July 25, 2014

Dr. Alejandro Gaviria Uribe
Ministro de Salud y Protección Social
Ministerio de Salud y Protección Social
Carrera 13 N° 32-76
Bogotá D.C.
COLOMBIA

Re: *Proyecto de Decreto del Ministerio de Salud y Protección Social "Por la cual se establecen los requisitos y el procedimiento para las Evaluaciones Farmacológica y Farmacéutica de los medicamentos biológicos en el trámite del registro sanitario"* (Draft Ministry of Health and Social Welfare Decree "Regulating the requiremetns and procedure for Pharmaceutical and Pharmacological Evaluations of biological medicines for sanitary registration purposes")

Dear Minister Gaviria:

The Biotechnology Industry Organization (BIO) appreciates this fifth 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 2012[1], June 12th 2012[2], February 21st 2013[3], and October 4th 2013[4] for background about BIO and its interest in this Decree. These comments respond to the fifth draft of the proposed Decree, published July 10, 2014.

BIO represents more than 1,000 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,

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[1] BIO Comments to Colombian Ministry of Health, http://www.minsalud.gov.co/Politicas%20Farmaceuticas/Biotecnológicos/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/Politicas%20Farmaceuticas/Biotecnológicos/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/Politicas%20Farmaceuticas/Biotecnológicos/Comentarios%20Tercera%20Ronda/BIO%20ingles.pdf, http://www.minsalud.gov.co/Politicas%20Farmaceuticas/Biotecnológicos/Comentarios%20Tercera%20Ronda/BIO%20español.pdf and http://www.bio.org/advocacy/letters/bio-comments-colombia-biologics-and-biosimilars-regulations.

[4] BIO Comments to World Trade Organization, http://www.bio.org/sites/default/files/BIO%20WTO%20Comments_Colombia%20Proposed%20Biologics%20&%20Biosimilars%20Regulations.pdf

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

GENERAL COMMENTS:

For more than two years, BIO and its member companies have participated actively in public consultations and have engaged extensively with the Ministry of Health and their technical experts regarding the development of regulatory requirements for the registry of medicines of biological origin. While BIO commends the government of Colombia for taking steps towards developing these regulations, we retain serious reservations about their failure to meet international scientific consensus on the appropriate regulation of biosimilars and their potential negative impact on public health and patient safety. ***Therefore, BIO strongly opposes the enactment of these regulations in their current state.***

A. General Regulatory Considerations for Biologics and Biosimilars

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. 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.

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).[5] In May of 2014, The World Health Assembly resolution on *Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety, and efficacy*[6] reiterated the importance of the WHO SBP Guidelines by

[5] WHO *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)*, http://www.who.int/entity/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.

[6] Sixty-Seventh World Health Assembly (27 May 2014) *Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety, and efficacy;* http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R21-en.pdf

urging member states "to develop the necessary scientific expertise to facilitate development of solid, scientifically-based regulatory frameworks that promote access to products that are affordable, safe, efficacious and of quality, ***taking note of the relevant WHO guidelines that may be adapted to the national context and capacity*** [emphasis added]."

B. Concerns Regarding Abbreviated Pathway (Article 5, Section 3)

BIO and its member companies have serious concerns with the current state of the "Abbreviated Pathway" as included in Article 5, Section 3 and further described in Article 9 of the Decree. At best, based upon wording in Article 9,[7] BIO believes this proposed pathway would rely upon undefined preclinical and clinical information submitted solely at the discretion of the Sponsor. At worst, based on revised wording in the current version of the Decree under Article 10,[8] BIO believes it would be possible to market a biological product through the abbreviated pathway with no supporting clinical data, not even clinical pharmacology data to establish comparative bioavailability, which represents a standard lower than that applied to generic small molecule drugs.

It is our understanding that the complexity of a potential product would also be taken into account when considering the appropriateness of the Abbreviated Pathway for registration, yet these and other key parameters are vague and undefined, other than the mischaracterization in Article 9 that the "…active pharmaceutical ingredient is adequately described if it has a monograph incorporated in the pharmacopoeia." In particular, the revised wording in Article 9 includes two provisions that represent an unprecedented and inappropriate application of pharmacopeia standards for biological substances. First, as stated by the WHO Expert Committee, international or national standards are not intended for use as a reference biologic for the purpose of inferring the similar safety and efficacy profile of the candidate biologic.[9] Second, contrary to the implications of Article 10, the provisions of a pharmacopeia monograph are not sufficient to conclude that a product is adequately described.[10] Because of the complexity of biological products and their dependence upon specific manufacturing processes, the

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[7] "…additionally he/she shall submit the pre-clinical and clinical information ***on which he/she wants to rely*** on for showing quality, safety and efficacy, referred to the active pharmaceutical ingredient contained in such drug [emphasis added]"

[8] "For purposes of the abbreviated pathway, it is possible that the overall evidence [of the product's safety and efficacy profile] ***only refers to information on drugs containing the same active pharmaceutical ingredient*** [emphasis added]"

[9] "Therefore, international or national standards and reference reagents … are not intended for use as a RBP during the comparability exercise." (WHO Expert Committee on Biological Standardization, 2009, Guidelines on Evaluation of Similar Biotherapeutic Products (SBP), at §8.2.2)

[10] "It should be noted that pharmacopoeial monographs may only provide a minimum set of requirements for a particular product and additional test parameters may be required." (WHO Expert Committee on Biological Standardization, 2009, Guidelines on Evaluation of Similar Biotherapeutic Products (SBP), at §8.3).

evaluation of biosimilars relies on a "totality of the evidence approach," which includes quality, pre-clinical, and clinical comparative assessment with the commercially available reference biological product. The approach outlined in Articles 9 and 10 is consistent with the "end product testing" paradigm used for generic chemically-synthesized drugs and fails to recognize the international regulatory consensus that the generic drug regulatory construct is inappropriate for biosimilar products due to scientific differences between the two classes of products.

Additionally, given that the "Full Dossier" (*i.e.*, "innovator") and the "Comparability" (*i.e.*, "biosimilar") pathways (included in Article 5, Sections 1 and 2, and further described in Articles 6 and 7, respectively) encompass the spectrum of biologics subject to this Decree 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 the "Comparability" pathways, the "Abbreviated Pathway" described in the current Decree 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. However, any pathway lacking clear definitions and reliant upon undefined global information that may be poorly controlled is unprecedented internationally and raises significant concerns. 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 in a manner consistent with international scientific and regulatory consensus.

It is BIO's firm position that the "Abbreviated Pathway" included within the 5th draft Decree fails to meet such standards, is inconsistent with WHO Guidelines on Evaluation of Similar Biological Products (SBPs), and raises substantial concerns with the safety of products that could be approved under such a pathway.

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,

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Biotechnology Industry Organization (BIO)