21 May 2014
EMA/559452/2013
Committee for Medicinal Products for Human Use

Overview of comments received on 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance (revision 1)' (EMA/CHMP/BWP/247713/2012)

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

Stakeholder no.	Name of organisation or individual
1	Apotex Inc.
2	Biotechnology Industry Organization (BIO)
3	CURAXYS, S.L.
4	DGGF (German Society for Good Research Practice), GMP workgroup
5	EBE (European Biopharmaceutical Enterprises)
6	European Pharmacopoeia
7	European Generic medicines Association-European Biosimilars Group (a sector group of the EGA)
8	The Janssen Pharmaceutical Companies of Johnson & Johnson
9	LEEM (Les Entreprises du Médicament – France)
10	Malik Osmane
11	Medicines Evaluation Board, the Netherlands
12	Pierrette Zorzi
13	Teva
14	Voisin Consulting Life Sciences

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1. General comments – overview

N°	Stakeholder no.	General comment (if any)	Outcome (if applicable)
1.	2	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency (EMA or Agency) for the opportunity to submit comments on the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)" (the Guideline). 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 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 commends EMA for the issuance of this science-based revision on quality requirements for a biological medicinal product claiming to be similar to one already marketed. The document addresses many relevant issues associated with the topic, and we believe it will assist manufacturers that are developing biosimilar products and help ensure that patients will receive high quality biosimilar products, especially since the Guideline facilitates a global development approach for biosimilars, including embracing the concept of Quality Target Product Profile (QTPP). BIO welcomes the inclusion of Quality Target Product Profile (QTPP), and we request greater clarity on its intended use. BIO believes that	Not accepted. The scientific principle for the biosimilar comparability exercise (quality aspects) is the same as for 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-product comparability as described in ICH Q5E.

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		the QTPP has a recognized place in the development of biosimilar products, as it is acknowledged that the first step in developing a biosimilar molecule is to characterise, as fully as possible, the reference product to allow for a meaningful comparability program and process. Accordingly, we agree that the QTPP should be "detailed at an early stage of development" and "form the basis for the development of the biosimilar product and its manufacturing process." BIO continues to welcome EMA's distinction between comparability exercises for process changes introduced during development and exercises intended to demonstrate biosimilarity (see line 77 stating that "This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (*i.e.*, changes during development and post-authorisation), as outlined by ICH Q5E;" and line 123 stating "That for the purpose of clarity, any comparability exercise(s) for process changes introduced during development should be clearly indentified in the dossier and addressed separately from the comparability exercise versus the reference medicinal product."). Accordingly, in the past, BIO has requested EMA ensure that it uses the term "comparability" to apply to intramanufacturer situations only, as consistent with other regulatory documents including the International Conference on Harmonization's (ICH) *Q*5E – *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*. (See BIO Comments Draft Guideline on Similar Biological Medicinal Products (CHMP/437/04) available at http://www.bio.org/sites/default/files/20050228.pdf; and on *Draft Guideline on Similar Biological Medicinal Products Containing*	

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		Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005) available at http://www.bio.org/sites/default/files/20050617.pdf) However, because the draft Guideline continues to use the terms "comparability" and "similarity" interchangeably, we urge EMA to formally make a statement explicitly recognizing the difference between conducting a comparability assessment of an innovator product before and after a manufacturing change versus assessments required to establish biosimilarity. This recognition would serve to clarify the extremely important point that information contained in documents concerning changes within a company's own process are not to be considered and adopted as adequate scientific guidance for the development of similar biological medicinal products by a second company. Specific, detailed comments on the text are included below. We would be pleased to provide further input or clarification of our comments, as needed.	
2.	4	Justification for the comments in section 2: Post-translational modifications have profound effects on protein structure and protein dynamics[1]. Even in the absence of unusual glycosylation structures, biosimilar and reference medicinal product may vary in the number, type, and location of their oligosaccharides.	Comment acknowledged. It is expected that the Applicant uses multiple orthogonal approaches for structural and functional analyses; the selection of particular assays is the responsibility of the Applicant. The example of

[1] Arnold JN, Wormald MR, Sim RB, Rudd PM, Dwek RA. (2007). The impact of glycosylation on the biological function and structure of human immunoglobulins. Annu Rev Immunol; 25:21-50.

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		For example in the case of therapeutic antibodies FcγR binding is strongly influenced by their glycan structure and composition[2] and may cause a different cytokine release induced by originator or biosimilar with similar, but not identical carbohydrate profiles, respectively. These differences will be undetectable in a receptor-binding assay. Receptor-binding assay formats (as well as enzymatic assays) are unable to detect differences in biological activity between originator and biosimilar beyond receptor binding and signal transduction. Therefore, these assays are considered inappropriate as 'stand alone' assays and should be supplemented by at least one functional assay (e.g. *in vitro* cytokine release of appropriate cells) in each comparability exercise. In its present form, the guideline is ambiguous in this regard.	functional assays for characterisation and comparison of monoclonal antibodies is included in section 5.3.3 of the revised guideline, and furthermore, references to the guideline on biosimilar monoclonal antibodies has been added.
3.	5	**General remarks** EBE welcome the revision of the biosimilar quality guidance to reflect the additional experience from products being reviewed by the regulatory agencies since 2006 and appreciates the opportunity to comment on the proposed revision to the quality guidance (EMA/CHMP/BWP/247713/2012) EBE member companies are in general in support of the guidance, and congratulate the EMA for addressing key issues such as intra-product and inter-product comparability and the introduction of the QTPP and CQAs which are essential in the understanding and	Comment acknowledged.

[2] Houde D, Peng Y, Berkowitz SA, Engen JR. (2010) Post-translational modifications differentially affect IgG1 conformation and receptor binding. Mol Cell Proteomics; 9:1716-28.

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		execution of biosimilar development.	
4.	5	**QTPP** – We welcome the concept of the quality target product profile (QTPP) to be included in the guidance, however its purpose is not clearly defined. The QTPP has a recognised place in the development of biosimilar products. It is acknowledged that the first step in developing a biosimilar molecule is to characterise, as fully as possible, and start the assessment of quality attribute criticality at an early stage of development which will allow for a meaningful comparability program to be conducted. The QTPP of the innovator product can neither be requested from the innovator company nor disclosed by the agency. Therefore, we consider that the critical quality attribute (CQA) assessment should be developed as stated 'early in development' and form part of the marketing authorisation application documentation, although it should be noted that the complete QTPP may evolve as the knowledge of the reference medicinal product broadens during the development process of a biosimilar. Once identified, a QTPP for a registered and commercialised biological product, should be considered as valid as a reference for the biosimilar regardless of when that biosimilar reaches the stage for marketing authorisation application, i.e. should the reference product be varied during development of the biosimilar the QTPP for the initially authorised product should continue to be valid.	Partly accepted. The paragraph in question has been reworded, highlighting that the QTPP should be considered as a development tool for which some target ranges may evolve.
5.	5	**Removal of 'original' –** It is noted that 'original' has been removed from the guidance when discussing the reference medicinal product. Additionally, in Article 10(4) of Directive 2001/83/EC there is no	Partly accepted. The wording of the paragraph has been changed. In addition, reference to the Guideline on similar

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		reference to the legal approval path that the reference product must be authorised under. Thus, although it is currently stated in the Guideline on Similar Biological Medicinal Products CHMP/437/04, that a reference product is one that has been granted a marketing authorisation in the Community on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, it would be worthwhile to state this also in the quality guidance to avoid instances where biosimilar development is based on another biosimilar product. The current wording does not exclude an approved biosimilar being used as the reference medicinal product.	medicinal products has been introduced.
6.	5	**Reference product and biosimilar comparability after approval –** It is noted in the concept paper on the revision of this guideline that guidance on the evolution of the quality profile and the relative changes of the biosimilar and the reference product throughout their respective lifecycles was to be considered. It is clear, and agreed that, once authorised, the biosimilar product license becomes independent from the reference product license and the comparability exercise associated with manufacturing process changes should focus on the pre- and post-change assessment. However, bearing in mind that many small incremental changes to both products may be implemented over the lifecycle of the products, the resulting products may have differences between the resulting analytical profiles to one another which may or may not have relative safety or efficacy differences. We note that the draft guideline does not propose a regulatory mechanism for managing or controlling potential evolution of the quality profile. However, while we	Comment acknowledged. It is acknowledged that changes into the manufacturing process of both the biosimilar and the reference are introduced during the lifecycles of the products. In both cases, the impact of these changes is assessed according to the principles outline in the ICH Q5E guideline, ensuring that the clinical profile of the products is not changed. Issues related to product labelling are not within the scope of this guideline.

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		acknowledge that such a regulatory mechanism would be very difficult to develop and from a practical perspective would be very difficult to manage, we believe it is important that stakeholders, such as healthcare professionals and patients understand there is no such regulatory oversight on an inter-product basis after initial approval and that they are made aware of the potential for differences in safety and efficacy over time. Bearing this in mind, we recommend that the potential for these relative differences over time is made clear in the product labelling and also which studies have been used for the basis of the biosimilar approval.	
7.	5	**Biosimilar comparability changes** – It is acknowledged on line 123-126 of the draft guidance that the intra-comparability versus the inter-product comparability is defined in the guidance, however we believe the distinction between the two types of comparability exercise needs to be very clearly defined because it is known that there is mis-application of this terminology 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 the principles are the same for both, the 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.	Not accepted. See comment 1.

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		Indeed, the incorrect use of the terminology is leading to inappropriate understanding. This is a concern which is based on practical experience. Suggested wording to address this issue is provided in the Specific comments on the text section.	
8.	5	**Use of non-EU sourced comparator products –** It is clear that the reference product will have been granted a marketing authorisation in the Community to be considered eligible for comparability with the biosimilar product. In line with the recently announced flexible approach to allow the potential use of non-EU sourced comparator products to be used to generate data in support of an authorisation of a potential biosimilar in the EU, we would welcome the inclusion of language in the revision of the overarching guidance on similar medicinal products CHMP/437/04 and in other biosimilar guidelines as appropriate, to reflect this change in policy. We would also welcome the opportunity to be involved in the debate on the proposed criteria in due course.	Comment acknowledged. For consistency reasons, the use of non-EU sourced comparator products is handled solely in the revised overarching guideline.
9.	5	Comment: We welcome the removal of the need to demonstrate comparability with the drug substance alone and replaced with the need to demonstrate a similarity at the level of the finished product, however this needs to be consistent throughout the guidance. Proposed change (if any): Remove references to active substance to ensure that it is clear that it is similarity with the finished product which is key in the comparability exercise.	Not accepted. Biosimilarity is demonstrated for the final product at the quality, non-clinical and clinical levels. As part of demonstration of biosimilarity, it is still necessary to demonstrate similarity of active substance, which can be within the final formulation (as final product) or following isolation of the active substance if required.

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10.	6	There is no clear guidance as to how Ph. Eur. monographs should be considered by users of the guideline. Specific consideration should be added to the guideline in that respect. When reference is made to “publicly available standards”, it is suggested that the Ph. Eur. be cited in a more explicit way. Some sentences referring to Ph. Eur. in the current guideline have been deleted from the new guideline and the experts wish to know the reasons for these deletions. Examples: 1) The sentence in paragraph 1.1 "Comparison can be made against the official data, e.g. pharmacopoeial monographs or against other published scientific data." The following sentence has been added in the new guideline: "In contrast to the approach generally followed for generic medicinal products, a comparison of the biosimilar to a publicly available standard is not sufficient for the purpose of comparability." The overall message is welcome but an explicit reference to Ph. Eur. would be recommended. In addition, the sentence should be modified (see following page). 2) The sentence in paragraph 5.1, referring to Ph. Eur. standards: "However, the use of these standards plays an important role during development, as discussed further below."	Comment acknowledged. The role of the Ph. Eur. and Ph. Eur. monographs has been better highlighted through several changes. For details, see comments 26-30, 124, 125 and 145.

