal product also	See comment 262

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		applies to the biosimilar."	
148-150	20 265	**Comment:** We feel it would be more in line with the need to demonstrate the similar (i.e. not identical) nature of the biosimilar to slightly reword the guiding principle as indicated: "The guiding principle of a biosimilar development programme is ……., ensuring that the previously proven safety and efficacy of the reference medicinal product **also applies** to the biosimilar" **Proposed change:** The guiding principle of a biosimilar development programme is ……., ensuring that the previously proven safety and efficacy of the reference medicinal product ~~also applies~~ **may be assumed with high certainty to apply** to the biosimilar.	Not accepted. No clarity added.
148-166	18 266	**Comment:** The approval of a biosimilar for commercial use must take into consideration both the pre-clinical and clinical trials required by European law, with special attention given to studies performed with the most sensitive and homogeneous study populations. The biosimilar medications are by definition products that are "similar to" but not equal to the reference products, which means that their levels of effectiveness and safety can vary.	Not accepted. Extrapolation of indications is allowed, provided appropriate justification is given.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		For this reason, it should be mandatory to demonstrate that the biosimilar medications produce the same pharmacotherapeutic effects as the reference biological medications, and for every indication for which they have been targeted.	
149-150	11 267	**Comment:** The wording is vague and allows for much debate and interpretation. **Proposed change:** Consider amending the text as follows: The guiding principle…reference product ~~by the best possible means~~, ensuring that the ~~previously proven~~ safety and efficacy **proven for** the reference medicinal product also applies to the biosimilar.	See comment 262
149-150	13 268	**Comment:** The wording is vague and allows for much debate and interpretation. **Proposed change:** "The guiding principle…reference product ~~by the best possible means~~, ensuring that the ~~previously proven~~ safety and efficacy <u>proven for</u> the reference medicinal product also applies to the biosimilar."	See comment 262
151	21 269	**Comment:** The significance of the manufacturing process to the quality	Not accepted. See comment 149.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		of a similar biological medicinal product needs to be considered in the biosimilarity concept (see also 'General Comments' and comment to line 83-84). **Proposed change:** *"A biosimilar should be highly similar to the* ***biological*** *reference medicinal product in physicochemical and biological terms,* ***taken together with the production process and its control."***	
151-153	19 270	**Comment:** "A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed difference would have to be duly justified with regard to their potential impact on safety and efficacy and could contradict the biosimilar principle." We fully agree that the potential clinical consequences of observed differences between a proposed biosimilar and its reference product must be duly justified, and that observed differences have the potential to make the biosimilar approach inappropriate. It is a fundamental principle that a biosimilar applicant has the responsibility to identify and assess physicochemical and biological differences between its proposed product and the reference product to establish with reasonable confidence an absence of clinically meaningful differences.[8]	Comment acknowledged.

[8] *See, e.g.,* Draft Guideline, at § 3.3 (lines 165-165) ("The ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product.").

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
151-155	10 271	**Comment:** It seems premature to state - on the basis of limited safety data from clinical trials in a model population - that the biosimilar might have a safety “advantage” over the originator product. This will not be known until greater clinical experience after marketing has been gained. Finally, from a labelling perspective it appears to be EMA’s policy that the biosimilar product will have a ‘Summary of Product Characteristics’ (SmPC) identical to that of the reference product; this will suggest to patients and physicians that the biosimilar has an identical safety profile. Therefore, the patient would be better served by a labelling which correctly spells out the basis of approval in terms of both safety and efficacy. **Proposed change:** “A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed difference would have to be duly justified with regard to their potential impact on safety and efficacy and could contradict the biosimilar principle. Differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) ~~should be explained, but~~ may not preclude biosimilarity **but needs to be thoroughly explained and substantiated after greater clinical experiences are available following marketing authorization**.“	Not accepted. The proposal does not add clarity.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
153	11 272	**Comment:** We are in agreement that differences which could have an advantage in terms of safety maybe acceptable if appropriately justified and within the boundaries of biosimilarity. However we consider that this should not lead to any observed change in efficacy which should be reflected in the text. In addition we suggest adding the word 'unintended' to clarify that the intent of the development plan is to produce a biosimilar and not a next generation biological product with specifically engineered advantages. Also as noted above it would be helpful to include the analogous phrase on efficacy here also. **Proposed change:** Consider amending the text as follows: **Unintended** ~~D~~**d**ifferences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be **within the boundaries of biosimilarity and** explained, but may not preclude biosimilarity. **In such an instance it must be demonstrated that there is no difference in efficacy from that of the reference medicinal product.**	Not accepted. The proposal does not add clarity. See also comment 271
153	22 273	**Comment:** It is not always going to be possible to relate differences in impurity levels to benefits in safety so we recommend that	Not accepted. 1. The statement regarding impurities

