Comments and suggestions from reviewers

Title: WHO Questions and Answers: Similar Biotherapeutic Products (WHO/BS/2018.2352)

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Question No. /page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
General/Overall comment				
	The World Health Assembly requested to "update the 2009 guidelines" Although the Q&A document mentions in its background that "In April 2015, an informal consultation on the possible amendment of the Guidelines was organized. All participants from national regulatory authorities (NRAs) from both developing and developed countries, as well as industry recognized and agreed that the evaluation principles described in the WHO Guidelines were still valid, valuable and applicable in facilitating the harmonization of			

	SBP requirements globally. It was therefore concluded that there was no need to revise the main body of the existing guidelines on SBPs", we encourage the WHO Secretariat to attend the request made by the WHA to the DG "(4) to convene WHO's Expert Committee on Biological Standardization to update the 2009 guidelines, taking into account the technological advances for the characterization of biotherapeutic products and considering national regulatory needs and capacities and to report on the update to the Executive Board" through the resolution WHA67.21. An informal consultation can not reverse a request of the World Health Assembly This consideration takes particular importance due to the fact that, as the Q&As' background says, "These Q&As are produced for guidance only and should be read in conjunction with relevant WHO guidelines". Therefore, even if the Q&As may address the need raised by the WHA ("taking into account the technological advances for the characterization of biotherapeutic products and considering national regulatory needs and capacities"), the primary WHO source on this matter are the 2009 guidelines. While kindly insisting on the above, we proceed with our comments with regards to specific aspects of the "WHO Questions and Answers: Similar Biotherapeutic Products" (WHO Q&A)	
Background		
	The need for an update of the WHO 2009 guidelines is evidenced by the background of the WHO Q&A. Its focus, of both the guidelines and the Q&A, needs to emphasize: ● *The importance of having WHO regulatory guidelines that consider national regulatory capacities.* There are three expressions in the background that reflect that WHO approach towards biologics regulation is still missing to consider national regulatory capacities: 1) "... in some countries and for a variety of reasons, biotherapeutic products have been licensed as generics or as small molecule drugs using data which do not now meet current WHO regulatory **expectations**" 2) "...WHO has convened meetings to identify the **needs**, as well as the parts of the guidelines which should be updated." 3) "All participants from NRAs from both developing and developed countries, as well as those from industry, recognized and agreed that the evaluation principles described in WHO's 2009 Guidelines on evaluation of similar	

biotherapeutic products (SBPs) were still valid, valuable and applicable in facilitating the **harmonization of SBP requirements globally**."

Considering national regulatory capacities of all national regulatory authorities (NRAs) implies that the regulatory guidelines encouraged by WHO are the basic and essential regulations needed that can be met by all NRAs and not the highest unnecessary standards, which are possible to be achieved only by NRAs of high income countries.

- *WHO's regulatory approach on biologics needs to permanently promote the possibilities that scientific advances provide for the marketing authorization of SBPs*

  The background says "WHO's Guidelines on evaluation of similar biotherapeutic products (SBPs) (also called "biosimilars"), adopted by the WHO Expert Committee on Biological Standardization (ECBS) in 2009, have raised awareness of the complex scientific issues related to the licensing of SBPs." This affirmation clearly shows that WHO is still pending to emphasize within its general discourse the possibilities that scientific advances provide for the characterization of SPBs, and therefore, for its marketing authorization.

  The scientific and technical advances and the advanced state of the art of the analytical procedures, make of them the key in the process of biologics' characterization. In other words, the argument of the complexity of biotechnological drugs as an impediment to their characterization is false, to the extent that science and technology have been developing highly specific analytical processes that have resolved the complexity of these drugs.

- *The importance of having WHO's regulations on biologics that are guided by a principle of affordability of these medicines.*

  The scope and approach of the "Resolution on Access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy"[1][1] (WHA67.21) timely brought into the discussion the necessary consideration of biologic medicines to be affordable and of quality. Considering that quality is the only important focus for the regulation of biologic medicines misses the need for quality medicines to be affordable for countries and people.

[1] http://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf#page=25

	Affordability of biologics matters. “Currently, most high-cost medications are biotechnological. The exponential increase in health spending associated with their high prices represents a factor of the first order in the crisis of the systems of health, characterized by the difficulty of providing people with services and products that meet your needs.”[2] Therefore, the importance of promoting competition in biologics market through a regulatory framework that takes into account the technological advances for the characterization of biotherapeutic products. ● *Therapeutic benefits of biotherapeutic products are subject to continuous evaluation* The WHO Q&A background states “Very little is known about the safety and efficacy of these individual products”, making reference to “biotherapeutic products (that) have been licensed as generics or as small molecule drugs using data which do not now meet current WHO regulatory expectations.” This affirmation needs to be adapted since are the therapeutic benefits of all biotherapeutic products the ones that are, and should be, subject to a continuous evaluation.			
I. Concept for licensing similar biotherapeutic products (SBPs):				
QI-1 / Page 8 and lines 7 - 9	In addition to “SBP”, a variety of terms – such as “similar biological medicinal products”, “biosimilar products”, “follow-on protein products” and “subsequent-entry biologics” – have been used to describe these products.	Due to the psychological burden of the expressions “similar”, “follow-on” and “subsequent-entry” on the prescribers and patients, and its subsequent effects on the success of pro-competition initiatives in the pharmaceutical market that aim at increasing access and decreasing public expenditure, we kindly request to include the expression “biocompetitors”	In addition to “SBP”, a variety of terms – such as “similar biological medicinal products”, “biosimilar products”, “follow-on protein products”, “subsequent-entry biologics” and “biocompetitors”– have been used to describe these products.	
QI-2 / Page 9 and lines 29 - 32	The demonstration of high similarity is based on an	Since it is expected that the evolution of science will lead us	The demonstration of high similarity is based on an	