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		has been deleted. The Ph. Eur. experts would like to know whether there is a specific reason why this sentence could not be kept.	
11.	7	The revision of this guideline reflects the recent learning in the biosimilar development in an excellent way. The biosimilar principles are described in a very clear manner and ambiguity present in the previous version has strongly decreased. Overall all this revision represents a path-breaking guideline which is highly useful for biosimilar companies and other stakeholders.	Comment acknowledged.
12.	7	We would especially like to highlight the following three points: 1. We appreciate that the term “comparability (exercise)” is used for both, the demonstration of similarity of the proposed biosimilar product with a reference product and the demonstration of comparability of products following process manufacturing changes. This use of the term *comparability* should be preserved in the final guideline because this supports the fact that the scientific principles are the same for both scenarios. 2. According to the recently published EMA procedural advice EMA/940451/2011, the option to use a reference product sourced outside the European Economic Area (EEA) should be described – see also detailed comment below. 3. We appreciate the draft acknowledges that the manufacturing process of the reference medicinal product may evolve through its lifecycle, and may lead to detectable differences	1. Not accepted. See comment 1. 2. Not accepted. See comment 8. 3. Comment acknowledged.

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		in some quality attributes. We fully agree that both, the pre- and post-change profiles, can be regarded as representative for the reference product. The main reason is that any detectable differences have been assessed as being not meaningful and have been accepted by the CHMP in a variation procedure. This clarification reflects the science and risk-based approach endorsed by the CHMP and is highly appreciated.	
13.	8	The Janssen Pharmaceutical Companies of Johnson & Johnson (referred to as Johnson & Johnson below) are pleased to submit these comments on the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)' (EMA/CHMP/BWP/247713/2012). Johnson & Johnson has expertise in a broad spectrum of disease areas, including anaemia management, immune-mediated diseases, oncology, cardiovascular disease, pain, neuroscience, metabolic disease, vaccines, and virology. In addition, we are among the global leaders in biotechnology and have many years of experience with the development and manufacture of biopharmaceutical products. Johnson & Johnson supports the CHMP's decision to review and revise its 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues', which took effect in 2005. Since that time, the agency has reviewed more than a dozen marketing applications for biosimilars, and it has adopted or begun to draft more detailed guidelines for nine product classes.	Comment acknowledged.

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		As the existing Guideline on Similar Biological Medicinal Products (CHMP/437/04, 30 October 2005) makes clear, "The active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product." Although the active substances of biosimilars will seldom be identical to those of reference products, they should be as similar as possible in the current state of science and technology. If changes are introduced, they should be carefully scrutinized, and any doubt concerning their potential clinical effects should be resolved in favour of a robust program of comparative studies or an independent development program consisting full nonclinical tests and clinical trials. Experience has demonstrated that seemingly minor changes in the manufacturing process; formulation, and even packaging, handling, and storage of a biological product can have significant clinical consequences, including changes to and increases in the product's immunogenicity. Johnson & Johnson has extensive experience with this issue in connection with epoetin alfa sold under the brand name EPREX. This experience has informed regulatory and labelling requirements in Europe for erythropoietin products, and it profoundly affected Johnson & Johnson's views regarding biosimilar product development and testing.	
14.	9	This guideline revision is useful and clearly written for most part.	Comment acknowledged.

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15.	9	The clarification according to which the principles explained in this document could apply to other biological products, on a case by case basis" is welcome.	Comment acknowledged.
16.	9	It is acknowledged that there is no regulatory requirement for re-demonstration of biosimilarity once the Marketing Authorisation is granted. However considering that the biosimilar and its reference product may evolve differently during their respective lifecycles, this aspect should be dully taken into consideration when considering interchangeability and/or substitution and the various stakeholders should be made aware of this aspect (e.g. through a statement in the SmPC and PL).	Not accepted. Issues related to interchangeability and product labelling are not within the scope of this quality guideline.
17.	10	Letter to EMA This biosimilar guide from EMA addresses an array of questions and is again great step forward in biosimilar regulation. In the proposed guide EMA acknowledges some comments from previous discussions and gave meaningful guidance, as EMA recommends to evaluate multiple lots of the reference biologic at various stages of its shelf life, as a basis to establish a QTPP for the biosimilar. This precision/clarification is very much appreciated. I am delighted that this precision corresponds to some comments which were made in the past. *Stakeholder 13 comment:* *…"the Biosimilar requires to such an extend similarity to the Reference Medicinal Product, as the Reference Medicinal Product is similar to itself, when compared on a batch to*	Comments acknowledged. Regarding specific points: Point 3.1 Section 5.2 has been amended for clarification. Point 3.2 These issues are of general and/or clinical nature, and therefore are not within the scope of this quality guideline. However, the issue of quality profile drifts is acknowledged. Point 3.3 This issue is not within the scope of this guideline.

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		batch basis, as the optimum. *Deviation of this approach is generally acceptable, but requires justification and possibly additional clinical evaluation in order to assess associated risks"…* *"For non clinical setting it is advisable that the "Quality Profile", (refer to (1)) of the Biosimilar is within the levels of variation observed for the "Quality Profile" of the Reference Medicinal Product.* *Thoroughly determination of the "Quality Profile" of the Reference Medicinal Product can be used to set the margins of tolerance (for variation) for the Biosimilar "Quality Profile".* *Deviation of this approach is generally acceptable, but requires justification and possibly additional clinical evaluation in order to assess associated risks"* *EMA response:* *…"These topics are addressed in the " Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues " which is currently under revision"…* *EMA/205886/2012, Page 154/422, stakeholder 13.* As in any new document there is room for further clarification improvement. I would like to bring to your attention three points, where some further improvement could be made or some clarification would be required. The aim is to contribute to patients health with useful and stimulating input to this guide and while appreciating EMAs leading role in tackling the challenges associated with biosimilars. My best regards, Malik Osmane (Diplom Biologe)	

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		--- **3rd Comment**: Here I would like to focus on the understanding of the heterogeneity/variation of the two biologics (reference biologic and biosimilar) and their combined impact on the regulatory situation. 3.1 First, I would like to ask EMA to kindly clarify some comments on the quality profile and to highlight if these points were incorporated into this guide as announced: *Stakeholder 13 comment:* *"…The EMA guide EMEA/CHMP/BWP/49348/2005 and subdivides variability in:* *i) Product variability* *ii) Process related variability.* *Those two variability types form what is called the "Quality Profile" of the Biosimilar."* *EMA response:* *"The "quality profile" is these two sorts of variability PLUS the usual stand-alone physicochemical and biological characterisation PLUS a comprehensive comparability exercise. As such, the "quality programme" for a biosimilar is more extensive than that of a stand-alone."* *EMA/205886/2012, Page 29/422, Stakeholder 13* I consider variability/heterogeneity (derived from product/process) of the biosimilar as something which is to discover and to determine by characterization. The Q-profile is based on characterization data (physicochemical and	

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		biological). Characterization methods do have an error margins (as any assay/method) and one could add that margin to the context of variability/heterogeneity. However the link between to Q-profile of the biosimilar and the "comparability exercise" between biosimilar and reference biologic remains unclear! How does this relate to variability/heterogeneity and where is this incorporated into this guide? 3.2 Then I would like to highlight a general conceptual issue when taking the variation/heterogeneity and the life- resp. development-cycle of the reference biologic and the biosimilar into account. The main issue with the life- resp. development-cycle of the reference biologic and the biosimilar is, that safety and efficacy findings during the clinical comparability exercise could be controversial. This guide acknowledges already that the reference biologic might drift in its Q-profile, as part of its normal life-cycle. This bears the risk for the biosimilar developer that the QTPP might drift as well over the biosimilar development phase. For example for the clinical trial phase, it would be very advisable to conduct the comparability exercise against an unchanged (not drifted in its Q-profile) reference biologic, which served as QTPP for the biosimilar initially, if possible. As the time point if/when such a potential drift of the Q-profile of the	

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		reference biologic might occur cannot be foreseen by the biosimilar developer, the challenges and risks are considerable in the biosimilar developers eyes. (Always taken into account that the EMA already acknowledged the difficulties, that even minor differences in the Q-profile might have an impact on safety and efficacy, refer to below, for mAbs for example). *However, it may at the current stage of knowledge be difficult to interpret the relevance of minor quality differences in the physicochemical and biological characterization when comparing a biosimilar mAb to a reference mAb. EMA/CHMP/BMWP/403543/2010* I do not expect EMA to solve those case presented below, but would like to highlight potential complications and would like EMA to acknowledge those constrains. 3.2.1 Scenario 1: EMA permitted a process change for the reference biologic, which was considered acceptable. When compared head to head with the biosimilar in a clinical trial setting this change resulted in a measurable impact/difference (beyond the margins of equivalence). The Q-profile change of the reference biologic shifted, whereas the QTPP of the biosimilar was based on the pre-change Q-profile of the reference biologic. The post-change reference biologic had to be used for clinical trial comparability exercise due to normal shelf-life	

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		limitations. The biosimilar was shown to possess a better safety and efficacy profile compared to the reference biologic. (Example mentioned verbally in London during last meeting with EMA about: "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues") • What is the consequence of that for the EMA? • What is the consequence of that for the reference product? • What is the consequence of that for the biosimilar? 3.2.2 Scenario 2: EMA permitted a process change for the reference biologic, which was considered acceptable. When compared head to head with the biosimilar in a clinical trial setting this change resulted in a measurable impact/difference (beyond the margins of equivalence). The Q-profile change of the reference biologic shifted, whereas the QTPP of the biosimilar was based on the pre-change Q-profile of the reference biologic. The post-change reference biologic had to be used for clinical trial comparability exercise due to normal shelf-life limitations. The reference was shown to possess a better safety and efficacy profile • Is the comparability exercise considered failed? • Is refining of the QTPP required and some re-development? 3.3 Conclusion: All stakeholders of the biosimilar application process will need to get familiar with the idea that their respective work and evaluations will	

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		be subject to unprecedented counterchecking.	
18.	11	The revision of the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues' does not provide new principles, it merely is a consequence of the initial years of experience in biosimilar applications and scientific advices. In this report the differences between the (draft) new guideline and the current guideline are highlighted and commented: Section 4 Manufacturing process: - The term 'quality target product profile' is introduced. On the reference medicinal product it is stated that: "*Several different batches of the reference medicinal product should be used to provide a robust analysis and to generate a representative quality profile. The relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile*." This clearly refers to the principle that you can not define the quality attributes of the reference product by analyzing a single batch. This is a welcome addition since the principle was already applied by companies and requested by the EMA but not explicitly stated in the GL. - The new guideline now clearly indicates that the formulation and packaging in comparison to the reference product do not necessarily need to be the same, in the first guideline this had not explicitly been stated.	Comments acknowledged. With regard to the comment on the non-exhaustive lists of examples and allowable differences in section 5.2: The impact of such differences will always depend on the difference detected (quantitative and/or qualitative difference), as well as the product in question. This can therefore only be done on a case by case basis, based on scientific justification. For consistency reasons, the use of non-EU sourced comparator products is handled solely in the revised overarching guideline. See comment 8.

