**Comments of the Biotechnology Industry Organization (BIO)
to the Dirección General de Medicamentos, Insumos y Drogas
(DIGEMID) of Peru**

21 March 2013

Re: Sanitary Directive that Regulates the Submission and Content of the Documents Required in the Registration and Re-Registration of Biological Products: Biotechnological Products

About BIO and the Biotechnology Industry

As a global organization, the Biotechnology Industry Organization (BIO) appreciates the opportunity to provide the views of its members on the proposed *Sanitary Directive that Regulates the Submission and Content of the Documents Required in the Registration and Re-Registration of Biological Products: Biotechnological Products*, hereinafter referred to as "Directive."

BIO is a not-for-profit trade association representing more than 1,100 companies, universities, research institutions, investors, and other entities in the field of biotechnology across the United States and in more than 32 countries. The vast majority of our members are small- and medium-sized enterprises working to develop and commercialize cutting-edge products in the areas of healthcare, agriculture, energy, and the environment. Since its inception roughly 30 years ago, the biotechnology industry has spurred the creation of more than one million direct jobs, and millions of related jobs in countries throughout the world.

The biotechnology industry has developed hundreds of innovative products that are helping to heal, feed, and fuel the world. In the healthcare sector alone, this industry has developed and commercialized more than 300 biotechnology therapies, cures, vaccines and diagnostics that are helping more than 325 million people worldwide who are suffering from cancer, HIV/AIDS, diabetes, and numerous other serious and debilitating diseases and conditions. In the agricultural field, biotechnological innovations are boosting crop yields and food supplies, increasing farm incomes, and improving agricultural sustainability. BIO members are also developing the next generation of biofuels and other renewable energy sources in order to reduce climate change and dependence on fossil fuels, while still others are focused on bio-based products and other technologies to help clean and sustain our global environment.

General Comments on the Registration and Approval of Biological Products

BIO commends the Government of Peru for its endeavor to create a pathway for the approval of biological and biotechnological products. Peru is a growing market for biotechnology products and with the implementation of the US-Peru TPA, it promises to become an even bigger market. Before making specific comments, BIO would like to take this opportunity to express its general views on the regulation of biological products.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6301 F
bio.org

BIO believes that it is critically important to ensure that patent safety is not compromised and that incentives for innovation are preserved.

First, patients should not have to sacrifice safety or accept greater risks in using a biological product, whether an innovator or biosimilar product. For patient safety, it is important that sufficient data, including clinical trials, are required for biosimilar products. Because biological products are much larger and more complex than small molecule chemical drugs, biologics cannot be scientifically characterized to the same degree as small molecule drugs. For this reason, many foreign regulatory agencies have established a high threshold for determining similarity of biological pharmaceutical products. These safety concerns also led the World Health Organization (WHO) to adopt *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs*),[1] hereinafter referred to as "WHO Guidelines," to serve as a model for regulatory health authorities.

Second, with respect to the approval of biological products that follow the innovator drug of biological origin, it is important to ensure that intellectual property rights are respected. In this regard, it is essential that data exclusivity is provided for the clinical and test data generated and submitted to regulatory authorities to support the approval of biological pharmaceutical products. The test data required by governments for approval of innovator biologic products requires enormous investment and is proprietary and thereby deserving of adequate protection. In addition, a similar biological product should not be approved until all statutory protections, including data exclusivity and patent protections, have expired. Therefore, while BIO supports the creation of an abbreviated pathway for biosimilars, providing effective intellectual property protection for biologics is a key focus for BIO. Measures that operate to lessen the economic incentive for developing and commercializing biologics translate into fewer products and therapies, to the detriment of patients with unmet medical needs.

We have divided our specific comments to the Directive into first tier priorities, which are outlined below, and additional technical concerns.

Key Issues not Addressed in Directive

BIO is concerned that several topics of importance do not appear to be reflected in the Directive. For example, BIO notes that the issue of pharmacovigilance is noticeably absent. This is especially important for biosimilars because adverse effects are unlikely to be encountered in the limited clinical trials for a biosimilar. Hence, careful post-marketing monitoring of the safety is necessary. As per the WHO Guidelines, the manufacturer of the proposed biosimilar should submit a "pharmacovigilance plan at the time of submission of the marketing authorization application."[2] Moreover, any specific safety monitoring plan imposed on the RBP should be incorporated into the pharmacovigilance plan for the biosimilar. Further, attribution

[1] http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
[2] WHO Guidelines, section 11, pages 11-12.

measures to facilitate identification of similar biologics, i.e., traceability, should also be required for effective pharmacovigilance.[3] BIO urges that the Directive incorporate WHO-consistent pharmacovigilance requirements and standards.

