EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May, 2011

Submission of comments on 'Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues'

Comments from:

Name of organisation or individual
EBE (European Biopharmaceutical Enterprises) Contact: Piers Allin (piers@ebe-biopharma.org)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	General remarks EBE welcome the revision of the biosimilar quality guidance to reflect the additional experience from biosimilar products being reviewed by the regulatory agencies since 2006 and appreciates the possibility to comment on the EMA concept paper (EMA/CHMP/BWP/617111/2010). EBE believe there should not be an expectation for ongoing comparability of the biosimilar product with the reference (originator) product. Further remarks are provided below. EBE also believe that is also important to identify critical quality attributes that may impact the safety and efficacy of the product and ensure an ongoing assessment of a positive benefit risk. EBE further endorse that the different expectations for biosimilar process development (as outlined in biosimilar guidance) and process changes (for biosimilars or innovators alike covered by ICH Q5E) should be clearly distinguished in the forthcoming amended guidance.	
	EBE advocates the retention of some information from the original guideline The general focus of the Quality guideline should be retained including: • Clear scientific foundation based on requiring full module 3 as well as comparability between the biosimilar and reference product • Reference product must be approved and batch released in EU to ensure EMA/EU regulatory experience with the product, including the safety profile. • State of the art methods must be used both for manufacturing and for analytical/characterisation methods for biosimilars	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	• Limited differences between biosimilar and reference product may exist but must be justified, if necessary via nonclinical and clinical studies, ie an emphasis on the impact of any differences to safety and efficacy • Comparability exercise should include a comparison of the biosimilar and reference product drug substances, unless testing at the finished drug product stage can be justified. • Full adherence to ICH quality guidelines is expected • Relevance of comparison to a pharmacopoeia monograph alone is insufficient to conclude that an appropriate quality standard has been achieved. • Relevance of post-approval monitoring of product post initial authorisation or post-change implementation and the ability to identify products by invented name and batch therefore being of importance.	
	<u>Scope</u> • The current guideline (EMEA/CHMP/BWP/49348/2005) should be revised to clarify that the scope of the guidance relates to the requirements to support a biosimilar Marketing Authorisation Application and post authorisation, to avoid confusion with clinical trial applications submitted within the EU. • The complexity of the life-cycle management of a biosimilar is recognised as providing unique challenges that are not reflected within other product classifications. As such it would be appropriate to expand the scope of the current guideline to include some recommendations that are specific to biosimilars. It is not proposed that the scope of this guideline supersedes the elements addressed in ICH Q5E, but rather that it draws out specific challenges that are associated with biosimilars	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	and provides recommendations that are consistent with the principles outlined within ICHQ5E.	
	<u>Requirement to access drug substance from Reference Product</u> • The requirement to isolate drug substance from the Reference Product (medicinal product) should be dependent on the ability to complete suitable analytical assessment with the final drug product formulation. The demonstration of appropriate sample preparation and the absence of any interference with analytical techniques would be required. Proposed change (if any): • The guideline should be revised to confirm that the comparability exercise is required to be conducted with Biosimilar (drug substance and drug product) and Reference Product (drug product), and that the need to isolate drug substance from the Reference product is dependent on the ability to demonstrate suitable analytical assessment with the final drug product formulation. The demonstration of appropriate sample preparation and the absence of any interference with analytical techniques would be required.	
	<u>Stability</u> • It is anticipated that the shelf-life of the biosimilar (drug substance and Drug product) should be demonstrated and supported with an appropriate stability program which would be an exercise independent of the comparative stability exercise. The shelf-life of the biosimilar would not automatically be assigned the same shelf-life and storage recommendation as the reference product and could even be extended beyond that of the reference product, upon availability of suitable	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	stability data. It should be acknowledged that the comparative stability with the reference product might be demonstrated most effectively with the use of accelerated or stress stability conditions.	

	<u>Reference Product source</u>
	• EBE would welcome additional clarification on the regulatory expectations for reference products. EBE endorse the view that for data to be considered pivotal to approval, that the reference products should be a valid EU product (approved in the EU, with any non-EU sourced reference material demonstrated to be similar to the EU sourced material) approved in the EU on the basis of a complete dossier (ie in accordance with the provisions of article 8 of Directive 2001/83/EC, as amended).