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		"*The formulation of the biosimilar does not need to be identical to that of the reference medicinal product. The applicant should take into account state-of-the-art technology and, regardless of the formulation selected, the suitability of the proposed formulation with regards to stability, compatibility (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and strength of the active substance should be demonstrated. If a different formulation and/or container/closure system to the reference medicinal product is selected (including any material that is in contact with the medicinal product), its potential impact on the safety and efficacy should be appropriately justified*." This clear statement prevents unnecessary inflexibility or misinterpretation and allows for a rational approach. Section 5 Comparability exercise 5.1 Reference medicinal product: Compared to the current guideline the new guideline does not specifically request that reference products in the comparability exercise must be authorized in the Community. The deletion of such a statement reflects the European Commission's position that a more global approach is needed and not all comparability data need to be obtained from batches sourced in the EU. At a more general level, i.e. section 1.1 'Introduction, purpose' the request that "*the biosimilar should be demonstrated to be similar to a reference medicinal product approved in the Community*" is maintained. Clarification to what extend under and which circumstances non-EU sourced material can	

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		be used as reference in comparability studies is not given in this quality guideline. This is subject for discussion in the revision of the overarching biosimilar guideline. 5.2 Comparability exercise: General comment This section is clearly aimed at covering all possible situations and has intentionally been left rather vague. Assessors and future applicants can hardly derive any concrete, specific guidance from this section. It is recognized that it is practically impossible to give all-encompassing guidance; a case-by-case approach is most likely needed. However, more specific guidance should be given than is now present in the document. A non-exhaustive lists of examples include: -The use of the term highly similar quality profile in line 164. Although it may be expected that the remainder of section 5.2 is devoted to further specifying the term highly similar, this is not sufficiently the case. Lines 178-179 seem to repeat the requirement of 'highly similar' without any further explanation. -The use of the term minor differences in line 173, without further defining what may be considered minor and what not. This is probably the most relevant shortcoming of this section and further elaboration on the concept of 'minor' is warranted. -Several occurrences of the term justified/justification,	

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		without further discussion on what kind of justification could be acceptable (a.o. line 173, 183, 188, 192). Specific comment "*The applicant should demonstrate that the desired product and product-related substances present in the finished product of the biosimilar are highly similar to that of the reference medicinal product.* *Where quantitative differences are detected, such differences should be demonstrated to have no relevance for the clinical performance of the product. Qualitative differences (i.e. presence or absence of product-related substances and/or impurities) require a thorough justification, which may include non-clinical and/or clinical data, as appropriate. It is however preferable to rely on purification processes to remove impurities rather than to establish a preclinical testing program for their qualification."* The wording 'should be demonstrated' suggests that quantitative differences should always be clinically evaluated. This may not always be needed (e.g. lower levels of impurities, lower levels of degradation products) and a wording to allow justification should be introduced. See conclusion. The new guideline acknowledges the situation that a reference medicinal product may have been altered in particular quality attributes during development of the biosimilar and thus the QTPP is not fully representative	

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		anymore for the reference product.as available on the market. In such a situation the ranges before and after the quality shift in the reference product are considered representative for the reference product and quality attribute values outside these ranges remain to be justified. This approach prevents blocking of biosimilar development when reference products undergo production changes. From a scientific point of view it is considered rational. 5.3 Analytical considerations: this section is further elaborated: - Physicochemical properties: the paragraph is extended to reflect state-of-the-art in characterization of r-DNA proteins (= the scope of this quality guideline) in particular glycosylation characterization is added. The new guideline now expresses the expectation that the amino acid sequence of the reference product is the same as the reference medicinal product. This often debated issue is not a new requirement since this is also stated in the overarching biosimilar guideline. - Biological activity: more guidance is provided on complementary approaches and validation aspects. - A section of immunochemical properties is introduced to provide guidance for monoclonal antibodies and related compounds.	
19.	13	The revised guideline addresses the issues in the biosimilar development in a clear and very good way and reduces substantially	Comment acknowledged.

N°	Stakeholder no.	General comment (if any)	Outcome (if applicable)
		ambiguity present in the previous version. Overall this revision is very helpful for companies developing biosimilar medicinal products as well as other stakeholders.	
20.	14	We welcome this guideline dedicated to Quality aspects of biosimilar products.	Comment acknowledged.

Specific comments on text

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
21.	48-51	12	Comment: This statement is too strong and could lead to some misinterpretation; Conclusion of Biosimilarity cannot be based solely on « physicochemical and biological », This is also contradictory with the spirit of the guideline. Biosimilarity is based on a Comparability Exercise which i)starts at the level of Quality, ii)and continues with non-clinical/clinical data (based on product specific guidelines). Proposed change: See L60-61 more appropriate : « similar profile in terms of quality, safety and efficacy to the reference medicinal product »	Not accepted. Statements regarding the need for clinical data are not within the scope of this quality guideline.
22.	49-50	5	Comment: The requirement for similarity of “active substance” appears insufficient as it may be interpreted to only apply to product-related variants which are a subset of the clinically relevant components of drug substance. Proposed change: Ensure that the term ‘active substance’ is clearly understood to refer to the entire contents of the purified biosimilar (or reference product) preparation before it is formulated in secondary manufacture to derive the drug product.	Not accepted. It has been a consistent policy not to require that ‘the entire contents’ need to be similar; for example, process-related impurities may be different. The proposed change would therefore cause confusion. Furthermore, active substance is a term with a formal definition in a.o. the Ph. Eur. This definition cannot be replaced by another definition in the context of this Guideline.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
23.	50	8	Comment: Add “highly” before “similar”. Proposed change: [...] demonstrated to be highly similar [...]	Not accepted. ‘Highly’ is not added to remain consistent with legal texts.
24.	52-54	1	Comment: In the discussion of ‘The product development should be performed in accordance with relevant ICH and CHMP guidelines’, please clarify if the QBD principles should also be applied to the definition of design space for biosimilars? Also, it would be helpful to add clarification if that would be a requirement?	Not accepted. The manufacturer may choose an enhanced QbD approach for the development and control of a biosimilar medicinal product. This issue is not specific for biosimilars.
25.	54	5	Comment: For clarification, please insert the word quality. Proposed change: "… with relevant ICH and CHMP **Quality** guidelines".	Accepted.
26.	56	9	Comment: The term “*Available standard*” is not very clear. Please clarify. Indeed, it could be difficult to understand it in the context of this guideline requiring comparison with a marketed medicinal product (reference) and the “Questions and answers on biosimilar medicines (similar biological medicinal products)” recently published regarding the batches to be used during non-clinical and clinical studies. Proposed change : To be clarified.	Accepted. Example has been added for clarity.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
27.	55-56	9	Comment: It could be interesting to mention pharmacopoeial monographs as examples of publicly available standards. Proposed change: In contrast to the approach generally followed for generic medicinal products, a comparison of the biosimilar to a publicly available standard; e.g. a pharmacopoeial monograph, is not appropriate for the purpose of comparability.	Accepted.
28.	55 – 56 And 194-196	5	Comment: The language disclaiming the use of public standards for assessment of similarity is not strong enough. The term "not sufficient" implies that the evaluation is relevant to the comparability exercise, although it is acknowledged that it may be appropriate for ensuring compliance with identity, quality and potency. A public standard is never the basis of comparison with the reference medicinal product, even if the standard may have originally derived from the same sponsor. In addition pharmacopieial monographs could be provided as examples of publicly available standards. Proposed Change: Revise text as follows: "In contrast to the approach generally followed for generic medicinal products, a comparison of the biosimilar with respect to a publically available standard e.g. a pharmacopoeial monograph may be relevant to ensure compliance with compendial requirements for identity, quality and potency, but is not otherwise appropriate for the purpose of assessing	Partly accepted. "Pharmacopoeial monograph" has been included as an example of available standards. A biosimilar should comply with the requirements of relevant monographs; however, this is not appropriate for demonstrating comparability to a reference medicinal product. See also comment 30.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			comparability to the reference medicinal product."	
29.	55–56 and 194-196	2	Comment: The language disclaiming the use of public standards for assessment of similarity is not strong enough. The term "not sufficient" implies that the evaluation is relevant to the comparability exercise. A public standard is never the basis of comparison with the reference medicinal product, even if the standard may have originally derived from the same Sponsor. Proposed change: BIO proposes to revise the text as follows: *"Evaluation of a biosimilar with respect to a publically available standard may be relevant to ensure compliance with compendial requirements for identity, quality and potency, but is not otherwise relevant for the purpose of assessing comparability to the reference medicinal product."*	Partly accepted. See comment 28 for justification.
30.	55-56	6	Comment: An explicit reference to Ph. Eur. would be recommended. In addition, the statement relating to generics is not correct as a comparison to a pharmacopoeial monograph is not sufficient to establish bioequivalence. It is therefore proposed to delete it Proposed change: A comparison of the biosimilar to a publicly available standard, such as pharmacopoeial monographs, is not sufficient for the purpose of comparability."	Accepted.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
31.	56-58	1	Comment: The statement, 'The biosimilar should be demonstrated to be similar to a reference medicinal product approved by a community, which is selected by the company developing the biosimilar', is not very supportive of global biosimilar development – would require further clarity or some qualifiers added to this.	Not accepted. Under the European legal framework for biosimilars, it is a requirement to refer to a reference medicinal product authorised in the EEA for regulatory purposes For consistency reasons, the use of non-EU sourced comparator products is handled solely in the revised overarching guideline. See comment 8.
32.	56-58	7	Comment: The guideline should describe that the use of a reference product sourced outside the European Economic Area (EEA) can be used if appropriately justified. This is in line with the recently published EMA procedural advice EMA/940451/2011 and we propose to add also the same wording as used in the EMA procedural advice. Proposed change: The biosimilar should be demonstrated to be similar to a reference medicinal product approved in the Community, which is selected by the company developing the biosimilar. The use of reference product sourced outside the EEA could be acceptable if the applicant can establish through an extensive analytical comparison that the batches sourced outside the EEA are representative of the reference medicinal product authorised in the EEA. Consequently, an extensive…	Partly accepted. Reference to the overarching guideline has been added. See also comment 8 and 31.
33.	56-58	14	Comment: The sentence 'The biosimilar should be demonstrated to be similar to a reference medicinal product approved in the Community, which is selected by the company	Not accepted. See comments 8 and 31 for justification.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			developing the biosimilar.' should be amended to reflect the announcement of 28/09/2012 and future update to GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS. Proposed change: 'The biosimilar should be demonstrated to be similar to a reference medicinal product ~~approved in the Community~~, which is selected by the company developing the biosimilar. Applicants will be responsible for establishing that batches sourced from outside the EEA are representative of a reference medicine authorised in the EEA through an extensive analytical comparison.'	
34.	56-61	13	Comment: The guideline should include a statement as to the acceptability of a non-EEA reference product, if appropriately justified. Proposed change: The biosimilar should be demonstrated to be similar to a reference medicinal product approved in the Community, which is selected by the company developing the biosimilar. Consequently, an extensive comparability exercise with the chosen reference medicinal product will be required to demonstrate that the biosimilar product has a similar profile in terms of quality, safety and efficacy to the reference medicinal product. <u>If pivotal data for the demonstration of biosimilarity have been generated with batches of the reference product sourced outside the EEA, the company should demonstrate in</u>	Not accepted. See comments 8 and 31 for justification.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			an analytical comparison that the batches sourced outside the EEA are representative for the reference medicinal product authorised in the EEA.	
35.	62-65	2	Comment: The paragraph acknowledges that a biosimilar Sponsor would be unlikely to have complete information regarding a reference product and the process by which it is made to conduct an "exhaustive comparison." However, the Guideline requires the sponsor to provide a level of detail such that "firm conclusions can be made." BIO requests that the Guideline provide greater clarity regarding the levels of detail on what attributes (*e.g.*, comparative assessment of biosimilar candidate versus reference quality and safety attributes) are being asked for, including whether, as suggested by the text, manufacturing process comparisons are also being requested. BIO recommends that the Guideline assert the need for state of the art comparative characterization complemented by stepwise testing to resolve residual uncertainties.	Partly accepted. The paragraph has been reworded to improve clarity and avoid the suggestion that manufacturing process comparisons are being requested.
36.	67-68	12	Comment: The article 10(4) is clear about why a biologic cannot be a generic medicinal product : difference in raw materials and difference in manufacturing process; So why to refer only to « sufficiently analytical tools »? Proposed change: The old version (2005) is better : « Based on the comparability approach and when supported by sufficiently sensitive analytical systems, the comparability	Partly accepted. The paragraph has been reworded for clarity. See also comment 35; Statements regarding the amount and type of clinical data are not within the scope of this guideline, therefore this suggestion is not implemented.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			exercise at the quality level may allow a reduction of the non-clinical and clinical data requirements compared to a full dossier. The similar biological medicinal product may refer to the non-clinical and clinical data previously generated with the reference product; however, non- clinical and clinical data will normally be required as identified in related non-clinical and clinical guidelines on similar biological medicinal products. »	
37.	69	12	Proposed change: Delete « normally »	Not accepted. No justification provided for deletion of 'normally'. The word 'normally' reflects that exceptions may exist.
38.	66-71	5	Comment: Although we acknowledge that as analytical testing methods improve there may be an opportunity for biosimilar products to be authorised on limited non-clinical and clinical data, it is important to ensure that it is clear that the data demonstrates that the two molecules, reference product and biosimilar, are highly similar and not that the completion of the comparability exercise could be sufficient, which could be inferred from this paragraph. Additionally, as stated in Article 10(4) of Directive 2001/83/EC, 'the results of appropriate pre-clinical test or clinical trial relating to these conditions must be provided [in support of an MAA]', which would appear to be direct conflict with this paragraph which seems to imply that analytical data alone may be sufficient for authorisation and that situations where no non-clinical or clinical data is required are possible.	Not accepted. Statements regarding the amount and type of clinical data are not within the scope of this guideline.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: Amend text to ensure that it is clear that it must be the data that demonstrates that the reference product and the biosimilar are highly similar and clinical and pre-clinical testing will be required prior to authorisation.	
39.	Following line 71	5	Comment: The guidance would benefit from an integrated explanation of how the quality assessment could inform non-clinical and clinical study requirements. Alternatively, these elements could be placed in the non-clinical and clinical guidance, but seem to fit in the context of this section. Proposed change: The following text is suggested: "The comparability exercise at the quality level should inform whether a product is sufficiently similar to a reference medicinal product, at the level of the active ingredient, such that an abbreviated pre-clinical and clinical development program is merited. When significant uncertainties exist about the analytical similarity of the candidate medicinal product the protection of human clinical trial subject safety should take priority over efforts to abbreviate a development program. Even when an abbreviated overall program can be justified, the comparability exercise at the quality level should inform the scope of required pre-clinical safety and pharmacology evaluations. Considerations for performing toxicology studies are provided in relevant technical guidelines. The comparability exercise at the quality level should also inform the scope of required clinical studies under an abbreviated development paradigm.	Not accepted. The proposed change does not add clarity. It should also be noted, that the guidance is given in relation to the requirements for marketing authorisation applications, while investigational medicinal products are outside the scope of the guideline. Statements regarding amounts and extent of clinical data for marketing authorisation are not within the scope of this guideline.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Sponsors may seek Scientific Advice regarding these questions."	
40.	75 - 76	5	Comment: It is stated that that this guidance may be applied to other biological products in addition to recombinant DNA-derived proteins and derivatives on a case-by-case basis. Proposed change: Provide clarification on the principles that would allow other types of products to be covered by this guidance.	Partly accepted. In principle the guideline applies to all biological products. A decision on the applicability will be decided on a case-by-case basis. Section 1 has been reworded, to reflect that from a quality perspective, the analytical data submitted should be such that firm conclusions on the physicochemical and biological similarity between the reference medicinal product and the biosimilar can be made.
41.	75-76	9	Comment: Does the term "other biological products" cover plasma-derived products and other extractive products?	Comment acknowledged. See comment 40.
42.	77 – 79 and throughout the text	5	Comment: It is welcomed that the revised guidance acknowledges the need for the two distinct aspects as to the development of a biosimilar, i.e. 1. the requirement to demonstrate comparability to the reference medicinal product (inter-quality assessment) at the time of MAA assessment and 2. the requirement for a demonstrated, reliable robust manufacturing process which also includes a comparability exercise for changes introduced in the manufacturing process (intra-quality assessment) throughout the product life-cycle.	Partly accepted. The scientific principle for the biosimilar comparability exercise (quality aspects) is the same as for 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 as the 'biosimilar comparability exercise' or comparability of the biosimilar product with the

