



04 October, 2013

National Center for Standards and Certification Information (NCSCI)
National Institute of Standards and Technology (NIST)
100 Bureau Drive, MS-2160
Gaithersburg, MD 20899-2160

**Re: World Trade Organization Committee on Technical Barriers to Trade
Colombia Notification G/TBT/N/COL/196: *Proyecto de Decreto del Ministerio de Salud y Protección Social "Por el cual se reglamenta, para propósitos del registro sanitario, el procedimiento de evaluación de calidad, seguridad y eficacia de los medicamentos biológicos y se dictan otras disposiciones"* (Draft Ministry of Health and Social Welfare Decree "Regulating the procedure to assess the quality, safety and efficacy of biological medicines for sanitary registration purposes, and adopting other provisions").**

To Whom It May Concern:

The Biotechnology Industry Organization (BIO) appreciates this fourth opportunity to formally respond to the Colombian Ministry of Health's Draft Decree on Regulatory Requirements for the Registry of Medicines of Biological Origin and we refer you to our previous comments filed to the Colombian Ministry of Health on April 24th 2012¹, June 12th 2012² and February 21st 2013³ for background about BIO and its interest in this Decree. These comments respond to the fourth draft of the proposed Decree, notified to the World Trade Organization's (WTO) Committee on Technical Barriers to Trade on July 19th, 2013 (G/TBT/N/COL/196).

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 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products,

¹ BIO Comments to Colombian Ministry of Health, <http://www.minsalud.gov.co/PoliticasyFarmaceuticas/Biotecnologicos/Comentarios%20recibidos%20biotecnologicos%20-%201%20ronda/BIO%20Comments%20on%20Colombia%20Biologics%20Regulations%20FINAL.pdf>.

² BIO Comments to Colombian Ministry of Health, <http://www.minsalud.gov.co/PoliticasyFarmaceuticas/Biotecnologicos/Comentarios%20recibidos%20-%202%20ronda/BIO%20Comments%20on%20Revised%20Colombia%20Biologics%20Regulations%20FINAL.pdf>.

³ BIO Comments to Colombian Ministry of Health, <http://www.minsalud.gov.co/PoliticasyFarmaceuticas/Biotecnologicos/Comentarios%20Tercera%20Ronda/BIO%20ingles.pdf>, <http://www.minsalud.gov.co/PoliticasyFarmaceuticas/Biotecnologicos/Comentarios%20Tercera%20Ronda/BIO%20español.pdf> and <http://www.bio.org/advocacy/letters/bio-comments-colombia-biologics-and-biosimilars-regulations>.



thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

BIO commends the government of Colombia for taking steps towards developing regulatory requirements for the registry of medicines of biological origin. BIO and its members have participated actively in the public consultations and have engaged extensively with the Ministry of Health and their technical experts.

Biotherapeutic medicines (“biologics”) are substances, generally proteins, produced by living organisms (such as mammalian cells and bacteria), that are intended to be used for the diagnosis or treatment of human diseases. Because of their origin, these medicines are uniquely sensitive to changes in their environmental conditions. Thus, even seemingly small changes in manufacturing can alter the final quality and most importantly, clinical characteristics of biotherapeutic medicines. The high complexity of this manufacturing process requires precision, conformance to the most current good manufacturing practices and defined specifications in order to maintain the safety and efficacy of the product over time.

As their name implies, similar biotherapeutic products (“biosimilars”) are “similar” but not identical versions of the reference innovator biotherapeutic medicine. Producing a biosimilar is far more complicated than producing a generic version of a small-molecule drug. Indeed, unlike chemically-synthesized medicines, and because no follow-on manufacturing process will be identical to the original one, it is impossible for biosimilars to be exact copies of the reference innovative biotherapeutic. In light of this, it has been recognized that distinct regulatory approaches are necessary to assess efficacy and ensure patient safety with respect to biosimilars.