	  ○ Notwithstanding, it is understood per ICH Q5E that there continues to be the need for comparability between different batches of reference products used in the phases of biosimilar product development.
	• The choice of reference product is of critical importance for the evaluation of a biosimilar application. The development of a biosimilar for global commercialisation may need to consider the reference product from a global perspective.
	• Biosimilar Applicants should make a valid comparison by choosing appropriate representative reference product samples to ensure comparability is not concluded inappropriately. We believe the guideline should remark on:
	  ○ Choice of batches should be random and in no way pre-selected for specific criteria or ranges of data for specific attributes	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	○ Applicants sourcing multiple reference batches should consider that this may not translate to multiple drug substance batches, as this can lead to a conclusion of a valid range of reference product data that reflects less experience than assumed. ○ Applicants may not be aware of the age of each batch (on the stability timeline) and may want to consider the impact on specific analytical results that may decrease/increase over time on assumptions for actual values. As preselection of specific batch criteria is not possible care should be taken when considering a assumed selection of a 'recent' batch as representative of the 'current' manufacturing process of the reference product. ○ Quantitative assessments alone may not provide a good assessment of batch to batch variability. Orthogonal methods should be recommended and utilized whenever appropriate. ○ The functional effects of some quality attributes may not be independent of one another. Multiple quality attributes of the reference product may shift together during its manufacturing history. In these cases, it may not be appropriate to assume that matching any attributes within their historical ranges would provide highly similar functional performance.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Problem Statement Process changes • EBE believes that the concept paper, as written, is open to interpretation, because it does not distinguish between "comparability" (comparison of process change made by same manufacturer) and "similarity" (comparison between processes of different manufacturers). • One way in which process changes are different to new process development is that a manufacturer planning process changes (to their own process) will normally involve a thorough risk assess of the likely impact of the change based on their existing knowledge/data on their process. This analysis is important in evaluating what potential new/change in purity profile can be expected and thereby what analytical methods need to be in place for the evaluation. Regulatory expectations for such quality risk assessments should therefore be well defined and based on scientific rigour. • Analytical studies for biosimilar product development must comprise a comprehensive side-by-side comparison of the biosimilar and reference product using sensitive and orthogonal biochemical,	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		biophysical, and biological techniques that focus on both the similarities and potential differences in quality attributes. • EBE considers it appropriate for a greater degree of evaluation to be required for more complex changes. • EBE also consider it would be inappropriate to constrain either originator or biosimilar manufacturers from making process changes should they need to (eg change in raw material supplier) or choose to (eg to improve process efficiency or ensure utilisation of state of the art technology over the lifecycle of the product). Existing ICHQ5E principles of demonstrating comparability to the pre-changed product remain. • Based on EMA experience with biosimilar approval, acceptable formulation changes and their justification could be discussed (e.g. ratio of active to excipients, use of alternative buffer excipients) • Guidance on the comparability exercise to be conducted following manufacturing process changes by the same manufacturer is provided in ICH Q5E (Comparability of biotechnological/biological products subject to changes in their manufacturing process - CPMP/ICH/5721/03, June 2005). This guidance is applicable to manufacturers of both reference and biosimilar products alike. • It should be clarified that evolution of biosimilar product quality profile will have no	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		impact on the innovator in terms of comparability requirement. • Intended guidance should also be clear that there is no intention for disclosure of confidential commercial information related to the manufacturing process or quality of the reference or biosimilar product.	