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			However, as it is clear in section 2. Scope that this guidance is specifically focused on the inter-quality assessments, it is proposed that the term biosimilarity exercise is used at the end of section 2 (see proposal below) and throughout the guidance as a replacement for the term comparability Furthermore, we consider that it is important to add further distinction between a comparability exercise which, according to ICH Q5E applies to the same manufacturer making a change to their own process, and a biosimilarity exercise as described in section 5 of this guidance. We suggest amending the section using text taken from Weise et al. Biosimilars – why terminology matters. Nature Biotechnology (2011)29: 690-693) to ensure that this concept is fully understood. Proposed change: '..as outlined by ICH Q5E. As this guideline describes the required exercise to demonstrate the biosimilarity of a product with its corresponding reference product. In order to maintain this important distinction the term '*biosimilarity exercise*' is used. Nonetheless it is important to distinguish between a comparability exercise which according to ICH Q5E applies to the same manufacturer making a change to their own process and a biosimilarity exercise as described in section 5 of this document. The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product and for the development of a biosimilar product are the same. Even so	reference medicinal product, to distinguish it from intra-product comparability (ICH Q5E).

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			data requirements for the latter are higher and, at least in the EU, always include clinical studies because, due to the completely independent manufacturing processes, some differences between the biosimilar and the reference product can be expected, and the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone.	
43.	81 – 82	5	Comment: The reference to the Directive 2001/83 should be correctly presented. Proposed change: *This guideline has to be read in conjunction with the introduction and general principles described in Article 10(4) and part II of the Annex I to Directive 2001/83 as amended.*	Accepted.
44.	85-87	5	Comment: It is outlined in section 4, that comparability between the reference medicinal product and the biosimilar medicinal product is a fundamental part of the overall authorisation documentation submitted as part of the Marketing Authorisation Application for a biosimilar product. However, it is not clear where this data should appear within the Common Technical Documentation format. Proposed change: Considering the comparability exercise is an additional element to the normal requirements of the quality dossier, and to facilitate post-approval eCTD lifecycle management, we propose	Accepted. According to the "EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications", it is recommended that the comparability exercise is presented in section 3.2.R. This has been clarified in Section 3 of the revised guideline.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			that this assessment is located within CTD section 3.2.R.	
45.	87	14	Comment: Please could the Agency provide an indication of where they would like to see the comparability data of the biosimilar vs the reference product. Should data be placed in each section of module 3.2.S/3.2.P as appropriate, under a separate subtitle?	Accepted. See comment 44
46.	92-93	12	Comment: QTPP is not appropriate in this sentence and should be deleted (see comment below)	Not accepted. It is essential that the target product profile is comparable to the reference product.
47.	95-98	12	Comment: QTPP of the ref product cannot be based on «extensive characterisation of the reference medicinal product » (as mentioned in the following sentence, the QTPP refer to early stage of development, stage at which the extensive characterisation is not yet performed) See also definition in: i) Q11 : A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8) ii) ICH/IWG EMA/CHMP/ICH/902964/2011 / The Quality Target Product Profile (QTPP) describes the design criteria for the product, and should therefore form the basis for development of the CQAs, CPPs, and Control Strategy.	Not accepted. This comment seems to be based on a misunderstanding. In case of a biosimilar, the QTPP should be based on appropriate characterisation of the reference product, which should form the basis for the development of the biosimilar

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: - Delete second part of the sentence «extensive characterisation of the reference medicinal product » - Next sentence to be modified: “The applicant must provide information on the QTPP defined for its biosimilar, this can be based on publicly availble information on the ref product …"	
48.	94 and 107	10	Comment: As rightfully highlighted in this guide, the QTPP of the biosimilar is founded on the permitted variability of the reference biologic. This good direction given from this guide to the biosimilar developer to “understand the variability of the reference biologic first”, is an important step to successfully mimic the quality profile (Q-profile) of the reference biologic by using the QTPP approach (at least in an initial phase of the biosimilar development program, refer to later comment). 1.1 The aims of this guide for the Q-profile of the biosimilar are aligned with the principle that similarity should be achieved but not necessarily a bio-better. This principle was repetitively highlighted by EMA, refer to below for example: *…”The biosimilarity exercise follows the main concept that clinical benefit has already been established by the reference medicinal product, and that the aim of a biosimilar development programme is to establish similarity to the reference product, not clinical benefit”… EMA/CHMP/BMWP/572643/2011*	Not accepted. The purpose of this guideline is not to tell how to develop a biosimilar, but what data are expected to be presented in the MAA. The development is the sole responsibility of the Applicant It is stated in L92/93 that the molecular characteristics of the biosimilar should be comparable to the reference product. L94 is addressing a different issue.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			A biosimilar mAb should be similar to the reference mAb in physicochemical and biological terms. Any observed relevant difference would have to be duly justified and could contradict the biosimilar principle. For quality aspects the principles as laid out in the guidelines on biosimilars including the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues" (EMEA/CHMP/BWP/49348/2005), and the "Guideline on development, production, characterisation and specifications for monoclonal antibodies and related substances" (EMEA/CHMP/BWP/157653/2007) apply. EMA/205886/2012 1.2 If the reference biologic is "relative" heterogenic in its Q-profile which is likely to be the case with increasingly large and glycosilated biologics, the chances are considerable due to improvements in purification and analytical technologies that the biosimilar developer will have the following two choices: 1) to mimic the (within a lot) variation of the reference medicinal drug substance 2) to focus on homogeneity/purity of the biosimilar drug substance and as a consequence to aim potentially for a Q-profile which is better than the one of the reference biologic. The approach 1) might be technically more challenging as more process knowledge is required, to mimic the biological diversity of the reference drug substance (but would be in line with my understanding of the requirements for Biosimilar), whereas the approach 2) bears the risk that the safety and efficacy profile	

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			will be different and therefore the Q-attributes not the same, compared to the reference medicinal product. 1.3 With regard to that, one sentence should be amended to make this point clearer, as otherwise the biosimilar developer has a development choice on which he should be given some guidance: *…"performance and consistency of the manufacturing process of the biosimilar on its own"…* (Line 94) Particular for biologics the process and the product are closely interlinked therefore this sentence can be well interpreted as: performance and consistency of the biosimilar itself, as the process output (product or drug substance). Consistency of the biosimilar then leads to think of homogeneity/purity and the reader is confused when compared to sections such as: …"The applicant should demonstrate that the desired product and product-related substances present in the finished product of the biosimilar are highly similar to that of the reference medicinal product"…(Line 156, 157) (I) Therefore a sentence at that stage (line 94) shall state that: "the initial or cardinal biosimilar development aim is to mimic the quality profile of the reference biologic drug substance including its variation/heterogeneity (on a lot basis[*1]) where possible."	

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			[1*]Taken into account that individual lots of reference biologic and biosimilar will be compared at clinical trial stage with the aim to show comparability. A purer/more consistent biosimilar could have different kinetics and clinical performance compared to the reference biologic, therefore the development should focus on mimicking the Q-profile of the reference biologic at an initial stage. 1.4 Further a sentence is required to clarify that through successive analysis and characterization (correlation of critical Q-attributes to physico-chemical-, biological-properties and the manufacturing process) a more consistent/purer (less heterogenic) Q-profile could be chosen for the biosimilar drug substance, compared to the reference biologic drug substance as long as the safety- and efficacy- profile are comparable (within the margin of equivalence). (II)Therefore EMA should state that for in section 4 line 107 for example: “the better the correlation of molecular characteristic (including process understanding) of the biosimilar drug substance with quality attributes is understood, the more the biosimilar developer can shift the focus (of this development strategy) from mimicking the Q-profile of the reference biologic including its variability/heterogeneity; towards manufacturing a more consistent/pure biosimilar drug substance and therefore eliminating some of the heterogeneity of the reference biologic,	

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			as long the safety and efficacy remain comparable within the margins of equivalence" 1.5 By adding **(I)** and **(II)** to this guide, all ambiguity is removed. It gives a comprehensive solution for the development strategy of the biosimilar developer and aligns different sections within this guide, which per se read may be understood to be conflicting with each other. I believe that this reflects the intention of EMA.	
49.	95-100	10	Comment: The scope of ICH Q8 R2 is the life-cycle of a drug, including the whole development program. The QTPP (based on ICH Q8 R2) is a combination of mainly quality-attributes, but takes also into account safety- and efficacy-attributes. Therefore when utilizing the QTPP approach this is not limited to the quality section of the drug substance, as utilized for this guide, refer to Note 1 below: *Note 1* *Classically the QTPP consist of the following attributes with relation to:* *Quality:* • *Physical and chemical attributes of the dosage form,* • *cosmetic elements such as shape, color, size,* • *Container* • *etc.* *Safety:*	Not accepted. QTPP is a prospective summary that should form the basis for development of the biosimilar product and its manufacturing process; it corresponds to the target that should ideally be achieved, and not an outcome of development work. If quality issues arise from the clinical studies the biosimilar approach is in question.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			• *Impurities and degradation products* • *etc.* *Efficacy:* • *Clinical performance,* • *Biopharmaceutical and pharmacokinetics* • *etc.* 2.1 It is clear that some of the Q-attributes can only be partially predicted and tested by the methodologies mentioned in this guide (due to the only predictive nature for those tests), refer to below. *Various assays have been established in the past years that allow for more in-depth characterisation of complex proteins, both on a physicochemical and a functional level, e.g. with potency assays, and there is experience in the assessment of minor quality differences due to changes in manufacturing processes for monoclonal antibodies. However, it may at the current stage of knowledge be difficult to interpret the relevance of minor quality differences in the physicochemical and biological characterization when comparing a biosimilar mAb to a reference mAb.* *EMA/CHMP/BMWP/403543/2010* EMA therefore acknowledges the need to confirm those predictions in clinical trials. As QTPP terminology was consciously chosen by EMA for this guide. This should be more incorporated in this guide by EMA, by making the link with guidance documents such as *"Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues"* (*EMA/CHMP/BMWP/403543/2010*).	

