Biotechnology Industry Organization

21 February, 2013

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: Public Consultation: Third Round of Discussion

Dear Minister Gaviria:

The Biotechnology Industry Organization (BIO) appreciates this additional opportunity to 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 on April 24th and June 12th 2012 for background about BIO and its interest in this Decree. These comments respond to the third draft of the proposed Decree, published on January 21st, 2013.

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, 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. Many elements of the revised draft appear to have addressed BIO's previous comments with respect to clarity of structure and definitions of terms, as well as expectations for data requirements. We have divided our remaining comments into first tier priorities, outlined below, and additional concerns.

A. Concerns Regarding Abbreviated Pathway (Article 7)

BIO applauds the Ministry of Health for proposing distinct pathways to market for both innovator biologics and biosimilars; however, BIO and its members have serious concerns with the current state of the "Abbreviated Pathway" as outlined in Article 7. The proposed pathway would rely upon "information available globally" that "the applicant considers relevant." It is our understanding that the complexity of a potential product would also be a factor, yet these and other key parameters are vague and undefined. Given that the "Full Dossier" and the "Comparability" pathways (Articles 5 and 6, respectively) encompass the spectrum of biologics subject to this Decree and would be sufficient to provide a reliable approval pathway for either an innovator

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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 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.

Any pathway lacking clear definitions and reliant upon undefined global information that may be poorly controlled is unprecedented internationally and raises significant concerns. In fact, the World Health Organization (WHO) initially considered developing a similar alternate pathway to market, deemed the "clinical comparability approach," but it was not included in the final *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)* issued in 2009 after objections were raised concerning its scientific justification and potential for public health risk.

B. Include Explicit Language Outlining Criteria for Establishing a High Level of Similarity and the Appropriate Use of Reference Products in the Comparability Pathway.

The Decree provides for a "Comparability Pathway" that permits approval of a non-innovative biological product based on a comparison to a Reference Biotherapeutic Product (RBP). The RBP is the original biomedicine "whose sanitary license has been authorized by INVIMA or any other agency with high surveillance standards, by means of a full dossier, and which is used as a comparator in said exercise." (Article 2.) BIO supports the creation of such a pathway, which is generally consistent with WHO guidelines and the approach taken by other experienced foreign regulatory agencies. However, BIO believes that the Decree needs to be clarified or altered in several important respects before finalization.

While the Decree discusses the comparability exercise in general terms and notes that pharmacological evaluation will be guided by WHO recommendations to the extent not inconsistent with the Decree, the Decree itself does not provide any clear criteria by which to judge whether comparability has been achieved. For example, as Brazilian regulations for this same type of pathway make clear, it should only be permissible to utilize this pathway where the comparability exercise "establishes that there are no detectable differences in terms of quality, efficacy and safety between the products." (ANVISA National Health Surveillance Agency Collegiate Board Resolution – RDC No. 55, Article 2.V., December 16, 2010) (hereinafter, ANVISA Resolution).) Alternatively, as WHO guidelines describe it, the comparability exercise should be "designed to show that the [similar biological product] has highly similar quality attributes when compared to the RBP." (WHO Guidelines on Evaluation of Similar Biotherapeutic Products, p.8, October 2009 (hereinafter, WHO Guidelines).) This requires a head-to-head comparison between the biosimilar and an RBP, compared in the same quality, non-clinical and clinical studies using the same procedures. (See ANVISA Resolution, Article 27 Paragraph 3, Article 43, and Article 46; see also WHO Guidelines, at pps. 8-9.) The Decree should be modified to expressly convey these indispensable requirements, given

that, without them, the justification for a reduced package of clinical and non-clinical data is not scientifically supported.