24-33		<u>Problem Statement</u> <u>Single or ongoing comparability</u> Text: *'the conclusion of a comparability exercise performed with a reference product at a given time may not hold true from the initial development of the biosimilar, through marketing authorisation'* • EBE propose that upon approval of a biosimilar, the requirement to demonstrate continued similarity to the Reference Product should cease. Having established that the biosimilar product is indeed similar to the Reference product, the comparability exercise for all subsequent changes to the manufacturing process biosimilar should be in accordance with ICH Q5E. In this sense 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, if the meaningfulness of minor	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		structural differences that result from process changes for the biosimilar need to be investigated, structural comparisons to both the historic dataset generated on the reference product during the biosimilar development and the current reference product could be useful, as considered on a case-by-case basis. • There is no legislative provision that requires an ongoing demonstration of similarity post-approval, but only of an ongoing favourable risk-benefit balance. • An ongoing analytical evaluation should not be required. There is no determination in Europe where the reference and biosimilar are deemed to be interchangeable without the intervention of the prescribing physician. In many member states Pharmacists are not permitted to automatically substitute products in Europe. Therefore, an ongoing analytical evaluation of similarity to the reference product should not be required. EBE continue to understand that the demonstration of initial analytical comparability/similarity does not assume a conclusion of product interchangeability and that the regulatory assessment for biosimilar approvability does not suggest the regulators have made an assessment of interchangeability of the biosimilar with its reference (or other products). A regulatory pathway would need to be established including further clinical data supporting interchangeability would be required for	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		this to be supported. • It is suggested that this section, when elaborated in the guidance, differentiates between the analytical and holistic aspects of the biosimilarity exercise. The wording suggests that analytical comparison alone may be sufficient to allow reference to safety and efficacy data from the originator. The conclusion of biosimilarity should be based on a holistic evaluation of comparative analytical, and as required, non-clinical and clinical studies performed. Biosimilarity does not require the products to be indistinguishable but any differences should be evaluated for their impact on safety and efficacy. In this context, the premise of the discussion appears to be that changes in quality attributes of the biosimilar or reference product during their respective lifecycles could impact the holistic conclusion of comparability of the biosimilar product. This should be true only to the extent that the changes would have a significant potential to influence the safety or efficacy of the drug product. Otherwise, the changes should not impact the conclusion of the overall comparability exercise. For example, as the originator or biosimilar product makes manufacturing changes they must evaluate the impact of their change on the quality of their product and potentially any impact on safety and efficacy. If the biosimilar manufacturer is unable to establish comparability (as	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		opposed to biosimilarity) to the previous version of the product additional non-clinical or clinical data may be required. This may also have an impact on the risk-benefit profile of the biosimilar. In either case this evaluation should be performed, in isolation, by the biosimilar sponsor making the proposed change, and, if implemented, the change should not impact the previous holistic conclusions of biosimilarity. Proposed change (if any): • If the text in the problem statement is intended to be used in the draft guidance it is proposed that it be modified as follows (additions in bold): *"the conclusion of **the analytical component of a** comparability exercise performed with a reference product at a given time may not hold true from the initial development of the biosimilar, through marketing authorisation, until the product's discontinuation.* The comparability exercise between the Reference product and a biosimilar will be conducted over several years prior to approval of the biosimilar, d*uring which time th**e Innovator Reference Product** may undergoing changes which could result in the evolution of the quality profile. The quality profile of the Reference product observed during the clinical development of the biosimilar should constitute a val*id range for the biosimilar as a target. As long as the Reference Product remains an approved product, it continues to	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		have acceptable safety and efficacy, regardless of the changes that may have been introduced. Thus at any point during the lifecycle of the Reference Product it should be possible to develop a biosimilar product. • The revised guideline should reflect that at anytime during the Innovator reference product life-cycle, a biosimilar can be developed and it is the responsibility of the Company developing the biosimilar to establish the quality profile of the Reference Product, using suitable analytical techniques and to demonstrate that the quality profile of the biosimilar product is similar to the reference product.	