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			(III) therefore EMA should state in section 4 that: "…at later development stages the established Q-attributes require confirmation in clinical trials and may be amended/completed, as the trial outcome cannot be foreseen. This could result in adjustment of the QTPP." This statement would satisfy better the application and scope of ICH Q R2 for this guide.	
50.	95-97	13	Comment: The clarification that data to establish the QTPP can include publicly available information is very helpful and should be preserved in the final guideline.	Acknowledged.
51.	90-100	7	Comment: The clear description of these two distinct but complimentary aspects of biosimilar development provides highly welcome clarification of the biosimilar concepts. No change – the paragraph should be preserved in the final guideline.	Acknowledged.
52.	99 - 100	5	Comment: We suggest to make the requirement to "identify critical quality attributes" within the context of "early stage of development" less categorical. Identification of all relevant CQAs can be a process going beyond "early stage of development". Proposed change: It is important to identify critical quality attributes that may impact the safety and efficacy of the	Accepted. The sentence in question has been removed

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			product, and start the assessment of quality attribute criticality at an early stage of development.	
53.	99-100	9	Comment: The QTTP should identify critical quality attributes that may show non similarity with the reference product and identify specific target for safety issues different from that of the reference product.(e.g. variants or process specific impurities)	Not accepted. It is not possible to comprehensively identify such CQA at early stage of development.
54.	101-104	1	Comment: Please specify any additional requirements in terms of characterization of the biosimilar if the manufacturer of a biosimilar product chooses to use completely different technology for USP or DSP process than that of a reference product.	Not accepted. No change The Biosimilar manufacturer will develop its own manufacturing process, and thus could use completely different technology as compared to the reference product; this basic principle is already addressed in the document.
55.	101-110	13	Comment: This section underlines the importance of the characterisation of the drug substance of a biological medicinal product and points out the issues and risks to be addressed if alternative manufacturing technologies and expression systems are used for the development of a biosimilar. This should be preserved in the final guideline.	Acknowledged.
56.	107	12	Comment: Wording “novel” not appropriate; by definition a biosimilar has always a novel exp system i.e. Coli A vs Coli B (not the same)	Accepted. Terminology was changed to “expression system differences”.

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
57.	105-110	1	Comment: In addressing 'potential risks introduced by the proposed manufacturing process', please clarify the pathway and basic requirements for evaluating the risk specific to the biosimilar manufacturing process.	Not accepted. The Guideline is not intended to describe how to perform a risk assessment.
58.	105 - 110	7	Comment: This paragraph describes the concepts that alternative manufacturing technologies and expression systems can be used in a perfect manner and highlights the concerns that need to be addressed with regard to the potential risks that could be introduced. This clarification reflects the science and risk-based approach endorsed by the CHMP and is highly appreciated. No change – the paragraph should be preserved in the final guideline.	Acknowledged.
59.	106-110	9	Comment: The fact that a biosimilar would be manufactured with a different process than the reference product does not always imply additional or higher risks, but most likely different ones, as compared to the reference product. Proposed change: … as they may introduce ~~additional~~ <u>specific</u> risk, such as ~~atypical~~ <u>different</u> glycosylation pattern, ~~higher~~ <u>different</u> variability or even a different impurity profile, as compared to the reference medicinal product.	Accepted. Wording has been changed.
60.	107	5	Comment: It is unclear whether the term "novel expression systems" is used to refer to expression systems that are simply different from the one used to manufacture the reference medicinal product, or newly introduced expression systems that	Accepted. Terminology was changed to "expression system differences".

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			are starting to be utilized by the biotech industry. Proposed change: Provide clarification on the term 'novel expression systems'.	
61.	107	8	Comment: Replace "kept in mind" with "adequately controlled". Proposed change: [...] product, should be adequately controlled during the development of a biosimilar.	Accepted. The wording was changed.
62.	107-110	1	Comment: Would any differences in attributes such as 'atypical glycosylation patter, higher variability, etc.', even if they are not clinically meaningful, translate into the product NOT being considered a biosimilar?	The comment is noted. Differences have to be evaluated and would be assessed on a case-by-case basis.
63.	110	8	Comment: Add a sentence related to "additional risk". Proposed change: Add a sentence to Line 110 as follows: A comprehensive risk assessment for the biosimilar medicinal product should be presented in Module 3.	Not accepted. The guideline is not intended to give guidance on risk assessment.
64.	115-117	1	Comment: At what point is the difference in formulation considered significant enough that the newly developed product will be considered a new drug product rather than a biosimilar? Please provide clarification.	Not accepted. It is not possible to predefine all possible criteria.
65.	115 - 117	5	Comment: It is not always possible to determine all potential differences in container/closure system. The scope of study described on Lines 111-115 encompasses the studies needed	Not accepted. It is not required/stated to identify and study all potential differences; it is necessary to 'appropriately

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			whether there is a difference or not. Proposed change: Remove this sentence.	justify' that there is no impact.
66.	123	14	Comment: We would recommend removing the sentence '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 medicinal product.' This is out of scope of this guideline, and separation of the Biosimilar comparability data in Module 3 has already been addressed in line 85-87.	Not accepted. The wording is maintained as it adds clarity that comparability upon process changes should be handled separate from demonstrating biosimilarity.
67.	123-126	1	Comment: In addressing 'process changes introduced during development', Please clarify as to how detailed the comparability study for process changes during PD should be. Is it sufficient to demonstrate changes only in the QTPP or is additional data required for other parameters? What specific EU guidelines are proposed to be followed to demonstrate comparability in such instances?	Not accepted. Comparability upon process changes is covered by ICH Q5E and is not within the scope of this guideline.
68.	126	14	Comment: To avoid confusion of which comparability study is being discussed, we recommend to clarify the wording. This sentence may be better placed under section header 5 (referred to again on line 173). Proposed change: In addition, acknowledging the possible changes made to the process during the development of the biosimilar product, it is	Partly accepted. For more clarity changes have been made to the text lines 126-129. To avoid duplication text has been removed from the Comparability section 5.

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			advisable to generate the required quality, safety and efficacy data for the biosimilar comparability study against the reference product with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised.	
69.	127	8	Comment: Replace “advisable” with “should be generated”. Proposed change: The required quality, safety and efficacy data for the biosimilar comparability study should be generated with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised.	Partly accepted. Text has been changed to ‘strongly recommended’.
70.	127-130	2	Comment: *“[I]t is advisable to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised.”* The word “advisable” is used in the context of which material may be used by the biosimilar Sponsor to perform a comparability assessment (*i.e.*, small or pilot scale versus final scale). It appears the intent is to encourage such a Sponsor to use material from an at-scale commercially viable process intended for licensure. BIO believes that any Sponsor should be expected to conduct such definite comparability assessments specifically using materials from their “final manufacturing process,” and thus the Guideline language should be strengthened accordingly.	Accepted. Text has been changed to ‘strongly recommended’.

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			Proposed change: BIO proposes the phrase “it is advisable to” be replaced with “Sponsors should be strongly encouraged to” so that the new sentence reads as follows: *“[S]ponsors should be strongly encouraged to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised.”*	
71.	126-130	9	Comment: We believe that demonstration of similarity should be made already at a very early stage of development and throughout the whole development. In addition, each substantial process change should go through process comparability demonstrated throughout the development: as mentioned above (see 3. Legal basis), two different types of documentation are required: normal requirements of the quality dossier discussed separately in Module 3 which allows earlier development versions of the product during biosimilar product development and separate requirement for the comparability exercise done with the final manufacturing process product in the context of a marketing application To request the comparability exercise done with the product manufactured with the final manufacturing process means that there would be no regulatory requirement for early demonstration of quality similarity in the development process.	Not accepted. This guideline includes the regulatory requirements at the level of marketing authorisation and not at earlier stages (i.e. clinical trial approval). It is acknowledged that similarity is a starting point for the development of the biosimilar, however for the marketing authorisation application it is strongly advisable to use product manufactured with the commercial manufacturing process.

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			In case the quality exercise does not show similarity, the whole development of the product would have to repeated years after the beginning, in order to allow a "new" product to apply for a full MA.	
72.	134	2	Comment: The Guideline currently specifies that "several different batches of the reference medicinal product should be used to provide a robust analysis and to generate a representative quality profile." Developing a sufficiently sized reference product specific data set should be a key element of the biosimilar comparative assessment strategy. "Several" could be interpreted to be as few as two. It seems unlikely that a biosimilar Sponsor would be able to develop a reasonable snapshot of reference product variability with such limited data. Proposed change: BIO suggests replacing the word "several" with "multiple" so that the sentence reads: "*Multiple different batches of the reference medicinal product should be used to provide a robust analysis and to generate a representative quality profile.*" Proposed change: BIO proposes adding the following additional language: "*The relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile. The number of batches of reference product characterised should be sufficient to ensure that the extent of variability in the reference product profile is understood throughout its shelf life.*"	Partly accepted. The proposed change from 'several' to "multiple" is accepted. It is accepted that the relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile. It is not accepted that *'the number of batches of reference product characterised should be sufficient to ensure that the extent of variability in the reference product profile is understood throughout its shelf life.'*

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
73.	134	1	Comment: Please clarify as to how many batches are proposed be used.	Not accepted. No specific number is required. Multiple different batches of the reference medicinal product should be used to provide robust comparability data in order to generate a representative quality profile.
74.	134-136	5	Comment: This draft revision has eliminated the requirement to use the same reference medicinal product for all phases of development. Proposed change: This requirement should be replaced in the overarching guidance if it is removed here.	Not accepted. Not accepted, intentionally removed to allow global development and to avoid misunderstanding. The issue of global development is further discussed in the overarching guideline.
75.	134-136	5	Comment: This draft revision has eliminated the text on the use of the same pharmaceutical form and strength as the reference product to “facilitate the comparability exercise”. That should be a non-negotiable requirement per Directive 2001/83/EC, so it is appropriate to remove the qualified language. Proposed change: It would be preferable to keep the point, but strengthen it: “The comparability exercise should be performed using a proposed biosimilar medicinal product with the same pharmaceutical form and strength as the reference product.” The parameter of age of the reference product lots should be emphasised since changes during the product shelf life will contribute to the overall variability of the reference product from which the biosimilarity acceptance criteria will be derived.	Not accepted. Section 5.3.5 is including a statement on the strength, which should be comparable to that of the reference product. In section 4 it is clarified that the formulation of the biosimilar does not need to be identical to that of the reference product. This leaves some flexibility also in relation to the pharmaceutical form, e.g. possibility to develop a liquid formulation where the reference medicinal product is lyophilised.

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			Reference product lot age and the age dependence of quality attributes should therefore be explicitly mentioned. It will be necessary to ensure that sufficient data are collected to establish the age related variability in the reference product quality attributes. Proposed change: *The relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile. The number of batches of reference product characterised should be sufficient to ensure that the extent of variability in the reference product profile is considered.*	
76.	134-136	5	Comment: The current guidance does not discuss the situation wherein the reference medicinal product comprises several strengths and presentations. Proposed change: It is suggested to add text as follows: "A reference medicinal product may be available in multiple strengths or presentations. The sponsor may also seek to develop a corresponding biosimilar medicinal product strengths and presentations. The sponsor should justify the strategy for assessing the quality profile of the various reference medicinal products strengths and presentations for the purposes of demonstrating comparability of the proposed biosimilar medicinal product. For example, it may be reasonable to assume that the same drug substance is used for all strengths	Partly accepted. Relevant guidance was added to section 5.1, where it is now stated: Where several strengths or presentations are available, their selection should be appropriately justified.