BIO also notes that other topics of importance do not appear to be adequately represented in the Directive. These include the recognition of the issues relating to interchangeability/substitution Due to the fact that biosimilars, by definition, are similar and not identical to the reference products at issue, current science does not support automatic substitution of one biologic product for another. Determinations of this nature, e.g., to alter a treatment regimen, must be made by physicians in consultations with patients, and requires consideration of immunogenicity and other facts to ensure patient safety.

In addition, the Directive does not address indication extrapolation. Extrapolation of indications may be allowed in certain circumstances but only when certain preconditions are met to ensure patient safety, i.e., when CMC/quality and non-clinical data demonstrate high similarity to the reference product; head-to-head clinical comparative and equivalence studies demonstrate high comparability between the RBP and biosimilar products; the mechanism of action and/or the receptor(s) of the innovator reference product is the same across all indications intended for extrapolation; and equivalence and clinical comparative studies have been performed in the most sensitive indication or, if pertinent, in a well-defined and understood population of the patients most sensitive to the effects of the biosimilar within that indication. The Directive should be clarified to reflect these standards.

The Directive also fails to articulate requirements for naming and labeling. Such requirements, consistent with WHO practices, are important for accurate prescription by health care professionals to avoid risks of inappropriate substitution, and for traceability and pharmacovigilance. For each biologic product, there must be a way to identify and link the discrete data sets associated with the product so that physicians can make the best decision for their patients. As such, each product must have a unique identifier that allows this discrete data to be collated. The unique identifier should allow for a product to be identified as an innovator or a product approved as highly similar.

Specific Areas of Concern

A) Concerns Regarding the "Similarity" Pathway

BIO applauds the Ministry of Health for proposing distinct pathways for marketing approval of innovator and similar biologics. In particular, BIO appreciates that Section 6.3 of the Directive, which permits approval of a non-innovative drug product based on a comparison to a reference biological product (RBP), establishes distinct criteria for

[3] WHO Guidelines, section 11, page 12.

biosimilars based on standards and recommendations in the WHO Guidelines. BIO supports the creation of a similarity pathway, which is generally consistent with WHO Guidelines and the approach taken by other experienced foreign regulatory agencies. However, BIO believes that several important aspects of the Directive require clarification or modification.

1) Definition of Similarity

While Section 5 of the Directive defines "similarity" in general terms, the Directive does not provide clear criteria by which to judge whether similarity has been achieved. In this regard, it is important to recognize that the terms "similarity" and "comparability," which are used interchangeably in the Directive, are distinct concepts. A showing of comparability between two products permits manufacturers of innovator products to make post-approval changes to their products. In contrast, the sponsor of a biological product, which is not the innovator product, but purports to be similar, would not have access to the cell line or the clinical manufacturing processes that are essential to production of the innovator product. In these cases, it will be necessary to perform a complete analytical comparison with the innovator's product in support of approval of the biosimilar. This recognition serves to clarify the extremely important point that information contained in documents concerning changes within a company's own processes are not to be considered as adequate scientific guidance for the development of similar biological medicinal products by a second company. Therefore, the term "comparability" should be reserved for such evaluations, and should not be used to describe the process of evaluating biotechnology products from different manufacturers.

BIO also notes that the Directive does not provide an adequate explanation of the similarity exercise. As described in the WHO Guidelines, the similarity exercise should be designed to "show that the [biosimilar] has highly similar attributes when compared to the [innovator's product]."[4] This requires a head-to-head comparison between the biosimilar and the referenced biologic, compared in the same quality, non-clinical, and clinical studies using the same procedures.[5] The Directive should be modified to expressly convey these definitions and requirements, given that, without them, the justification for a reduced package of clinical and non-clinical data is not scientifically supported.