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		reference to impurities is deleted. Recommend further clarifying text is added. We suggest adding the word 'unintended' to clarify that the intent of the development plan is to produce a biosimilar and not a new biological product with specifically engineered advantages. Also as noted above it would be helpful to include the analogous phrase on efficacy here also. **Proposed change:** Consider amending the text as follows: **Unintended** differences that could have an advantage as regards safety (for instance ~~lower levels of impurities or~~ lower immunogenicity) should be **within the boundaries of biosimilarity** and explained, but may not preclude biosimilarity. **In such an instance it must be demonstrated that there is no difference in efficacy from that of the reference medicinal product.**	is clearly meant as an example. 2. See (Non-) clinical GL for further discussion of point raised.
153-155	9 274	**Comment:** Merck Serono supports the clarification provided in this section. Advantages in safety would not necessarily preclude biosimilarity. However, the Company would also suggest adding a statement on efficacy. In order to develop a high quality product, companies may decide to further eliminate process- and/or product impurities which may be associated with risk of immunogenicity. By reduction of impurities, the concentration of the active ingredient may be slightly increased which may not result in any differences in *in vivo* bioanalytical assays (given the	Not accepted. Changes which directly affect efficacy (e.g. through potency or bioavailability) are not deemed compatible with the biosimilar principle.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		limitations of these assays). However, this does not preclude that slight differences in PK or the efficacy profile may arise. Such products should still be considered biosimilar as such small variations would not be considered as significant clinically meaningful differences. Thus the Company would propose the following change: **Proposed change:** Differences that could have a *slight* advantage as regards *efficacy* *and* safety (for instance lower levels of impurities *which may slightly increase bioavailability* or lower immunogenicity) should be explained, but may not preclude biosimilarity.	
153-155	13 275	Comment: Through advances in technology, it is plausible that the safety profile of a given biosimilar may be more advantageous: for instance if the biosimilar has lower immunogenicity. In instances where such a reduction in immunogenicity is apparent, it should be noted that a non-inferior immunogenicity profile may be accompanied by a reduced incidence of loss of efficacy and in some cases that could manifest as non-equivalent long-term efficacy on a population basis (as highlighted in the draft guidance on non-clinical and clinical principles released for comment). We therefore consider that the biosimilar concept should allow for such unintended differences subject to the caveat that studies are designed to show equivalent efficacy profile in patients that have not experienced ADA-associated loss of	Comment acknowledged. This is addressed in the (Non)clinical GL but not in this overarching guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		efficacy and provided that the biosimilar remains within the limit of being 'highly similar' to the reference medicinal product. For example, such studies could include sub-analysis with the ADA-negative population to exclude the "noise" created by immunogenicity on efficacy (and in selected cases, safety) on a population level.	
153-155	19 276	Comment: "Differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be explained, but may not preclude biosimilarity." Lower immunogenicity may be associated with clinically meaningful differences in pharmacokinetics, bio-distribution, purity, or potency, or could signal other differences that a biosimilar applicant should explore. Even lower levels of, and differences in, what are thought to be inactive impurities could have unanticipated impact on stability, microaggregation, adherence to containers of administration devices, or pharmacologic behaviour. We recommend that the final guideline note that in some cases differences with a hoped for safety advantage may require additional testing to assess the likelihood of an effect on efficacy or the presence of other (undetected) differences. The guideline should also state that, as any intentional difference carries some risk of having an adverse effect, reasonably avoidable differences should be avoided.	Not accepted. See comment 275
153-155	23 277	**Proposed change:**	Not accepted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		Differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be explained, but ~~may~~ in general do not preclude biosimilarity.	
154 (and line 107)	20 278	**Comment:** It is highlighted in line 154 that changes that have a safety advantage do not preclude biosimilarity. This includes lower immunogenicity. It is noted that lower immunogenicity could lead (in case of neutralising antibodies) to higher efficacy. This seems in contrast with what is mentioned in line 107.	Not accepted. This is addressed in the (Non)clinical guideline but not in this overarching guideline.
154-156	1 279	**Comment:** We agree that biosimilars may have advantages in safety if they demonstrate to have lower levels of impurities or lower immunogenicity.	Comment acknowledged.
155-158	6 281	**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	Accepted. New wording has been added.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		stand-alone development **requiring a full Marketing Authorisation Application** should be considered instead.	
155-158	9 282	**Comment:** Merck Serono supports the clarification that for products where *early on significant differences* between the intended biosimilar and the reference product are detected, a stand-alone development should be considered. However, the Company would welcome a further clarifying statement that a stand-alone development program would not necessarily demand to perform more non-clinical or clinical studies than for biosimilar development. Here further explanations would be helpful in support of adequate development guidance. **Proposed change:** ..... a stand-alone development should be considered instead. *A stand-alone development may not automatically require a different set of non-clinical and clinical studies but may result in different clinical margins or endpoints depending on the underlying product differences.*	Not accepted. A stand alone development is a full dossier (Article 8.3 Application) and its requirements are therefore not within the scope of this guideline.
155-158	14 283	**Comment:** Please clarify what is considered to be a “significant difference” that would justify a stand-alone development.	Comment acknowledged. Wording has been changed to improve clarity.
155-158	19 284	**Comment:** “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	Comment acknowledged. Wording has been changed to improve clarity.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		established, a stand-alone development should be considered instead." We agree with the general principle that if a "biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product" a stand-alone development programme may be necessary. Regardless of when significant differences between the two products are detected during the development process, however, they may mean that the biosimilarity approach is not scientifically justified. We therefore suggest stating in the final guideline that significant differences between the two products that are identified at any stage (not just early on) may make it unlikely that biosimilarity can be established.	
159	11 285	**Comment:** The stepwise approach is always recommended throughout the development programme. However, it should be emphasised that some studies may be performed in parallel depending on the underlying evidence on comparability. **Proposed change:** Consider amending the text as follows: A stepwise approach is ~~normally~~ recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation **although some studies may be performed in parallel depending**	Not accepted. The scientific reasoning should be based on a stepwise approach. This does not exclude that, for logistical reasons, certain studies may in practice be performed in parallel.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		on the underlying evidence on comparability, and with appropriate justification.	
159	13 286	**Comment:** The stepwise approach is always recommended throughout the development programme. **Proposed change:** Consider amending the text as follows: 'A stepwise approach is ~~normally~~ recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation.	Not accepted. See comment 285
159	22 287	**Comment:** The stepwise approach is always recommended throughout the development programme. However, it should be emphasised that in practice some studies may be performed in parallel depending on the underlying evidence on biosimilarity. **Proposed change:** Consider amending the text as follows: 'A stepwise approach is ~~normally~~ recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation **although some studies may in practice be performed in parallel**	See comment 285