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			and presentations in the reference medicinal product. In this case, it may be possible to bridge between the strengths and presentations for the purposes of defining the QTPP, but such an analysis should be justified."	
77.	135-136	13	Comment: The sentence "*The relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile*." is not completely clear. Proposed change: The ~~relative~~ age of the different batches of reference medicinal product <u>relative to their expiration dates</u> should also be considered when establishing the target quality profile.	Accepted.
78.	138	5	Comment: Although the explicit expectation of a high degree of similarity in quality attributes between the biosimilar and the reference product is welcomed, please provide guidance on what is meant by 'highly similar' compared to 'similar'? Proposed change: please clarify the differences between 'highly similar' and 'similar' in the document	Partly accepted. At the beginning of Section 5.2, it is stated that an extensive comparability exercise will be required to demonstrate that the biosimilar has a highly similar quality profile when compared to the reference medicinal product. This is to give a clear indication of what is expected for the biosimilar product. Thereafter, this is simply stated as 'similar' throughout the guideline.
79.	139-142	1	Comment: What are the considerations for batch to batch variability if seen in the RMP – would that also be allowed for the biosimilar product?	Comment acknowledged. Batch-to-batch variability is a recognised feature of all biological products. This issue is discussed in section

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				5.2 of the Guideline.
80.	140-141	9	Comment: We believe that orthogonal methods for side-by-side analyses of the proposed biosimilar and reference medicinal product should only be requested when usually done for any biological product development.	Comment acknowledged. Orthogonal methods should be used; it is expected that robust information can be derived from the use of orthogonal (instead of only one) methods. The details have been clarified.
81.	143	5	Comment: "Significant quality differences" terminology has not been defined in this document. It is our understanding that any quality differences for which an impact on safety or efficacy cannot be excluded following relevant nonclinical and clinical studies will prevent the conclusion of biosimilarity. We suggest that any quality differences that either historically or during the biosimilarity exercise have been shown to have impact on clinical safety and/or efficacy, and/or affect the proposed product's critical quality attributes should be considered to be *'significant quality differences'*. Proposed change: clarify 'significant quality differences' as any quality differences that either historically or during the biosimilarity exercise have been shown to have impact on clinical safety and/or efficacy, and/or affect the proposed product's critical quality attributes.	Partly accepted. The terminology has been changed from 'significant' to 'relevant', since significant can imply statistically significance or having a major impact. In any case, qualitative or quantitative differences have to be justified in terms of impact on safety and efficacy.
82.	143-144	9	Comment: 'Significant' has different interpretations depending on what is demonstrated.	Partly accepted. The terminology has been changed from 'significant' to

N°	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: If substantial quality differences… safety and efficacy"	'relevant', since significant can imply statistically significance or having a major impact. See comment 81.
83.	149 - 151	5	Comment: We are in agreement that the drug product is ultimately relevant. However, in the similarity assessment, some elements can be fully demonstrated at the drug substance level. Proposed change: there should be an option to use drug substance or drug product in the comparison, as appropriate.	Not accepted. Biosimilarity should be based on the final product including data related to the active substance present in the final product. This does not exclude use of the isolated active substance to generate relevant data.
84.	150	8	Comment: Add "highly" before "similar". Proposed change: [...] by the applicant are highly similar […]	Not accepted. See comment 78.
85.	151	8	Comment: Add text at the end of the sentence. Proposed change: […] treat the patient **and there are no clinically meaningful differences between the biosimilar product and reference product in terms of the safety, purity and potency of the product.**	Partly accepted. A reference to the overarching and nonclinical/clinical guideline has been included.

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86.	151	5	Comment: Reference is *"made to the material that will be used to treat the patient"*. It should be clarified if there is any expectation to demonstrate biosimilarity in in-use conditions, post clinical trials. Proposed change: To be clarified	Partly accepted. There is no requirement to demonstrate comparability for in-use conditions and so the statement 'i.e. the material that will be used to treat the patient' has been removed.
87.	151	9	Comment: Reference is *"made to the material that will be used to treat the patient"*. It should be clarified if there is any expectation to demonstrate biosimilarity in *in use* conditions (e.g. on reconstituted solutions if the Drug Product is a lyophilisate) or if focus of the finished product.	Partly accepted. See comment 86.
88.	151-152	1	Comment: Please provide examples of acceptable minor differences between the biosimilar and the reference product.	Partly accepted. This sentence has been re-worded.
89.	153	9	Comment: Degradation pathways need to be considered with respect to potential immunogenic impact or other patient safety issues. One product may dissociate whilst the biosimilar may aggregate under stressed conditions	Acknowledged.
90.	152-155	1	Comment: Does this refer to the critical release criteria or any and every characterization test related to immunogenicity or potency?	Acknowledged. This refers to the requirements for the comparability exercise.

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91.	156	2	Comment: “The applicant should demonstrate that the desired product and product-related substances present in the finished product of the biosimilar are highly similar to that of the reference medicinal product.” Proposed change: Because, by definition, product includes product-related substances, BIO proposes the phrase “and product-related substances” be removed from the sentence in order to avoid confusion. The edited sentence would read: “*The applicant should demonstrate that the pattern of heterogeneity of the desired product present in the finished product of the biosimilar is highly similar to that of the reference medicinal product.*”	Partly accepted. This has been rephrased for clarity.
92.	158-161	12	Comment: Why to differentiate « quantitative » (first sentence) and « qualitative » (second sentence); the 2 sentences deal with the same idea and have to be combined Proposed change: Where quantitative or qualitative differences are detected, such differences should be demonstrated to have no relevance for the clinical performance of the product. Qualitative differences (i.e. presence or absence of product-related substances and/or impurities) require a thorough justification, which may include before initiating non-clinical and/or clinical data, as appropriate. And perhaps to be completed with the sentence from old version (2005) already mentioned above (under L67-68) : « the comparability exercise at the quality level may allow a reduction of the non-clinical and clinical data »	Partly accepted. This has been rephrased for clarity.

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93.	159-160	1	Comment: The acceptable differences in the process-related substances should be specified.	Not accepted. The term 'process-related substances' is not understandable.
94.	159-161	1	Comment: Provide clarification as to whether or not a biosimilar product that is purer than the RMP would require a justification. Please provide clarification for "preferable to rely on purification process to remove impurities…" as the statement is in complete contrast.	Partly accepted. The section has been clarified on this point.
95.	159 - 161	5	Comment: Determining presence or absence of qualitative differences can be ambiguous. e.g., a novel product-related substance might be reported by definition either for peaks > reporting limit, or peaks > LOQ, or peaks > LOD. Proposed change: A description about expected thresholds would contribute to clarification.	Not accepted. This can only be discussed on a case-by-case basis.
96.	159 - 161	7	Comment: The absence of product-related substances and especially impurities in the biosimilar candidate should not raise the same concerns as the presence of additional product-related substances and/or impurities. Proposed change: Qualitative differences (i.e. presence ~~or absence~~ of product-related substances and/or impurities) require a thorough justification, which may include non-clinical and/or clinical data, as appropriate.	Partly accepted. The sentence has been modified.

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97.	159-161	9	Comment: Determining presence or absence of qualitative differences can be ambiguous, e.g., a novel product-related substance might be reported by definition either for peaks > reporting limit, or peaks > LOQ, or peaks > LOD. Description about expected thresholds would contribute to clarification.	Not accepted. This can only be discussed on a case-by-case basis.
98.	159-161	13	Comment: The absence of impurities in the biosimilar candidate should not raise the same concerns as the presence of additional product-related substances and/or impurities. Proposed change: Qualitative differences (i.e. presence ~~or absence~~ of product-related substances and/or impurities) require a thorough justification, which may include non-clinical and/or clinical data, as appropriate.	Partly accepted. The section was modified.
99.	163 – 194	11	This section is clearly aimed at covering all possible situations and has intentionally been left rather vague. Assessors and future applicants can hardly derive any concrete, specific guidance from this section. It is recognized that it is practically impossible to give all-encompassing guidance; a case-by-case approach is most likely needed. However, more specific guidance should be given than is now present in the document. A non-exhaustive lists of examples include: -The use of the term highly similar quality profile in line 164. Although it may be expected that the remainder of section 5.2 is devoted to further specifying the term highly similar, this is	Partly accepted. Several clarifications have been introduced to the text.

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			not sufficiently the case. Lines 178-179 seem to repeat the requirement of 'highly similar' without any further explanation. -The use of the term minor differences in line 173, without further defining what may be considered minor and what not. This is probably the most relevant shortcoming of this section and further elaboration on the concept of 'minor' is warranted. -Several occurrences of the term justified/justification, without further discussion on what kind of justification could be acceptable (a.o. line 173, 183, 188, 192).	
100.	164	2,5	Comment: The requirement for "target acceptance criteria" for comparability is not clearly linked to the earlier requirement to develop a Quality Target Product Profile (QTPP). BIO requests clarity as to whether these are the same or different concepts? Proposed change: BIO proposes adding the following additional language: "These criteria may be derived from the QTPP defined during process development, with refinements as needed based on further characterization of the reference medicinal product."	Partly accepted. The section has been improved for clarity. While the QTTP is a development tool, the quantitative ranges for biosimilarity should be based primarily on the measured quality attribute ranges of reference product and should normally not be wider than the range of variability of the representative reference product batches. The sentence 'The target acceptance criteria used in the biosimilar comparability exercise should be justified' has been deleted
101.	164	12	Comment: "Target" does not bring any added value Proposed change: delete "target"	Partly accepted. The sentence 'The target acceptance criteria used in the biosimilar comparability exercise should be justified' has been deleted.

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102.	164	12	Comment: “Qualitative” to be included as well (to be consistent with L 158-161) Proposed change: Quantitative / qualitative limits should be established,	Not accepted.
103.	165 - 167	5	Comment: The parameter of age of the reference product lots should be emphasised since changes during the product shelf life will contribute to the overall variability of the reference product from which the biosimilarity acceptance criteria will be derived. Reference product lot age and the age dependence of quality attributes should therefore be explicitly mentioned. Proposed change: Remove the following text: *The relevance of these limits should be discussed, taking into account the number of reference medicinal product lots tested, the quality attribute investigated and the test method used.* And replace with: *The relevance of these limits should be discussed, taking into account the number and age of reference medicinal product lots tested, the quality attribute investigated, its age dependent variability and the test method used.*	Partly accepted. The text has been modified as follows; “The relevance of the ranges should be discussed, taking into account the number of reference medicinal product lots tested, the quality attribute investigated, the age of the batches at the time of testing and the test method used.”
104.	167-168	9	Comment: Quantitative limits established: requesting that these limits should not be wider than the range of variability of the representative reference medicinal product batches, unless	Not accepted. A sufficient number batches of reference medicinal

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			otherwise justified implies that the reference product has set limits that are no wider that the range of variability of the representative reference medicinal product batches itself. However, other batches from the reference products than the ones used in the comparability exercise might have values outside these limits. Limits are set to allow enough safety variability within the production. And more even if the product has been developed according to an ICH Q10 QbD. This requirement should therefore be reconsidered.	product should be tested to give representative ranges for the different parameters. Values outside of these ranges need to be justified, which should give sufficient room to accommodate some variability. Use of QbD should not introduce further variability or warrant broader limits.
105.	168	8	Comment: Add additional text to define “acceptance criteria”. Proposed change: after [...] justified. Add: **Acceptance criteria should be based on the totality of the analytical data and not simply the observed range of product attributes of the reference product.**	Partly accepted. This section has been modified. We agree that totality of the data should be used for the final conclusion, however each QA should also be analysed to generate the required data.
106.	168-170	1	Comment: Provide an example of a statistical model to be used for result evaluation.	Not accepted. An example is not included as this might steer applicants towards a particular method. It is up to the applicant to decide on the statistical model to be used.
107.	168 - 170	7	Comment: The guidance that statistical approaches for establishing target acceptance criteria provides, despite all challenges in doing so, an important opportunity that should be preserved in the final guideline.	Comment acknowledged.