BIO also is concerned that the Decree appears to permit, in the sole discretion of the biosimilar applicant, a choice between using an RBP licensed by INVIMA or an RBP licensed by a foreign regulatory agency. (See Article 6: "When the applicant uses, for the comparability exercise, a RBP approved by a sanitary authority other than INVIMA, the Specialized Chamber shall accept it…."). As discussed infra (see Section C), such an approach could undermine the rights of the holder of the RBP license in Colombia. But it also raises important safety and regulatory considerations. WHO's guidelines note the traditional requirement by national regulatory agencies to use an in-country or domestically-licensed RBP, due to the greater degree of pre-approval and post-marketing data on, and familiarity and experience with, the product by the in-country regulators, as well as the potential differences between the foreign and domestic RBPs that may cause scientific flaws in the comparability exercise. For example, the European Medicines Agency, the U.S. Food & Drug Administration, and Brazil's ANVISA each require that an RBP be a domestically licensed and marketed product approved based on a full dossier (e.g., "The biological product to be used as comparer in the comparability exercise must be the product registered in ANVISA, whose registration has been based on a complete dossier." (ANVISA Resolution, Article 27).) Such a requirement also reinforces the sovereign regulatory authority of INVIMA for products to be sold and used in Colombia.

We note that, both WHO and ANVISA acknowledge that, *where there is no domestic RBP available*, it may be appropriate to utilize a foreign RBP; but in such case, only where that foreign regulatory authority "adopts technical-scientific criteria similar to ANVISA's criteria, and when there is possibility of full and unrestricted access to the registration information for ANVISA." (ANVISA Resolution, Article 27 Paragraph 2.) WHO similarly 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." (WHO Guidelines, at p.10.)

While the Decree uses language similar to WHO regarding an appropriate foreign regulatory authority, the Decree should be modified to make clear that a domestic RBP must be used whenever there is an appropriate INVIMA-licensed comparator product, and that a foreign RBP may be used only where an appropriate domestic RBP is lacking or unavailable and where INVIMA has sufficient access to all appropriate information regarding the foreign RBP. BIO recognizes that there may be instances where it would be useful to supplement a Comparability application with data from a foreign-approved comparator to the Colombian-approved RBP reference product, but cautions this is appropriate only where bridging data demonstrate that the foreign comparator is fully representative of the Colombia-licensed RBP. There is a high scientific hurdle in establishing the scientific bridge necessary to support the use of such foreign comparative data, and such bridging data should be characterized in the final regulation or guidelines. Such data should only be used when both the foreign and Colombia RBP product 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 Colombian RBP. Further, we urge that the Ministry of health take a highly cautious approach when accepting data from foreign comparative studies when the product may differ from the Colombian RBP, and foreign comparative data would generally not be appropriate for particularly complex biological products.

C. Implications for Incentives for Innovation

In order to preserve incentives to research, develop, manufacture, and launch in Colombia new innovative therapies and cures for patients suffering from serious, life-threatening conditions and unmet medical needs, as well as to develop and secure approval of new indications for such products, it is critical that Colombia's pathway for biosimilars include meaningful protections against unfair use of the reference product manufacturers' intellectual property (IP) and regulatory dossiers. Such protections also will help to enhance patient safety and access to novel biologics in Colombia.
In particular, BIO urges Colombia to clarify in its Decree that --

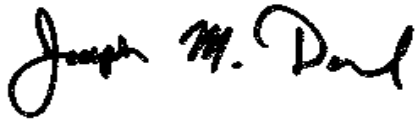
- ***If there is a reference product approved for marketing in Colombia, a biosimilar applicant should not be permitted to base its application on a foreign reference product instead.*** Such a policy – which comports with generally accepted international standards regarding approval of biosimilars as discussed above, as well as Colombia's own standards for the approval of traditional generic drugs – would provide incentives for innovators to timely enter the Colombian market by ensuring that approval of a full dossier would permit approval of a competitor product via the Comparability or Abbreviated pathway only after the period of protection afforded to Colombian-approved reference products. If a relevant reference product is approved in Colombia, an applicant should not be permitted to circumvent Colombian IP or regulatory data protection by referencing a foreign-approved product instead, although it may be permissible, as noted above, to supplement such an application with data from a foreign-approved comparator to the Colombian-approved reference product where appropriate. Such a policy also would support, as discussed above, greater patient safety, since Colombian regulators would have more pre-approval data regarding Colombian-approved reference products, as well as post-approval data from actual use of the innovator product by the Colombian population for a period of time. Further, the innovator generally takes on important patient safety and access responsibilities in markets in which it launches – including patient education and assistance programs, physician education and training on the benefits, risks, and proper use of such 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. It is important for Colombia's overall biologics regulation scheme to maintain the incentives for innovators to seek approval and launch novel medicines in the Colombian market by preventing biosimilar competitors from circumventing innovator protections.