2) Reference Biological Product (RBP)

BIO is concerned that Section 6.3.1.2 of the Directive appears to allow the biosimilar applicant a choice between using an RBP licensed by ANM or an RBP licensed by a foreign regulatory authority. Such an approach raises important safety and regulatory considerations. WHO Guidelines highlight the benefits of relying on an in-country or domestically licensed RBP, such as familiarity and experience with the

[4] WHO Guidelines, section 5, page 8.
[5] WHO Guidelines, section 5, page 8.

product by the in-country regulators, including a greater degree of pre-approval and post-marketing data.[6] Moreover, other regulatory agencies, including the European Medicines Agency, the U.S. Food and Drug Administration, and Brazil's ANVISA require the use of a domestically licensed RBP, which has been approved based on a full dossier.

BIO recognizes that both WHO and ANVISA acknowledge that, when there is no domestic RBP available, it may be appropriate to use a foreign RBP; but in such a case, ANVISA only allows such use when that foreign regulatory agency adopts "technical-scientific criteria similar to ANVISA criteria, and when there is a possibility of full and unrestricted access to the registration information for ANVISA."[7] Similarly, WHO recommends that a foreign RBP should be "licensed and widely marketed in another jurisdiction which has well-established regulatory framework and principles, as well as considerable experience of evaluation of biotherapeutic products, and post-marketing surveillance activities."[8] With respect to biological products approved by foreign regulatory authorities, Section 6.3.1.2 of the Directive recognizes that a biosimilar application may reference a biological product so long as the product was "authorized and commercialized in high sanitary surveillance countries." For safety reasons, BIO strongly recommends that "high surveillance countries" be further defined in the Directive using the WHO definition for "Stringent Regulatory Authority," and that other details regarding when such use of a foreign RBP may be appropriate be added into the Directive as well. Most important, BIO urges that the Directive be clarified to require the use of a domestically approved RBP whenever available, rather than giving biosimilar applicants the option to ignore a Peruvian-approved potential RBP.

BIO also recognizes that, even where there is a domestic RBP, there may be situations when it would be useful to supplement a "similarity" application with data from a foreign-approved comparator to the Peruvian-approved RBP. BIO cautions, however, that this is only appropriate when bridging data demonstrate that the foreign comparator is fully representative of the Peruvian-licensed RBP. It bears emphasis that there is a high scientific hurdle in establishing the scientific bridge necessary to support the use of such foreign comparative data. Such data should only be used when both the foreign and the Peruvian RBP are released by the same manufacturer, and the fundamental support for a biosimilar must include at least one adequate and well-controlled clinical trial comparing the immunogenicity profiles of the proposed biosimilar and the Peruvian RBP. Furthermore, foreign comparative data are generally not appropriate for particularly complex biological products. BIO urges that the Directive clarify that the use of data regarding a foreign-sourced comparator to the domestic RBP may be permitted provided the applicant establishes that the foreign-sourced product is representative of the domestic RBP through extensive analytical comparison.

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[6] WHO Guidelines, section 7, pages 9-10.
[7] ANVISA National Health Surveillance Agency Collegiate Board Resolution, RDC No. 55, December 16, 2010, Article 27, para. 2.
[8] WHO Guidelines, section 7, page 10.

3) Good Manufacturing Practices

BIO notes with appreciation that Section 6.3.2.2 of the Directive provides that the manufacturer must demonstrate "the consistency and the robustness of the manufacturing practices." Nonetheless, in order to guide industry and ANM decisions regarding good manufacturing practices, the Directive should establish appropriate and distinct criteria, consistent with WHO Guidelines, for assessing good manufacturing processes. WHO Guidelines emphasize that "[t]he manufacturing process should meet the same standards as required … for originator products."[9] This requires the biosimilar manufacturer to implement standards adopted by the WHO regarding good manufacturing practices for biological products.[10] BIO respectfully requests the Directive be amended to ensure that manufacturers of biosimilars comply with WHO standards regarding good manufacturing practices.

