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October 30, 2013

European Commission
Health and Consumers Directorate –General, Brussels
sanco-pharmaceuticals-d6@ec.europa.eu

Ref: EU Guideline on Similar Biological Medicinal Products
CHMP/437/04 Rev 1

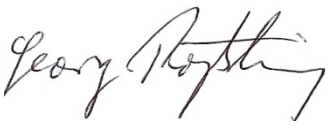
To the Committee for Medicinal Products for Human Use:

PDA is pleased to provide comments on this guideline submitted for public consultation. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our review was completed by an international group of expert volunteers with experience in biological medicinal products, regulatory affairs and GMP on behalf of our Regulatory Affairs and Quality Advisory Board and our Biotechnology Advisory Board.

To enhance clarity and consistency, PDA recommends this guideline make reference to existing directives and annexes in defining a biosimilar medicinal product including the recognition of the significance of the manufacturing process for the quality of a biosimilar. Reference should be made to the definitions of a 'biological' according to Directive 2001/83/EC, Annex I and also the EU 'Guideline on Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005) which states: "… the similar biological medicinal product is defined by the following two sets of characteristics: i) related to the characteristics of the molecule (including product related substances/ impurities), and ii) related to its process (which may affect molecular characteristics and includes process related impurities)."

If you have any questions, please contact me.

With very best regards,



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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 October 2013

Guideline on Similar Biological Medicinal Products
Comments from:

Name of organisation or individual
PDA (The Parenteral Drug Association)

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
Name	Comment	Decision to Submit/ withdraw comment
	To enhance clarity and consistency, PDA recommends this guideline make reference to existing directives and annexes in defining a biosimilar medicinal product including the emphasis on the significance of the -manufacturing process for the quality of a biosimilar. The 'physicochemical and biological characterisation' as stated e.g. in lines 83/84 and 151 of the current guideline is a much too weak argument for a 'biosimilar'. Reference should be made to the definitions of a 'biological' according to Directive 2001/83/EC, Annex I: "A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control." This is also explicitly stated in the EU 'Guideline on Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005): "Consequently, the similar biological medicinal product is defined by the following two sets of characteristics: i) related to the characteristics of the molecule (including product related substances/ impurities), and ii) related to its process (which may affect molecular characteristics and includes process related impurities)."	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	To enhance readability of the guideline, PDA recommends avoiding repetition of information in various parts of the document. Some examples are: (1) Executive Summary, lines 26-29, and chapter 1.2 Scope, lines 48-51: "where it is stated that 'the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency'."	

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)*
34		Comment: A biosimilar medicinal product cannot be a 'new' product in the sense of an innovative 'original' product. This is also addressed in Directive 2001/83/EC as amended, Section 4, Part II: *"When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product ..."* It is therefore recommended to delete the word 'new'. Proposed change (if any): *A company may choose to develop a ~~new~~ biological medicinal product claimed to be "similar" to a reference medicinal product, ...*	Decision to Submit/ withdraw comment
76		Comment: The definition of 'biosimilar' as provided in the current draft guideline is misleading and contradicts the definition as provided in Directive 2001/83/EC as amended: *"... the similar nature of two biological medicinal products, ..."* , Part II, 4.), whereas a 'biological medicinal product is defined as follows: *"A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control."* (Annex I, 3.2.1.1)	

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)*
		Proposed change: *"A biosimilar is a biological medicinal product that contains a ~~version~~ ~~of the active~~ **biological** substance **that is similar to** ~~of~~ an already authorised original biological medicinal product (reference medicinal product)."*	
77-78		Comment: For clarity PDA recommends modifying the wording. A biosimilar cannot demonstrate similarity, but an applicant has to do so. Proposed change: *"~~A~~ **B**iosimilar**ity** ~~demonstrates similarity~~ to the reference medicinal product **needs to be demonstrated** in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise."*	
80		Comment: To improve clarity, PDA recommends changing the phrase 'concept of a biosimilar'. Proposed change: It is recommended to replace as follows *In principle, the concept of ~~a~~ biosimilar**ity** is applicable to any biological medicinal product.*	
81		Comment: A 'similar' product cannot be a 'copy' of an original (which assumes to be a 1:1 version of the original); see also comment to line 76.	

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)*
		Proposed change: *"... to produce a product comparable ~~copy~~ to the reference medicinal product and demonstrate the similar nature of the concerned products."*	
83-84		Comment: The significance of the manufacturing process to the quality of a similar biological medicinal product needs to be considered in the biosimilarity concept (see also 'General Comments' and comment to line 151). Proposed Change: *"This includes physicochemical and biological characterisation **as well as any characteristics related to its manufacturing process** and requires knowledge on how to interpret any differences between a biosimilar and its **biological** reference medicinal product."*	
133		Comment: In order to avoid uncertainty about the exact expectations of an applicant to 'establish' that a 'non-EU-comparator product' is a representative of the reference product, it is recommended to revise the sentence by exchanging the verb 'establish' by 'demonstrate'. Consistent with the biosimilar approach, scientific data must ‘demonstrate’ that comparator material authorised outside the EEA is representative of the reference product authorised in the EEA." Proposed Change: *"In addition, it will be the Applicant's responsibility to ~~establish~~ **demonstrate** that the comparator*	

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)*
		authorised outside the EEA is representative of the reference product authorised in the EEA."	
151		Comment: The significance of the manufacturing process to the quality of a similar biological medicinal product needs to be considered in the biosimilarity concept (see also 'General Comments' and comment to line 83-84). Proposed Change: *"A biosimilar should be highly similar to the* ***biological*** *reference medicinal product in physicochemical and biological terms,* ***taken together with the production process and its control."***	

Please add more rows if needed.