- ***The Comparability and Abbreviated pathways must respect innovators' intellectual property and other legal rights***. Biosimilars should only be approved in Colombia after all statutory protections, including regulatory data and patent protections, are no longer available for the approved innovator product. In this regard, any biosimilars pathway should ensure that an innovator receives adequate notice of an application referencing its product or its data, so that any legal challenge involving the biosimilar product can be litigated promptly and prior to marketing approval of the biosimilar. Any biosimilars pathway also should fully respect existing trade secret protections for certain innovator data (such as chemistry, manufacturing and control data required as part of the new biological product approval process), and not permit the use of such information for the purpose of approving biosimilar products.

CONCLUSION:

We appreciate the opportunity to express our views and welcome the opportunity to discuss them further. Specific, detailed comments are included in the following chart. For additional information regarding the positions of the Biotechnology Industry Organization please see http://www.bio.org/category/biosimilars.

Respectfully submitted,



Joseph Damond
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Biotechnology Industry Organization (BIO)

ADDITIONAL CONCERNS

ARTICLE	COMMENTS	PROPOSED CHANGE
ARTICLE 2		
Article 2: Definitions **Reference biotherapeutic product (RBP)**: "*…whose sanitary license has been authorized by INVIMA or any other agency with high surveillance standards…*"	The "agency with high surveillance standards" should be defined and/or referenced, e.g., as per the definition of "Stringent Regulatory Authority" by the WHO; this establishes a clear framework.	***Those agencies with high surveillance standards referred to in this Article are those defined by the WHO.***
Article 2: Definitions **Comparability Exercise**	Include a statement that this "comparability exercise" is different than "*the comparability exercises for process changes introduced during development as outlined by ICH Q5E and that for the purpose of clarity, any comparability exercise(s) for process changes introduced during development should be clearly indentified in the dossier and addressed separately from the comparability exercise versus the reference medicinal product*". BIO has advised other regulatory agencies to ensure that it uses the term "comparability" to apply to intramanufacturer situations only, as consistent with other regulatory documents including the International Conference on Harmonization's (ICH) Q5E – Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing	"…between a biological drug seeking sanitary license and a reference biotherapeutic product (RBP). ***This process shall be distinguished from the comparability exercises for process changes introduced during development as outlined by ICH Q5E, which should be clearly indentified in the dossier and addressed separately from the comparability exercise versus the reference biotherapeutic product".***

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	Process: http://www.bio.org/sites/default/files/20050228.pdf; and on Draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005) available at http://www.bio.org/sites/default/files/20050617.pdf. The draft decree uses the terms "comparability" and "similarity" interchangeably. We urge INVIMA to formally make a statement explicitly recognizing the difference between conducting a comparability assessment of an innovator product before and after a manufacturing change versus assessments required to establish biosimilarity. This recognition would serve to clarify the extremely important point that information contained in documents concerning changes within a company's own process are not to be considered and adopted as adequate scientific guidance for the development of similar biological medicinal products by a second company.	
ARTICLE 3		
Article 3: Pharmacological Evaluation "Adverse effects"		b) Safety ***b.1.) Adverse effects***
Article 3: Pharmacological Evaluation "Immunogenicity"	"Immunogenicity" implies evidence (or lack thereof) of an immune reaction being triggered by the administration of a drug **to a human subject**. It becomes necessary to further define how	***"Immunogenicity will be evaluated through adequately designed clinical trial(s), and complemented by other sources of***