4) Clinical Studies

BIO is concerned that Section 6.3.3.2 of the Directive does not provide overarching criteria for designing clinical studies for biosimilars. It is necessary not just that the clinical studies be completed, but that they must be designed to show that the biosimilar product is as safe and effective as the chosen RBP. As stated in the WHO Guidelines, "[c]linical studies should be designed to demonstrate comparable safety and efficacy of the SBP [biosimilar] to the RBP and therefore need to employ testing strategies that are sensitive enough to detect relevant differences."[11]

More importantly, the Directive fails to adequately address the parameters of efficacy studies. In order to ensure that a biosimilar is clinically effective as the RBP, efficacy studies should be designed to enable detection of potential differences between the RBP and biosimilar. As per the WHO Guidelines, similar efficacy of the biosimilar and the RBP should be demonstrated in randomized and controlled clinical studies following the principles laid down in relevant ICH guidelines.[12] In addition, WHO Guidelines provide significant guidance regarding the advantages and disadvantages of equivalence and non-inferiority designs for SBPs.[13] BIO respectfully urges that the Directive include WHO-consistent standards for evaluating efficacy studies.

C) Implications for Innovation & Development of Biologics

BIO notes that the proposed Directive does not provide meaningful intellectual property protection. In order to preserve incentives to research, develop, manufacture,

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[9] WHO Guidelines, section 8.1, page 10.
[10] See WHO Guidelines, section 8.1, page 11. See also *Good Manufacturing Practices for Biological Products: WHO Expert Committee on Standardization,* Forty-Second Report, 1992, Annex 1 (WHO Technical Report Series, No. 822).
[11] WHO Guidelines, section 10, page 19.
[12] WHO Guidelines, section 10.4, page 21.
[13] WHO Guidelines, section 10.4, pages 22-25.

and launch new therapies for Peruvian patients suffering from debilitating and life-threatening conditions, as well as to develop and secure approval of new indications for such products, it is critical that Peru's similarity pathway include meaningful protections against unfair use of the innovator's intellectual property and regulatory dossiers. Such protection also will help to enhance patient safety and access to novel biologics in Peru. In particular, BIO urges Peru to incorporate the following principles in its Directive.

1) *The similarity pathway must respect innovators' intellectual property and other legal rights.*

Of critical importance to BIO, the Directive must include measures that provide exclusivity for the clinical and test data that are generated and submitted to regulatory authorities to support the approval of biological pharmaceutical products. Peru has obligations under Article 39(3) of the TRIPS Agreement to provide data exclusivity for pharmaceutical products against unfair commercial use and under Article 16.10 of the US-Peru TPA to provide a minimum period of data exclusivity for pharmaceutical products against reliance by third parties on the data supplied by the innovator to the relevant Peruvian authorities. During this period of exclusivity, manufacturers of biosimilars are prevented from relying on the innovator's data or any health authority's prior approval of the innovator biologic to support approval of a biosimilar product. Such data exclusivity is necessary to provide the necessary incentives for innovators of pharmaceutical products to perform the difficult, time consuming, risky and expensive trials needed to establish that a new pharmaceutical compound is safe and effective. This, in turn, prevents unfair competition in the marketplace and incentivizes innovation and investment in Peru. In the United States, for example, the term of such protection is 12 years measured from the date of marketing approval. Comparably, Europe provides 10-11 years of data and market exclusivity for innovative pharmaceutical products. Japan and Canada provide 8 years of data exclusivity for biologics while Korea and Australia provide 6 and 5 years of exclusivity for biologics, respectively. Thus, there is a consistent global practice of providing exclusivity for test data generated for biological products.

Moreover, BIO would like to emphasize that any biosimilar pathway should also fully respect trade secret protection for certain innovator information, e.g., chemical analyses and manufacturing processes, which must be submitted as part of the new biological product approval process. Such protection should include not permitting third parties to use this information for the purposes of approving biosimilar products.

Furthermore, biosimilars should only be approved in Peru after all statutory protections, including regulatory data protection and patent protections, are no longer available for the approved innovator biologic. It is also important to ensure that there is appropriate implementation of "patent linkage" provisions, as set forth in Article 16.10.3 of the US-Peru TPA. "Patent linkage" provisions will ensure that an innovator receives adequate notice of an application referencing its product or data, so that any legal challenge involving the biological can be resolved promptly and prior to marketing approval of a biosimilar.