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		depending on the underlying evidence of biosimilarity, and with appropriate justification.	
159-160	16 288	**Comment:** BIO believes that the stepwise approach is always recommended throughout the development programme. **Proposed change:** "A stepwise approach is ~~normally~~ recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation."	See comment 285
159-163	9 289	**Comment:** In line with the guideline on Monoclonal Antibodies, a stepwise approach has been introduced. However, it should be emphasised that some studies may be performed in parallel depending on the underlying evidence on comparability. This could substantially reduce development time lines and thus provide earlier access of lower priced medicines to the patients. Therefore the following addition is proposed: **Proposed change:** ..... the previous step(s) including the robustness of the physicochemical, biological and non-clinical in vitro data*. Based on the level of evidence, clinical studies may be performed in parallel.*	See comment 285
163	13 290	**Proposed change:** add "Immunogenicity of the biosimilar also has to be evaluated and established to be highly similar to the	Not accepted. The need for immunogenicity data is addressed in the non-

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		reference medicinal product.”	clinical and clinical GL.
164	22 291	**Comment:** please insert the word “clinical” to make it clear the context is clinical not preclinical Therefore, **clinical** studies should be sensitive enough with regard to design, population, endpoints and conduct to detect such differences.	Not accepted. The statement applies to any study which is performed as part of the comparability exercise. Wording has been modified for better understanding.
164 – 166	1 292	**Comment:** We fully agree with this statement and strongly recommend that it remains unchanged in the final guideline. We strongly support the wording in this current draft guideline that the ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and its reference product and that therefore sensitive clinical trials should be performed. This is in line with a pragmatic yet stringent scientific approach in the interest of patient safety and the current thinking of the EU regulators demanding a very science-based approach towards the development of highly similar and high-quality biosimilar products to be approved in Europe.	Comment acknowledged.
164 – 166	8 293	**Comment:** We strongly support the wording in this current draft	Comment acknowledged.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		guideline that the ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and its reference product and that therefore sensitive clinical trials should be performed. This is in line with a pragmatic, yet stringent scientific approach in the interest of patient safety and the current thinking of the EU regulators demanding a science-based approach towards the development of highly similar and high-quality biosimilar products to be approved in Europe. We fully agree with this statement and strongly recommend that it remain unchanged in the final guideline.	
164-165	23 294	**Proposed change:** The ultimate goal of the comparability exercise is to exclude any ~~relevant~~ significant differences between the biosimilar and the reference medicinal product.	Not accepted. Significant may be misinterpreted as referring to differences with statistical significance only. Differences which are clinically relevant are not allowed, regardless of statistical significance (e.g. regarding safety observations).
164-166	10 295	**Comment:** Add proposals for more clarity. **Proposed change:** “The ultimate goal of the comparability exercise is to exclude	Not accepted. See comment 110 Details on extrapolation are covered in the (Non)-clinical

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, population, endpoints and conduct to detect **any** such differences **that may be relevant to any clinical indication which is sought by the applicant. Each clinical parameter, such as PK/PD, safety, efficacy and immunogenicity should be tested in that indication with the most sensitive population relevant for the intended range of requested indications.**“	guideline.
164-166	11 296	**Comment:** A single patient population may not always be adequately sensitive to detect differences between the proposed biosimilar and the reference product in more than one indication, therefore a study in more than one population may be necessary. This is in line with a pragmatic yet stringent scientific approach in the interest of patient safety and the current thinking of the EU regulators demanding a very science-based approach towards the development of highly similar and high-quality biosimilar products to be approved in Europe. **Proposed change:** Consider amending the text as follows: The ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be	Not accepted. See comment 295