39-40		<u>Evolution of the quality profile</u> • Once an innovator product is approved, changes are first and foremost implemented to improve process efficiency and reduce process variability since large variability normally leads to more OOS. Biosimilars may optimise their own process independently of the innovator process. The biosimilar process may be based on different cell systems, different fermentation and downstream purification protocols and different analytical methods, it therefore cannot be excluded that differences will appear over time. The potential impact on safety and efficacy of the biosimilar would have to be assessed in each case. • It is to be questioned if the evolution of quality profiles	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		throughout lifecycles should be considered as a critical aspect for similarity, and also for comparability for changes within a marketed product. Argumentation: Any changes in the biosimilar manufacturing process are evaluated to demonstrate that modifications would not adversely impact safety and efficacy of the biosimilar drug product compared with its reference product (or other products). • A similarity exercise performed with a reference product usually is not based on the quality profile of the reference product, as it is not publicly available, but on the available data relating to the safety and efficacy of the reference product. Moreover, differences in the quality profile of the similar product and the reference product are considered acceptable, as long as the safety and efficacy of the biosimilar meets the criteria for similarity. As a consequence, if a biosimilar has been shown to be comparable/similar in efficacy and safety, the evolution in quality profile during the product lifecycle in both, the reference and biosimilar product, should not affect the evaluation in terms of safety and efficacy. This is not true, if an evolution in quality profile is suspected to impact efficacy and safety, which according to the requirements set forth in ICH Q5E would not fulfil the comparability exercise. Current guideline states: "*Although the comparability exercise can be facilitated*	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		when the pharmaceutical form, formulation, strength, etc. of the similar biological medicinal product are the same as the reference medicinal product, other approaches may be considered by the applicant. "It shows that beyond the evolution of quality profile linked to manufacturing change, the overall Quality Target Product Profile can be different from the start and evolved. Perhaps rather than focusing on evolution of quality profile, discussion could be extended to evolution of QTPP.	
41-42		<u>Clarifying Expectations</u> Comment: It is seen as both important and relevant to provide more guidance on some expectations in addition to those specifically listed, eg structure, expression system and formulation sample preparation and others: • <u>Structure:</u> It should still be emphasized that a prerequisite for being a biosimilar is identity in amino acid sequence. Further, it is well known that posttranslational modifications may impact a product's clinical properties. • <u>Expression system</u>: the nature of the expression system impacts the quality attributes of the drug substance itself (eg glycosylation) and the process related impurities (eg host cell proteins). To minimise potential impact for the patient, a biosimilar product should ideally be based on the same host cell type as	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		the reference product. However, the use a different expression system should not preclude the demonstration of similarity. It is the responsibility of the Company developing the biosimilar to demonstrate similarity to the Innovator Reference Product – thus it may be feasible to use a different expression system within the same requirement to demonstrate similarity. Proposed change (if any): The revised guideline should confirm that the selection of a different expression system should not, per se, preclude the demonstration of similarity. Indeed in some cases the use of an alternative expression system may represent state-of-the-art technology which should not be excluded *per se*. It is the responsibility of the Company developing the biosimilar to demonstrate similarity to the Innovator Reference Product – regardless of the expression system. Any differences in the quality attributes that may result as a consequence, would need to be thoroughly investigated and should be considered within the analytical comparability, non-clinical and clinical program. • Formulation It is not a requirement that the formulation of the biosimilar be identical to the Reference Product. Indeed, it may not be feasible for the Company developing a biosimilar to access information on the supplier / grade / specification of	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		excipients (or container closure) approved for use with the Reference Product and as such it is necessary for the biosimilar to demonstrate the selection of an acceptable formulation, which may be independent of the Reference Product. The potential impact of the formulation on PK/PD profile would be investigated within the non clinical comparability program. Within the Quality exercise, comparative stability studies, e.g. under stress conditions, (between biosimilar and reference product) can support the demonstration of similar quality • Formulation sample preparation: whereas some quality attributes can be measured directly in the drug product, in many cases the drug product will be too dilute, have too many excipients and other additives and other confounding factors to allow a direct comparison. Since reference product drug substance is not normally commercially available, in such cases scientifically valid methods must be developed to ensure that adequate comparable data can be generated to cover all relevant quality attributes based on the available drug product. • Analytical methods: the importance of the adequacy and sensitivity of analytical and protein characterisation methods (eg potency and characterization assays) cannot be emphasized enough. Examples from the literature are available (eg	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		for somatropin) illustrating that standard/ pharmacopeial methods cannot be relied upon to ensure that new impurities are detected and identified. Without enough attention to this part of the comparability exercise, new impurities can go unnoticed.	

Please add more rows if needed.