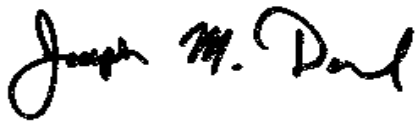
2) *If there is an applicable reference product approved for marketing in Peru, a biosimilar applicant should not be permitted to circumvent Peruvian IP protection by relying on a foreign reference product.*

If a relevant reference product is approved in Peru, a biosimilar applicant should not be permitted to circumvent Peruvian patent or data protection laws by referencing a foreign-approved product. Adopting such a policy would provide incentives for innovators to timely enter the Peruvian market by ensuring that approval of a full dossier would permit approval of a competitor product via the similarity pathway only after the period of protection afforded to Peruvian-approved products. This policy would also support greater patient safety because Peruvian regulators would have more pre-approval data regarding Peruvian-approved reference products, as well as post-approval data from actual use of the innovator product by the Peruvian population. Furthermore, the innovator generally takes on important patient safety and access responsibilities in markets in which it launches, including patient education, assistance programs, physician education and training on the benefits, risks, and proper use of the products, and the development of data and validation techniques for public and private payers necessary to secure coverage and reimbursement for patients seeking access to such products. Thus, it is important for Peru's overall biologics regulatory system to maintain important incentives for innovators to seek approval and launch novel medicines in the Peruvian market by preventing biosimilar competitors from circumventing innovator protections.

Conclusion

We commend the Government of Peru for taking steps towards developing a sanitary regime for drugs of biological origin. We also appreciate the opportunity to express our views and welcome the opportunity to discuss them further. For additional information regarding the positions of the Biotechnology Industry Organization, please see http://www.bio.org/category/biosimilars.

Respectfully submitted,



Joseph Damond
Senior Vice President, International Affairs
Biotechnology Industry Organization (BIO)

Biotechnology Industry Organization

ADDITIONAL CONSIDERATIONS

SECTION	COMMENTS
Section 2	
Section 2: Objective	The objective should be clarified to include the registration for biosimilar products.
Section 5	
Section 5: General Provisions **5.1.8 Equivalence clinical trials**	Equivalence trials do not strictly look at establishing that a new intervention is "at least" as effective as an established one. The terminology "at least" implies using just one margin, a lower one, which makes it indistinguishable from a non-inferiority trial.
Section 5: General Provisions **5.1.9 Non-inferiority clinical trials**	It is inappropriate to assume that non-inferiority is established by the product if it is not worse that the comparator in a "small and pre-specific" amount. Margins are narrower or wider depending on previous experience with the product.
Section 6	
Section 6: Specific Provisions **6.2.4 Stability studies of API and finished product**	This section should include a specific reference to the Sanitary Directive mentioned.
Section 6: Specific Provisions **6.2.8.1 Analysis of pre-clinical studies**	This section should also include a statement requesting the justification for the *in vivo* model used and its relevance to the target human disease(s).

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6301 F
bio.org

Section 6: Specific Provisions **6.2.8.2 Summary of pre-clinical studies** **6.2.8.3 Report of pre-clinical studies** **6.2.9.2 Summaries of the clinical studies** **6.2.9.4 Reports of PK studies**	These sections should include a reference to the pertinent ICH Guidelines mentioned.
Section 6: Specific Provisions **6.2.8.1.2 Analysis of pre-clinical studies**	It is a misstatement to allow *in vitro* studies to be the sole basis for an integrated and critical analysis of pharmacological evaluation, PK, and toxicology. Instead, it is *in vivo* animal testing that defines these pre-clinical features.
Section 6: Specific Provisions **6.2.9.3 Clinical Findings** **6.2.9.4 Reports of PK studies**	These sections do not reflect Phase II, dose-ranging, clinical studies, which are performed in the clinical development phase of any biotherapeutic.
Section 6: Specific Provisions **6.2.8 Pre-clinical studies** **6.2.9 Clinical studies** **6.2.10 Risk plans**	These sections do not make any reference to immunogenicity in pre-clinical and clinical studies. An evaluation of Immunogenicity should be added given the importance of immunogenicity assessment and its RMP for any biotherapeutic.
Section 6: Specific Provisions **6.3 Similarity route**	This section provides an incomplete list of excluded biologics. Allergens, as well as gene, cell, and tissue therapies should be excluded.

6.3.1.1 Scope	
Section 6: Specific Provisions **6.3 Similarity route** **6.3.3 Pre-clinical and clinical studies**	Any change in the manufacturing of a biosimilar during the similarity exercise should be reported and a comparability pre- and post- manufacturing change following ICH and Q5E should be carried out showing that both versions are highly similar.