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		sensitive enough with regard to design, population, endpoints and conducted to detect **any** ~~such~~ differences **that may be relevant to any clinical indication which is sought by the applicant.**	
164-166	16 297	**Comment:** BIO believes that a single study population may not always be adequately sensitive to detect differences between the proposed biosimilar and the reference product; therefore, depending upon the indication sought by the Sponsor, a study in more than one population may be necessary. **Proposed change:** "The ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, population, endpoints and conduct to detect ~~such~~ <u>any</u> difference~~s~~ <u>that may be relevant to any clinical indication which is sought by the applicant</u>."	Not accepted. See comment 295.
166	11 298	**Comment:** It would be helpful to include high level paragraphs outlining some principles relating to equivalence of efficacy and safety aspects, including: 1. That a formal demonstration of statistical equivalence of efficacy compared to the reference product in a main indication is considered necessary in order to demonstrate biosimilarity, and that a non-inferiority	Not accepted. See comment 295.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		design will only be considered in exceptional cases where this can be justified on scientific grounds. 2. That although efficacy and safety are complementary and sometimes overlapping aspects, they should be considered as distinct matters in the establishment of overall clinical similarity **Proposed change:** Consider amending the text as follows: **A formal demonstration of statistical equivalence of efficacy compared to the reference product in a main indication is considered necessary in order to demonstrate biosimilarity. Only in scientifically justified cases will a non-inferiority design be considered acceptable.** **Efficacy and safety should be considered as distinct matters in the establishment of overall clinical similarity .**	
166	13 299	**Comment:** It would be helpful to include high level paragraphs outlining some principles relating to equivalence of efficacy and safety aspects, including: 3. That a formal demonstration of statistical equivalence of efficacy compared to the reference product in the most relevant indication is considered necessary in order to	Not accepted. See comment 295.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		demonstrate biosimilarity, and that a non-inferiority design will only be considered in exceptional cases where this can be justified on scientific grounds. 4. That although efficacy and safety are complementary and sometimes overlapping aspects, they should be considered as distinct matters in the establishment of overall clinical similarity (i.e. demonstrating equivalence in efficacy does not necessarily imply similarity in safety) **Proposed change:** **"**A formal demonstration of statistical equivalence of efficacy compared to the reference product in the most relevant indication is considered necessary in order to demonstrate biosimilarity. Only in exceptional cases will a non-inferiority design be considered acceptable. Efficacy and safety should be considered as distinct matters in the establishment of overall clinical similarity (i.e. demonstrating equivalence in efficacy does not necessarily imply similarity in safety)." 	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
166	17 300	**Comment:** The most sensitive population should be used with regards to parameters. **Proposed change:** Add sentence Therefore, studies should be sensitive enough with regard to design, population, endpoints and conduct to detect such differences**. Each clinical parameter, such as PK/PD, safety, efficacy and immunogenicity should be tested in the most sensitive population relevant for the intended range of requested indications.**	Not accepted. See comment 295.
167 – 172	1 301	**Comment:** We fully agree with this statement and strongly recommend that it remains unchanged in the final guideline. We strongly support the wording that in specific circumstances, e.g. for structurally more simple biological products, a comparative clinical efficacy study may not be necessary, if similarity can be convincingly shown by physico-chemical and biological tests and similar efficacy and safety can be deduced from comparative PK data and fingerprint like PD approaches. We are convinced that this is not merely a theoretical possibility, but that this concept will find more and more application as science advances.	Comment acknowledged.
167 – 172	8 302	**Comment:** We strongly support the wording that, in specific	Accepted. The term structurally more