[2] http://www.mision-salud.org/wp-content/uploads/2015/06/Medicamentos-Biol%C3%B3gicos-sin-Barreras.pdf

	extensive head-to-head comparability exercise consisting of comparative state-of-the-art physico-chemical, structural and in vitro functional tests, as well as nonclinical and clinical studies.	to the point of not needing clinical studies to demonstrate therapeutic equivalence of biologic medicines and its reference product, we kindly request to make reference to this perspective in the text.	extensive head-to-head comparability exercise consisting of comparative state-of-the-art physico-chemical, structural and in vitro functional tests, as well as nonclinical and clinical studies, although it is expected that the evolution of science will bring the possibility of not needing clinical studies to demonstrate therapeutic equivalence of a biologic medicine and its reference product.	
QI-3 / Page 10 and lines 11 - 12	In some countries, for various reasons, biotherapeutic products were licensed as generics or as small molecule drugs using data that do not meet current WHO regulatory expectations.	More than expectations, WHO provide recommendations for NRAs	In some countries, for various reasons, biotherapeutic products were licensed as generics or as small molecule drugs using data that do not meet current WHO regulatory recommendations.	
QI-3 / Page 10 and line 13	Often little is known about the safety and efficacy of the individual products.	We kindly request to eliminate this sentence since safety is under permanent evaluation for all biotherapeutic products	(delete sentence)	
V. Clinical evaluation:				
QV-2 / Page 26 and lines 35 - 36	According to WHO guidelines, all new therapeutic proteins, including SBPs and RBPs, should be tested for ADAs in clinical trials.	By definition SBPs are not new therapeutic proteins.	According to WHO guidelines, all new therapeutic proteins, such as RBPs, should be tested for ADAs in clinical trials.	
QV-2 / Page 27 and lines 1 - 4	For final confirmation, an SBP is always compared head-to-head to its RBP in pre-marketing clinical trials to demonstrate comparable PK,	The composition of this sentence goes against what has been correctly stated in parts of the document: - "The purpose of the	Depending on the case (see QV-12) SBP could need to be compared head-to-head to its RBP in pre-marketing clinical trials to demonstrate its	

	immunogenicity, efficacy and immune-mediated adverse effects.	clinical comparability programme for an SBP is to confirm similarity to the RBP rather than independently to establish its own efficacy and safety profile." (QV-1) (underscored out of the text) - "some pre-licensing clinical data are always required for an SBP but the clinical development can be abbreviated, as outlined by the WHO guidelines for SBPs." (QV-12) (underscored out of the text)	similarity to the RBP.	
QV-6 / Page 28 and lines 32 - 33	Immunogenicity studies should be integrated in the clinical comparability studies because the purpose is to detect harmful immunogenicity.	It is important to modify this sentence considering: - The evolution of science and the possibility that it will bring to avoid clinical studies. - QV-12	Up to now, immunogenicity studies are integrated in the clinical comparability studies for most cases because the purpose is to detect harmful immunogenicity (See **QV-12**).	
QV-6 / Page 29 and lines 1 - 3	If other kinds of PD studies are conducted, additional specific immunogenicity studies may be needed pre- or post-marketing unless the product is expected to have a low risk of immunogenicity.	It is understandable that in products with low risk of immunogenicity there is no need for further studies. When there is a residual uncertainty on immunogenicity with regards to a PD study of products with a reasonable doubt of it, it is not possible to address the uncertainty through an additional clinical study. In those cases, are the post	If other kinds of PD studies are conducted, post marketing surveillance and the follow up patient by patient are the ones that address the management of the risk of immunogenicity, unless the product is expected to have a low risk of immunogenicity.	

		marketing surveillance and the follow up patient by patient the ones that address the management of the risk of immunogenicity		
QV-8 / Page 30 and lines 6 - 7	In these cases, additional PK/PD or clinical trials may be needed to address the residual uncertainty.	To complement the PK/PD trials, what we consider necessary to address the residual uncertainty is a deep analysis of the disease and the condition of each patient in particular	In these cases, additional PK/PD or clinical trials may be needed to address the residual uncertainty.	
QV-12 / Page 31 and lines 13 - 15	As noted in *WHO's Guidelines on evaluation of similar biotherapeutic products (SBPs)*, the demonstration of comparability of an SBP to its RBP in terms of quality is a prerequisite for the reduction of the nonclinical and clinical data set required for licensure.	There is need to clarify that it refers to analytical comparability	As noted in *WHO's Guidelines on evaluation of similar biotherapeutic products (SBPs)*, the demonstration of analytical comparability of an SBP to its RBP in terms of quality is a prerequisite for the reduction of the nonclinical and clinical data set required for licensure.	
QV-12 / Page 31 and lines 15-16	Thus, the WHO guidelines mention the reduction but not the complete omission of clinical data.	It is important to modify this sentence considering the evolution of science and the possibility that it will bring to avoid clinical studies.	Thus, up to now, the WHO guidelines mention the reduction but not the complete omission of clinical data.	
QV-12 / Page 31 and lines 37 - 38	In conclusion, some pre-licensing clinical data are always required for an SBP but the clinical development can be abbreviated, as outlined by the WHO guidelines for SBPs.	It is important to modify this sentence considering the evolution of science and the possibility that it will bring to avoid clinical studies.	In conclusion, given the current state-of-art of physico-chemical, structural and *in vitro* functional tests, some pre-licensing clinical data are always required for an SBP but the clinical development can be abbreviated, as outlined by the WHO guidelines for SBPs.	