REGULATING BIOSIMILAR PRODUCTS:

Regulatory authorities are increasingly aware of the need for specialized pathways and specific development and evaluation standards to address the unique nature of biosimilars. These standards require a thorough and directly comparative (“head-to-head”) analytical characterization and quality studies, followed by more or less abbreviated pre-clinical and clinical development programs to show high similarity to the reference innovative biotherapeutic medicine in terms of quality, safety and efficacy.

The use of similarity exercises is the core of the unique pathway needed to appropriately assess biosimilars and to ensure they are comparable to the innovative reference product. This risk-benefit assessment process should ensure that there are no clinically meaningful differences with the reference product ***before*** the biosimilar candidate receives marketing authorization, thus minimizing risks to patients. To this end, the World Health Organization (WHO) developed guidelines in 2009 to serve as a blueprint



for countries for the development and evaluation of Similar Biotherapeutic Products (SBPs).⁴

Purported similar versions of biologic medicines that have not undergone head-to-head comparisons with an appropriate reference product put patient safety at risk and should not be considered as true biosimilars unless licensed via biosimilar pathways.

COLOMBIA'S PROPOSED BIOLOGICS AND BIOSIMILARS REGULATIONS:

A. Concerns Regarding Abbreviated Pathway (Article 7)

While BIO applauds the Ministry of Health for proposing distinct pathways to market for both innovator biologics and biosimilars, BIO and its members have serious concerns with an additional proposed "Abbreviated Pathway" as a route for approval of a biosimilar product. Specifically, we are concerned that, as drafted, the proposed Abbreviated Pathway is not scientifically supported and may put patients at risk. Rather than relying on comparability studies between the biosimilar and the reference innovator biologic product, this proposed pathway would rely instead upon "information available globally" that "the applicant considers relevant" as the basis for approval of the product. It is our understanding that while the complexity of a potential product would also be a factor, these and other key parameters are also undefined. Given that the "Full Dossier" (i.e. "innovator") and the "Comparability" (i.e. "biosimilar") pathways encompass the spectrum of biologics subject to the regulation and would be sufficient to provide a reliable approval pathway for either an innovator biologic or a biosimilar, the Abbreviated Pathway is not necessary and may, instead, create public health concerns and confusion among patients and physicians. In contrast to the Full Dossier and Comparability pathways, the "Abbreviated Pathway" described in the current proposed regulation does not provide adequate controls or any reasonable certainty that a product approved via this pathway would indeed have an adequate benefit-risk profile for the Colombian population.

Sound, science-based regulations are essential if the promise of biotechnology is to become a reality for more patients around the world. We know from the experience in Europe that biosimilars approved under high standards can reduce prices without compromising patient safety. To protect the health and safety of patients, regulatory approval pathways for biosimilars must make every effort to employ rigorous, well-defined, science-based review standards that ensure the quality, safety and efficacy of approved products. ***It is BIO's firm position that the inclusion within the 4th draft regulation published by the Colombian government, and notified to the WTO, of an Abbreviated Pathway fails to meet such standards and is inconsistent with***

⁴ WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), http://www.who.int/entity/biologicals/areas/biological_therapeutics/BIOOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.



WHO Guidelines on Evaluation of SBPs, thus raising substantial concerns with the safety of products that could be approved under such a pathway.

Any pathway lacking clear definitions and reliant upon undefined global information that may be poorly controlled is unprecedented internationally and raises significant concerns. We continue to urge the Colombian government to remove the proposed "Abbreviated Pathway" from the proposed biosimilar regulations.