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		circumstances, e.g. for structurally more simple biological products, a comparative clinical efficacy study may not be necessary, if similarity can be shown convincingly by physicochemical and biological tests, and similar efficacy and safety can be deduced from comparative PK data and fingerprint like PD approaches. This again shows the pioneering role of the European regulators who are extremely science-oriented and encourage highly scientific approaches towards the approval of highly similar and high-quality biosimilar products without asking for unnecessary and unethical clinical studies. Also, we are convinced that this is not merely a theoretical possibility, but that this concept will find more and more application as science and technology advances. However, the expression “structurally more simple” is not well defined since it always depends on the currently available technologies that can be employed to fully characterize biological medicinal products. Since the spectrum of the available tools for characterization is rapidly evolving, the stress should not be solely on the complexity or simplicity of the molecule, rather the emphasis should be on the fact that the methods required to convincingly show the similarity of physicochemical characteristics and biological activity between the biosimilar and the reference biological medicinal products are available. 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 defined case-by-case and should rely on	simple has been deleted.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		the scientific data provided in the physicochemical, biological and non-clinical data package. We therefore, in principle, fully agree with this statement and strongly recommend the inclusion in the final guideline, and propose to delete the wording “structurally more simple” and suggest including a changed wording to reflect the argumentation above. **Proposed change:** In specific circumstances, e.g. ~~for structurally more simple biological medicinal products~~ **in those cases when similarity of physicochemical characteristics and biological activity/potency between the biosimilar and the reference products can be convincingly shown with state-of-the-art methodologies and similar efficacy and safety can clearly be deduced from these data and the comparative PK and/or PD data, the conduct of** ~~a~~ comparative clinical efficacy **and/or safety** studies 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~~	
167-170	16 303	**Comment:** BIO is concerned that, depending upon the interpretation of this passage, biosimilars could reach the market that have not been studied sufficiently in humans, meaning safety and	Not accepted. The approach as explained in the guideline will not lead to products that have been