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			No change – the paragraph should be preserved in the final guideline.	
108.	173	2	Comment: *"[I]t is advisable to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process."* The word "advisable" is used in the context of which material may be used by the biosimilar Sponsor to perform a comparability assessment (*i.e.*, small or pilot scale versus final scale). It appears the intent is to encourage such a Sponsor to use material from an at-scale commercially viable process intended for licensure. BIO believes that any Sponsor should be expected to conduct such definite comparability assessments specifically using materials from their "final manufacturing process," and thus the Guideline language should be strengthened accordingly. Proposed change: BIO proposes the phrase "it is advisable to" be replaced with "Sponsors should be strongly encouraged to" so that the new sentence reads as follows: *"[S]ponsors should be strongly encouraged to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process."*	Partly accepted. This sentence has been changed to include 'strongly recommended'. In order to avoid unnecessary repetition, this guidance only appears in Section 4.
109.	173	8	Comment: see Line 127, replace "advisable" with "should be generated".	Partly accepted. See comment 108.

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			Proposed change: Rewrite to read: The required quality, safety and efficacy data for the biosimilar comparability study **should be generated** with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised.	
110.	173-178	9	Comment: Unnecessary, repetition (line 126-130)	Accepted.
111.	178-179	1	Comment: Clarification on how to account for the difference in the Quality Attributes (QA) of the reference product that are caused by life cycle changes should be provided.	Comment acknowledged. If a clear shift in a quality attribute is identified by a biosimilar product developer in the reference medicinal product (as e.g. described in M. Schiestl et al., Nature Biotechnology (2011) Vol 29 (4) pp. 310-312), then this should be discussed in the biosimilar comparability exercise section (3.2R). This is covered in section 5.2.
112.	178 - 186	5	Comment: Lines 178-186 explain that during the lifecycle of the biosimilar and the reference product they may increasingly start to deviate. However lines 187-188 indicate that there is no intention to ask for "re-demonstration of biosimilarity" once the Marketing Authorisation is granted. Bearing this in mind, it is not clear how the ranges identified before and after the	Comment acknowledged. See comment 111. Once the MA is granted, the biosimilar product is considered a stand-alone product and re-demonstration of biosimilarity is not required.

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			observed shift are expected to be determined. Furthermore, it is, not clear what is meant by these ranges and what should be specified Proposed change: Please specify, especially with regard to the mentioned “ranges”.	This is covered in section 5.2.
113.	178 - 186	7	Comment: This paragraph acknowledges that the manufacturing process of the reference product as well as the QTPP ranges may evolve through its lifecycle. We highly appreciate that the draft further acknowledges that the manufacturing process of the reference medicinal product may evolve through its lifecycle, and may lead to detectable differences in some quality attributes. From a scientific as well as regulatory perspective, batches with such differences in some quality attributes can be considered representative for the reference product. The draft guideline clarifies that the ranges identified before and after the observed shift in quality profile could normally be used to support the comparability exercise at the quality level, as either range is representative of the reference medicinal product. This clarification reflects the science and risk-based approach endorsed by the CHMP and is highly appreciated. No change – the paragraph should be preserved in the final guideline.	Comment acknowledged.

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114.	178-186	13	Comment: This paragraph acknowledges that the manufacturing process of the reference product may evolve over time with potential impact on molecular characteristics and that pre- and post-shift ranges in quality attributes are considered representative for the reference product. As this is based on scientific and regulatory grounds, this should be preserved in the final guideline.	Comment acknowledged.
115.	181-182	11	Comment: The wording 'should be demonstrated' suggests that quantitative differences should always be clinically evaluated. This may not always be needed (e.g. lower levels of impurities, lower levels of degradation products) and a wording to allow justification should be introduced. Proposed change: '…….should be justified and where relevant demonstrated ……'	Accepted.
116.	184-186	1	Comment: In the discussion of "quality attribute values which are outside the range(s) of variability measured in the different profiles of the reference medicinal product should be appropriately justified with regard to their potential impact on safety and efficacy", further clarity and examples should be provided.	Not accepted. This will be done on a case by case basis, based on scientific justification.
117.	187-188	1	Comment: This approach is also applicable to the reference product; therefore the differences in QA could be significant and	After obtaining a MA, both products have an independent lifecycle. Once licensed, any changes have

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			outside of “biosimilarity” ranges. Please clarify.	to be justified by the Applicant making these changes.
118.	187 - 188	7	Comment: The note that there is no regulatory requirement for re-demonstration of biosimilarity once the Marketing Authorisation is granted is an important clarification. It is fully in line with the comparability concept according to ICH Q5E, which also provides guidance of how to handle potential drifts by stating that “the manufacturer should evaluate […] Historical data that provide insight into potential “drift” of quality attributes with respect to safety and efficacy, following either a single or a series of manufacturing process changes. That is, the manufacturer should consider the impact of changes over time to confirm that an unacceptable impact on safety and efficacy profiles has not occurred.” No change – the paragraph should be preserved in the final guideline.	Comment acknowledged.
119.	187-188	8	Comment: Delete Lines 187-188 or if retained add additional wording. Proposed change: After Line 188 add: **However, a robust control strategy and continued process verification should be elements detailed in the dossier to ensure process consistency over time.**	Not accepted. Any biological product is expected to have a robust control strategy and continued process verification to ensure process consistency. This is not specific to biosimilar products.
120.	187-188	9	Comment: It should be clarified if there is any expectation for re-demonstration of biosimilarity during development shall	See comment 112

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			changes in the manufacturing process of the reference medicinal product lead to differences in quality attributes outside previous ranges. Proposed change: To be clarified.	
121.	187-188	13	Comment: The clarification that there is no regulatory requirement for re-demonstration of biosimilarity after the Marketing Authorisation is granted is very helpful and should be preserved in the final guideline.	Comment acknowledged.
122.	189	14	Comment: Please could the Agency comment on where they would like to find the comparability summary in module 3.2.?	Accepted. This is now stated in Section 3.
123.	190	12	Comment: Proposed change (if any): delete “target” (meaning of the sentence unchanged)	Partly accepted. See comment 101.
124.	194-196	6	Proposed change: Direct comparison of the biosimilar to a publicly available standard, e.g. Ph. Eur., WHO, is not sufficient for the purpose of comparability. However, the use of these standards plays an important role during method qualification and standardisation, as discussed below.	Partly accepted. This is now clarified in Sections 1 and 5.3.1.

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125.	195	5	Comment: In later parts of the text it is indicated that Ph.Eur. and WHO reference standards could be used during the comparability exercise. Although it is acknowledged that a public standard may be relevant to ensure compliance with compendial requirements for identity, quality and potency but it is not otherwise suitable for the basis of comparison with the reference medicinal product For clarity, the following text is suggested. Proposed change: "... to a publicly available standard **alone**, e.g. Ph.Eur., WHO, is not appropriate for the purpose of comparability, although it may be to sufficient to ensure compliance with compendial requirements for identity, quality and potency…".	Partly accepted. See comment 124.
126.	199-207	9	Comment: Now that it is possible for a company to consult publicly disposable information from the competitors through EMA (Guideline Mars 2012), innovators would have access to data generated with their own products by the biosimilar developing company, using state of the art methods, unemployed at the time of development by the reference product. This should be a legal issue that needs to be looked at and solved.	Not accepted. This issue is not within the scope of this Guideline.
127.	202 - 204	5	Comment: It is not always possible to develop methods that are capable of detecting “slight differences in all aspects”.	Not accepted. The text already states ‘all aspects pertinent to the evaluation of quality’. This makes the change unnecessary, because the ‘all aspects’ are sufficiently

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			Proposed change: Amend text as following: '….would be able to detect slight differences in quality attributes (including all CQA).'	qualified.
128.	204	8	Comment: Add additional text. Proposed change: After evaluation of quality, add sentence as follows: **The ability of methods used to detect relevant molecular variants and sensitivity of these methods to changes in relevant variants should be considered.**	Not accepted. This message is already pointed out in the first part of Section 5.3: Analytical considerations.
129.	204-205	1	Comment: Provide clarification as to what an "appropriately qualified" method is and what the acceptable criteria for method qualification are.	Not accepted. Where necessary, this will be done on a case by case basis, based on scientific justification.
130.	214	8	Comment: Add additional text. Proposed change: Add after Line 214: **The type, nature and extent of any differences between the biosimilar product and the reference product, observed from comprehensive analytical characterization of multiple lots, should be clearly described and discussed, and the relationship of these differences to known critical quality attributes should also be discussed.**	Not accepted The impact of possible differences observed between the biosimilar and the reference is discussed in Section 5.2 Biosimilar comparability exercise.
131.	216	1	Comment: In addition to establishing a physicochemical characterisation programme for a biosimilar, is there a	Partly accepted. Yes, this is part of the development of a biotechnology

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			requirement to have a programme for impurity characterisation (in the same lines as the product characterisation)?	product and will also be part of the development of a biosimilar product. For process-related impurities, this is covered in Section 5.2, where additional clarification has been given.
132.	216-230	2	Comment: As drafted, the paragraph appears to focus on structure diversity associated with amino acid sequence and glycosylation related variants only. Proteins are subject to a variety of other post-translational modifications (*e.g.* oxidation, deamidation, phosphorylation, etc.) which also contributes to the heterogeneous nature of protein biologics. They are often comprised of diverse populations of related structural variants. For example, fifteen of twenty commonly occurring amino acids are subject to chemical modifications. Proposed change: As such, BIO believes that the Guidance should be broadened to recognize the possibility that multiple post-translational modifications may occur and that comparisons between biosimilar candidates relative to reference products need to take this into account unless suitable justification can be provided.	Partly accepted. Additional clarification has been given in Section 5.3.1
133.	217-222	3	Comment: Followed the sentence “The target amino acid sequence of the biosimilar should be confirmed and is expected to be the same as for the reference medicinal product.”, we propose to include an additional sentence in order to preserve the functional identity	Not accepted. It is a regulatory requirement that the target amino acid sequence is the same. A different amino acid sequence would imply new active substance status (as defined in the Notice to Applicants).

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			Proposed change: "Exception made for functionally irrelevant amino acid variants outside the active sites such as those related to allogeneic varieties of Antibodies. As long as the functional identity is preserved".	
134.	220	12	Comment: Proposed change: delete “target” (meaning of the sentence unchanged)	Not accepted. Deleting ‘target’ changes meaning of sentence, because this would exclude microheterogeneity.
135.	219-221	5	Comment: Although it is stated that the amino acid sequence of the biosimilar should be confirmed and is expected to be the same as for the reference medicinal product. This requirement can potentially exclude an otherwise similar product that may have naturally occurring, low frequency amino acid switches specific to the chosen expression system, but not to that of the reference medicinal product. Such low level or micro-heterogeneity in the protein sequence pattern should be assessed in the context of effect on safety, purity or potency, and may be justified by the applicant. However, we consider that it should be clear that in the majority of biosimilar products the amino acid sequence of the reference medicinal product and the biosimilar should be identical. Proposed change: Amend the sentence as following: ‘The target amino acid sequence of the biosimilar should be	Not accepted. It is a regulatory requirement that the target amino acid sequence is the same. As already indicated in the comment, low frequency amino acid switches are part of the micro-heterogeneity of the protein. Such micro-heterogeneity should be differentiated from the target sequence of the intended product; acceptability of such micro-heterogeneity is discussed in the second part of Section 5.3.1 (see also comment 136).

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			confirmed and is expected to be the same as for the reference medicinal product. **Any deviations should be justified and** any detected differences should be part of the micro-heterogeneous pattern of the reference medicinal product. The justification, in terms of quality which may impact on safety and efficacy, may require additional non-clinical and clinical studies.'	
136.	221 - 222	5	Comment: The sentence, "Any detected differences should be part of the micro-heterogeneous pattern of the reference medicinal product", may be interpreted as referring specifically to the amino acid sequence, or more generally to all of the attributes described in the paragraph. Proposed change: If the intent is to be specific, this should be revised to: "Any detected differences <u>in the sequence</u> should be part of the micro-heterogeneous pattern of the reference medicinal product." If the intent is to be general, then the sentence should be moved to the end of the paragraph.	Partly accepted. Section 5.3.1 has been re-worded for clarity and now states: Any modifications/truncations should be quantified and any intrinsic or expression system-related variability should be described. Any detected differences between the biosimilar and the reference medicinal product should be justified with respect to the micro-heterogeneous pattern of the reference medicinal product (e.g. C-terminal lysine variability).
137.	221 - 223	7	Comment: The sentence 'Any detected differences **should be part of** the micro-heterogeneous pattern of the reference medicinal product' can be interpreted as a contradiction to the next and totally correct sentence saying that N- and C-terminal	Partly accepted. See comment 136.