B. Indication Extrapolation Considerations

The draft regulations are not clear on whether Colombia intends to allow applicants to "extrapolate" (*i.e.*, to use clinical data from one indication to support approval of another indication). If so, the regulations should set forth factors that the regulatory authority will consider when determining whether extrapolation is warranted. This should include assessment of whether the mechanisms of action of the biologic across the different diseases are the same, whether the patient population tested is the most adequate and sensitive to detect potentially clinically meaningful differences between the biosimilars candidate and its reference biologic, and whether the indications share the same patient disease state and population. The extrapolation of clinical data to support approval in an indication for which the reference biologic has been approved should not be permitted unless the above conditions have been met. In addition, we have concerns regarding the reference to "pharmacological standards."

C. Naming & Labeling Not Addressed

As discussed previously, a biosimilar is not the "same" as the innovative product. Thus, the naming rules that apply to chemically synthesized, small-molecule drugs and their generic counterparts should not apply to biologics. Assigning identical names to products that are not the same would be confusing and misleading to patients, physicians, and pharmacists; could result in inadvertent substitution of the products; and would make it difficult to quickly trace and address adverse events that may be attributable to either the innovator or the biosimilar products. In light of the differences between products, all biologics (innovator and biosimilars) should have unique non-proprietary names. This will help ensure that adverse events can be correctly tracked and traced to the responsible product. In the case of biosimilars, it will also help to inform healthcare professionals that these products are highly similar to, but not the same as, their reference products and to ensure that patients get the intended treatment. Most important, this will allow Colombia's pharmacovigilance system to continually assess the benefit-risk profile of every biotherapeutic, including biosimilars, minimizing the risks associated with their use and understanding the potential hazards of medicines to prevent harm to Colombian patients.

A biosimilar also should not automatically have the same labeling as the innovative product (in contrast to what is generally provided for in the case of generic drugs). The labeling requirements for biosimilars should flow from the fundamental premise of these products – that they will be similar to, but not the same as, their reference products. It



is critical that the unique attributes of biosimilars, including the clinical and post-marketing safety data generated specifically for the biosimilar products, be clearly reflected in the labeling. Labeling that does not clearly identify the differences between a reference product and a biosimilar could be misleading to prescribers and patients. The labeling should include a prominently-displayed, standard warning regarding the risks of substituting or alternating innovator and biosimilar products. The labeling of the biosimilar product should state which indications have been approved and which have not in clear language that a user can understand and locate. Identification of the actual indication(s) studied will provide an additional tool to inform prescribers' selections of biological products and prevent unsafe substitution.

D. Interchangeability & Substitution Not Addressed

The proposed regulations also do not address the interchangeability or substitution of biologics. Currently, there is no scientific, regulatory or medical consensus regarding the interchangeability of biological products. Without additional, robust clinical and post-marketing data that provide a reasonable expectation that the biosimilar product will produce the same clinical result as the reference product in any given patient and that switching between them carries no increased risks in terms of safety and/or loss of efficacy, the approval criteria for biosimilarity do not meet the heightened standards necessary to safely enable substitution for the innovator product at the point of dispensation. Therefore, BIO proposes that the final regulations explicitly state that biologics should not be substituted for one another in the absence of regulatory determination of interchangeability and/or a physician's clinical determination that substitution is appropriate in a particular patient's treatment. It is notable that no country or region with an established pathway for biosimilars has approved any biosimilar as interchangeable. Indeed, some countries have even gone one step further, explicitly prohibiting automatic substitution in legislation.

E. Regulatory Data Protection

In addition, the proposed regulations do not discuss regulatory data protection. Data protection generally requires that a biosimilar product relying on the clinical data supporting approval for an innovator reference product not be approved for a defined period of time. This type of protection is essential for innovators to recoup their investment in research and development costs and thereby provides incentives for companies to develop innovative new therapies. We understand that Colombia grants data protection to innovative drugs, including biologics, and thus the final regulations should expressly note that a product may not be approved via the Comparability route (or, if maintained, the Abbreviated Pathway route) until the applicable data protection period for the reference product has expired.

CONCLUSION:

We 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,

A handwritten signature in black ink that reads "Joseph M. Damond". The signature is written in a cursive, flowing style.

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