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		efficacy will only be evaluated post-approval. Further, the biosimilar approach already allows for a case-by-case decision to further reduce the data package if warranted by the quality and robustness of the data, which raises the question as to why this specific provision is warranted.	studied insufficiently.
167-170	23 304	**Comment:** The guideline states that in justified cases (e.g. for structurally more simple biological medicinal products), a comparative clinical efficacy study may not be necessary provided that similar efficacy and safety can be deduced from physicochemical and biological activity comparison and comparative PK data. It is recommended to clarify whether in such cases also pre-authorisation safety study may not be necessary. If so, general conditions for such an approach are recommended to be provided. More detailed criteria could be presented in the „Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues". PD data are recommended to be included as an alternative for PK data. **Proposed change:** In specific circumstances, e.g. for structurally more simple biological medicinal products, a comparative clinical efficacy study and – in justified cases – pre-authorisation safety study may not be necessary if similarity of physicochemical characteristics and biological activity/potency of the	Comment acknowledged. Wording has been changed in section 3.3. to add clarity. Details are addressed in (Non)-clinical guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		biosimilar and the reference product can be convincingly shown and similar efficacy and safety can clearly be deduced from these data and comparative PK and/or PD data. Waiver of pre-authorisation safety data is only allowable if: - similar safety profiles of the biosimilar and the reference products may be sufficiently demonstrated based on physicochemical characteristics, biological activity/potency and comparative PK and/or PD data, - frequency of immune-mediate clinically relevant events is convincingly demonstrated to be low, and - risk that incidence of immunogenicity or other specific adverse effects of the biosimilar product exceeds that of the reference product has been convincingly demonstrated to be under control.	
167-172	10 306	**Proposed change:** "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 **clinical** PK **and immunogenicity assessments** ~~data~~. Such an approach may have to be supported by additional data, for example *in*	Not accepted. However, wording has been changed in section 3.3. to add clarity. Details are addressed in (Non)-clinical guideline.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		vitro and/or clinical PD data from a comprehensive comparative PD fingerprint approach.“	
167-172	11 307	**Comment:** In principle we support the need to avoid unnecessary clinical trials from a public health perspective, however we suggest that for clarity, the guidance provides conditions where comparative PK/PD studies between the test and the reference medicinal product may be sufficient to demonstrate clinical comparability, while reinterating the need for clinical safety studies regardless of the need for a clinical comparative study. In addition, in our view Article 10.4 of Directive 2001/83/EC refers to biosimilars in general and does not distinguish and build subgroups of biological substances. We recommend to delete “for structurally more simple biological medicinal products” since this unclear wording will lead to permanent subsequent discussions on which biological product is structurally simple. **Proposed change:** Consider amending the text as follows: In specific circumstance~~, e.g. for structurally more simple biological medicinal products,~~ a comparative clinical efficacy study may not be necessary if similarity of physiocochemical characteristics and biological activity/potency of the biosimilar and the reference product can be convincingly	Partly accepted. See comments 302 and 304

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		shown ~~and similar efficacy and safety can clearly be deduced from these data and comparative PK data~~ **from comparative PK/PD studies.** **For products meeting these conditions, pre-authorisation data to demonstrate clinical safety will be required to support any application for biosimilarity.** ~~Such an approach may have to be supported by additional data, for example in vitro and/or clinical PD data from a comprehensive comparative PD fingerprint approach.'~~	
167-172	19 308	**Comment:** "In specific circumstances, e.g. for structurally more simple biological medicinal products, a comparative clinical efficacy study may not be necessary if similarity of phsyicochemical 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. Such an approach may have to be supported by additional data, for example *in vitro* and/or clinical PD data from a comprehensive comparative PD fingerprint approach." In the interest of patient safety, the omission of a comparative clinical efficacy study should be considered only under very narrow circumstances. Specifically, we believe the final guideline should state that clinical efficacy data may be omitted only if: the proposed biosimilar and reference product have been extensively and thoroughly characterized; no differences were detected that might be clinically	Partly accepted. See comments 302 and 304.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		meaningful; comparative clinical immunogenicity testing has been conducted; comparative *in vivo* PK and PD testing has been conducted (and the PD markers are sensitive to clinically relevant differences and reflect relevant activities); and the biosimilar applicant submits data comparing the PK/PD relationship of the reference product and the proposed biosimilar showing that the PK/PD relationships of both products are highly similar. Further, we suggest that the final guideline state that, even where clinical efficacy testing is not needed, clinical testing for immunogenicity will be necessary and safety and pharmacodynamic data should be collected during that testing.	
167-172	22 309	**Comment:** In principle we support the need to avoid unnecessary clinical trials, however we suggest that for clarity, we provide conditions where comparative PK/PD studies between the test and the reference medicinal product may be sufficient to demonstrate clinical comparability, while reiterating the need for clinical safety studies regardless of the need for a clinical comparative study. **Proposed change:** In specific circumstances, e.g. for structurally more simple biological medicinal products, a comparative clinical efficacy study may not be necessary if similarity of physiocochemical characteristics and biological activity/potency of the biosimilar and the reference product can be convincingly	Partly accepted. See comments 302 and 304