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			amino acid sequences should be compared as appropriate, because these are also 'detected differences to the target amino acid sequence'. Proposed change: Any detected differences should be compared with ~~part of~~ the micro-heterogeneous pattern of the reference medicinal product.	
138.	221-223	13	Comment: The sentence "Any detected differences should be part of the micro-heterogeneous pattern of the reference medicinal product'" is not fully clear in the context of potentially acceptable differences as clarified in the preceding sentence. Proposed change: Any detected differences should be compared with ~~part of~~ the micro-heterogeneous pattern of the reference medicinal product.	Partly accepted. See comment 136.
139.	223	1	Comment: In addressing "any modifications/truncations should be quantified and any intrinsic- or expression system-related variability should be described, set at minimum and justified", 'minimum' should be clarified.	Partly accepted. See comment 136.
140.	237	4	Comment: The inclusion of examples for assay formats focuses on receptor binding- and biochemical formats. Therefore the need of assay formats focusing on biologic activity is disproportionately underrepresented in this draft version.	Partly accepted. Example of functional assays added.

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141.	238 - 239	5	Comment: The meaning of the following sentence in lines 238-239 is not clear: *Complementary approaches should be followed to accommodate the inherent limitations regarding validation characteristics of single bioassays.* It is assumed that this refers to the difficulty of validating inherently variable biological assays which have intrinsically wide margins of experimental error. Proposed change: *A complementary or orthogonal analytical approach should be investigated when there are significant difficulties in satisfactorily validating a bioassay which has inherently high variability and/or intrinsically wide margins of experimental error.*	Partly accepted. Section 5.3.2 has been re-worded for clarity.
142.	238 - 239	7	Comment: The word 'inherent' appears too strong and slightly misleading as in many cases the limitations in bioassays can be reduced substantially by better assay development and optimization. Companies putting much effort in this should not be discouraged. Proposed change: Complementary approaches should be followed to accommodate ~~the inherent~~ limitations regarding validation characteristics of single bioassays.	Partly accepted. See comment 141.
143.	241	4	Proposed change: In order to avoid the impression that receptor binding- and biochemical formats will be sufficient for comparing biological activity, the statement "detect changes in biological activity." should be completed to "detect changes in	Partly accepted. See comment 141.

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			biological activity, e.g. by functional assays."	
144.	241-242	1	Comment: The criteria for selecting the reference product as a standard should be specified in the case that an international reference standard is not available.	Not accepted. The guideline does not require that the reference product should be used as a standard.
145.	243-244	1	Comment: In addressing "These assays should comply with appropriate European Pharmacopoeia requirements for biological assays, if applicable", it should be clarified if in the case of global development, the assay developed in compliance with the other available pharmacopeia (for eg. USP) is acceptable or would that be a limiting factor.	Not accepted. Assays should comply with Ph. Eur. if and where applicable. Compliance with USP is not a EU requirement.
146.	248	1	Comment: In the discussion of "In addition, binding affinity of the Fc to relevant receptors (e.g. FcγR, C1q, FcRn) should be compared", relevant receptors should be clarified. It should also be clarified if this is dependent on the method of analysis.	Not accepted. Which receptor is relevant will be determined on a case by case basis, based on scientific justification.
147.	249-250	1	Comment: In the discussion of "appropriate methodologies should be employed to compare the ability to induce Fab- and Fc-associated effector functions", additional details and examples of the acceptable methodologies should be provided.	Not accepted. Acceptable methodologies will be determined on a case by case basis, based on scientific justification.
148.	252 -253	5	Comment: The sentence should be changed to clarify what is	Accepted.

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			being compared. Section 5.3 and its subsections all describe the comparison of the biosimilar active substance with the reference medicinal product (or with the active substance prepared from the reference medicinal product). It is assumed that section 5.3.4 is intended to be the same in this regard. The current text implies comparison of an active substance with its corresponding drug product; i.e. not between a biosimilar and the reference product. This is not consistent with the rest of the text in section 5.3.4 or with the other subsections in section 5.3. Proposed change: *The purity and impurity profiles of the biosimilar and the reference product should be compared both qualitatively and quantitatively by a combination of analytical procedures.*	
149.	252-253	9	Comment: Active ingredient of the reference product will usually not be accessible by the applicant. Instead, the active ingredient intended for the comparison of purity and impurity profiles has to be isolated from reference drug product. Therefore, its impurity profile reflects the reference drug product impurity profile that might be different from the active ingredient impurity profile. Therefore, the informative value of a comparison on active ingredient level might be limited. Proposed change: The purity and impurity profiles of the medicinal <u>product</u> should be compared [...]. Where justified by technical requirements of the analytical methods applied (e.g.	Partly accepted. See comment 148.

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			excipient may limit assay sensitivity), the comparison is performed on the active ingredient as well.	
150.	251 - 267	5	Comment: It is noted that the requirement for performing stress testing and accelerated stability studies has been removed, however as part of providing a full quality dossier (CTD Module 3) and Comparability exercise as per Section 3. Legal basis, we consider that this is an important part of overall pharmaceutical documentation which must be provided for biosimilar products, and are particularly important to demonstrate the similarity of the biosimilar to the reference product stored under different stress conditions. Proposed change: Addition of the following text to section 5.3.4: 'Information based on the analysis of samples stored under stress conditions, including selective degradation (e.g., oxidation, dimerisation) should be used for identification. Comparison of product-related substances and of product-related impurities should be based on specific degradation pathways and potential post-translational modifications of the individual proteins. Accelerated stability studies of the reference and of the similar biological medicinal product can be used to further define and compare stability profiles.	Not accepted. Although stress testing and accelerated stability studies are part of the requirement for product development for a full quality dossier, it is not required, although recommended to demonstrate the similarity of the biosimilar to the reference product stored under different stress conditions. A sentence has been added to cover this issue in section 5.3.4.
151.	259-261	9	Comment: Similarity of degradation pathways of reference product and the biosimilar:	Not accepted. There is no requirement for comparative studies under

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			Should be comparable under real time conditions in addition to stress/accelerated conditions. Differences could indicate different degradation mechanisms and different impurity profiles on storage	real-time/real-temperature conditions; this has been clarified in Section 6.
152.	266	5	Comment: It is clear that any potential risks related to any newly identified impurities (e.g. immunogenicity) will have to be appropriately documented and justified. However it is not clearly explained how this justification would be completed. We consider that some new impurities, e.g. different host cell proteins or new product related impurities should be qualified by appropriate non-clinical and clinical studies. Proposed change: We suggest amending the text as follows: 'Nevertheless, state-of-the-art analytical technologies following existing guidelines and compendial requirements should be applied, and the potential risks related to these newly identified impurities (e.g. immunogenicity) will have to be appropriately documented and justified, with non-clinical and clinical studies if appropriate.	Not accepted. Requirements regarding non-clinical and studies are outside the scope of this guideline. However, toxicological studies to address risks of product and process related (proteinaceous) impurities are in general not scientifically meaningful.
153.	267	8	Comment: Add additional text. Proposed change: After Line 267 add: **The potential impact of differences in the impurity profile upon safety and immunogenicity should be addressed**	Not accepted. See comment 152 regarding impurity profile. The issue of adventitious agents is not specific for biosimilars and therefore not within the scope of this

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			and supported by appropriate data. **The safety of the biosimilar product with regard to adventitious agents or endogenous viral contamination should be ensured by screening raw materials and confirmation of robust virus removal and inactivation achieved by the manufacturing process.**	Guideline.
154.	268	1	Comment: In addressing section '5.3.5. Quantity', it should be clarified if this refers to the assessment of actual amount of active ingredient in terms of strength/dose or the extractable volume (i.e. quantity or product in the respective container closure).	Partly accepted. Section 5.3.5 has been revised to clarify this point.
155.	269 - 270	5	Comment: This section says nothing about the expectations for comparability of the quantity attribute, even though it is placed under the section 5 "Comparability Exercise". Proposed change: Suggest adding the following text: "The comparability exercise should support that the total quantity of delivered dose per container is equivalent to the delivered dose in the reference medicinal product container. For a liquid dosage form this evaluation should take into account the product concentration and the volume in container."	Partly accepted. Section 5.3.5 has been revised to clarify this point.
156.	269 - 270	5	Comment: The word "normally" implies a preferred but occasionally different state. There should be no circumstances in which the activity of the biosimilar is reported in different units from the reference product. The use of different units	Accepted.

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			would not permit a direct comparison of the biosimilar and reference product activities. Consequently, the word “normally” should be deleted. Proposed change:Suggest amending the text as follows: ‘Quantity should be determined using an appropriate assay, and should be expressed in the same units as the reference medicinal product.’	
157.	269 - 270	7	Comment: That normally the same units should be used for the determination of quantity, is an important clarification that should be preserved. No change – the paragraph should be preserved in the final guideline.	Partly accepted. See comment 156.
158.	271	5	Comment: The clinical programme will be smaller than for the innovator product involving fewer batches. Proposed change: Handling of the ICH Q6B requirement (specifications are linked to the product tested in clinical trials) should be included.	Not accepted ICH Q6B gives sufficient guidance on setting of specifications during release and shelf-life, based on both clinical batches and manufacturing capability. Addition guidance is not deemed useful and may only be confusing.
159.	Section 6. Specificati	5	Comment: It is noted that in Section 5.2 Comparability exercise there is discussion regarding the target acceptance criteria for	Not accepted.

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	ons		the biosimilar and that 'limits should not be wider than the range of variability of the representative reference medicinal product batches, unless justified'. We consider that this is also true for biosimilar specifications, notwithstanding the requirement for both drug substance and drug product specifications to be defined as described in ICH Q6B: 'Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biologic Products'. Proposed change: Addition of the following text to Section 6. Specifications: 'The specification for the finished product should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified.'	Quantitative ranges for the comparability exercise are different from the specifications for Drug Substance and Drug Product. Specifications with associated acceptance criteria should be set as defined in ICH Q6B.
160.	276 - 278	5	Comment: The parameter of age of the reference product lots should be emphasised since changes during the product shelf life will contribute to the overall variability of the reference product from which the biosimilarity acceptance criteria will be derived. Reference product lot age and the age dependence of quality attributes should therefore be explicitly mentioned. Proposed change: Each acceptance criterion should be established and justified based on data obtained from lots used in non-clinical and/or clinical studies, and by data from lots used for the demonstration of manufacturing consistency, data from stability studies to determine age related variability, any other relevant development data	Not accepted. See comment 159.
161.	278	5	Comment: Currently "Stability" is mentioned in line 278, while line 118 states about compliance with ICHQ5 – for a new program.	Not accepted. See comment 158.

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			Proposed change: The following text should be added: Stability: (1) Should be within the equivalence window established with reference product throughout out the shelf life as well as under “stressed” conditions. (2) Discussion on degradation pathway and products as part of comparability exercise could also be helpful in ensuring that the Quality of the product is adequately ensured throughout the lifecycle/shelf-life.	
162.	280	8	Comment: Add new Section to address Stability. Proposed change: Add Section 7; Stability: “Accelerated and stress stability studies, or forced degradation studies, should be used to establish degradation profiles and provide direct comparison of the biosimilar product with the reference product. These comparative studies should be conducted under multiple stress conditions (e.g. high temperature, freeze thaw, light exposure, and agitation) that can cause incremental product degradation over a defined time period. Results of these studies may reveal product differences that warrant additional evaluation and also identify conditions under which additional controls should be employed in manufacturing and storage. Sufficient real time, real condition stability data should be provided to support the proposed dating period.”	Not accepted. See comment 150, 151, and 158.