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		shown and similar efficacy and safety can clearly be deduced from these data and comparative PK data **from comparative clinical PK/PD studies. This is only possible in situations where the following conditions are met:** • **A clear dose-response relationship has been demonstrated. If not, the recommended study design is to conduct a multiple dose-exposure-response study. This design would ensure that the biosimilar and the reference can be compared within the linear ascending part of the dose response curve (assay sensitivity, see ICH topic E10). In certain cases, a time-to-response study may be sensitive but it cannot replace dose comparative studies.** • **The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome.** **For products meeting these conditions, pre-authorisation data to demonstrate clinical safety will be required to support any application for biosimilarity.** ~~Such an approach may have to be supported by additional data, for example in vitro and/or clinical PD data from a comprehensive comparative PD fingerprint~~	

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		~~approach.~~	
167-174	13 310	**Comment:** The a priory inclusion of a general principle in the guideline that for 'structurally simple biologics a comparative efficacy study may not be needed' in our opinion is not in line with the stepwise and data-driven approach presented in lines 160-163 of paragraph 3.3 (Principles of establishing biosimilarity). The biosimilar approach, as further worked out in the guideline on non-clinical and clinical issues, already allows for a case-by-case decision to further reduce the data package if warranted by the quality and robustness of the data. Inclusion as a general principle therefore is not needed. **Proposed change:** to delete the two paragraphs.	Not accepted. See comment 304.
167-174	20 311	The a priory inclusion of a general principle in the guideline that for 'structurally simple biologics a comparative efficacy study may not be needed' in our opinion is not in line with the stepwise and data-driven approach presented in lines 160-163 of paragraph 3.3 (Principles of establishing biosimilarity). The biosimilar approach, as further worked out in the guideline on non-clinical and clinical issues, already allows for a case-by-case decision to further reduce the data package if warranted by the quality and robustness of the data. Inclusion as a general principle therefore is not needed. If it is included, the term 'structurally more simple biological' should be clearly defined. It should also be indicated	Not accepted. See comments 302 and 304

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		specifically whether clinical safety data need to be provided in this case.	
170 (167-172)	17 312	**Comment:** Safety and immunogenicity cannot be deduced from analytical means only**.** **Proposed change:** 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 **clinical PK and immunogenicity assessments**. Such an approach may have to be supported by additional data, for example *in vitro* and/or clinical PD data from a comprehensive comparative PD fingerprint approach.	See comment 306
170-172	14 313	**Comment:** Please provide clarification on this approach as it is similar to what the FDA states with respect to reducing unnecessary clinical studies.	Comment acknowledged. Wording has been changed in section 3.3. to add clarity.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
171-172	16 314	**Comment:** The draft guideline indicates that a comprehensive comparative 'PD fingerprint profile' may be sufficient to allow some products to avoid the need for comparative clinical efficacy study. Although it is acknowledged that a fingerprint 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, BIO does not consider that this is a useful or helpful concept for the guideline, as it should only be considered on a case-by-case basis depending upon the number of known PD markers and the complexity of the molecule in question and not as an overarching principle for biosimilarity. **Proposed change:** BIO suggests either omitting the reference to PD fingerprinting from this guideline or adding additional discussion explaining the limitations of this concept and providing specific criteria for use of multiple markers where none of them is an accepted surrogate for clinical efficacy.	Comment acknowledged. See comment 6 and 29
173	11 315	**Comment:** In line with Section 4 of the Annex to Directive 2001/83/EC it is our view that the guideline should not speak about "simplified approaches" that should always be discussed with Regulatory Authorities before commencement of such development but rather about the amount of product specific	Not accepted. Proposal does not provide additional clarity.

Line number(s) of the relevant text	Stakeholder number / comment number	Comment and rationale; proposed changes	Outcome
		data needed for the biosimilar approach.. **Proposed change:** Consider amending the text as follows: In general, ~~such simplified approaches~~ **the type and amount of non-clinical and clinical data taking into account the specific characteristics of the concerned biological medicinal product** should always be discussed with Regulatory Authorities before commencement of such development.	
173-174	23 316	**Proposed change:** ~~In general,~~ It is recommended to discuss such simplified approaches ~~should always be discussed~~ with Regulatory Authorities before commencement of such development.	Accepted.