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	immunogenicity will be tested in human subjects: will it be in the context of a clinical trial of adequate design, with a sufficient number of subjects, with the correct endpoints and with enough duration to detect at least the more frequent immunogenicity reactions (e.g. 6 months, 1 year)? Or will it be enough to reference Case Reports? Or observational data coming from Pharmacovigilence (PV) systems, Registries or other source? The proposed "pivotal" Guideline on Immunogenicity stated in Article 25 (and indirectly also in Articles 24 and 26) may be the ones used as the reference, but given the normative nature of this regulation, the minimum standard (e.g. through adequately designed clinical trial(s), and complemented by other sources of data such as global PV data, registries, case reports, among others) should be explicitly mentioned here, together with a clear reference at the use of the Immunogenicity Guideline when assessing this topic.	***data, if available, such as global PV data, registries, case reports, among others, and as reflected in the Immunogenicity Guideline issued by INVIMA as stated in Articles 23 through 25 of this Decree"***
Article 3: Pharmacological Evaluation "Pharmacokinetics"	Pharmacodynamics is an element that should also be included in the List.	"Pharmacokinetics ***and Pharmacodynamics"***
ARTICLE 4		
	There is no comparable abbreviated pathway among internationally accepted standards. Colombia would take a risk in implementing a shortened pathway that does not have the support of the international standards in this area; Colombian patients may be	

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	exposed to the risks inherent in products that have not sufficiently demonstrated safety and efficacy. Additionally, this abbreviated pathway appears to be based on erroneous and/or subjective criteria: • Allowing the use of "global evidence" of products based upon their "containing the same active ingredient" (as the innovator) would erroneously apply the same criterion to drugs of biological origin as to chemically synthesized drugs and their generic counterparts. This stands in direct contrast to the prevailing scientific acceptance, as indicated by the guidance of WHO and PAHO (amongst others), that protein biotherapeutics are large and complex molecules that are often impossible, to completely characterize and, therefore, cannot be deemed to contain "the same active ingredient." The clinical performance of biotherapeutic products can also be strongly influenced by the manufacturing process, thus requiring clinical trials to test the safety and effectiveness of a particular product. This does not mean that such studies cannot be conducted in the country of origin or need encompass all the studies made by the innovator, depending on the use of a proper comparability pathway. • Complexity of the molecule: This is very broad and can lead to subjective decisions that guide the information necessary for the application for licensing. In fact, the complexity cannot only be related to the size of the molecule itself, but with the manufacturing process, which may affect the profile	

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	of impurities and related substances that may generate changes in immunogenicity of a particular product.	
ARTICLE 6		
Article 6: Comparability Pathway	Please refer to Comments above on Article 2, "Definitions", on the utility of using "Comparability Exercise" vs. "Similarity Exercise"; also, there is a contradiction between these points, as Article 6 states that while adopting the guidelines of the World Health Organization (Article 23 paragraph b), these same guidelines will be used as long as they are not contrary to what is indicated in the decree and applicable regulations. WHO guidelines are clear that immunogenicity studies should be conducted in humans, while Article 25 letter a) speaks of immunogenicity *in vitro* alternatives that are not yet accepted as a test by any agency, reference, or group of experts, including from WHO and PAHO. WHO guidelines should remain the single reference to assure science-based decisions.	"Standardization of WHO shall apply, always in its latest version." DELETE: "~~provided they do not contradict this Decree and other current sanitary regulation, which shall prevail.~~"
Article 6: Comparability Pathway	Not all biologic products are suitable for inclusion in the comparability pathway option. Some products, such as plasma-derived factors or vaccines, remain beyond the capability of current analytical science to assess whether two products made by different manufacturing processes could be "highly similar". As per **WHO Guidelines on Evaluation of Similar**	Add a sentence clarifying scope of the Comparability pathway at paragraph 1: ***"This pathway shall apply only to those products within the scope of a comparability exercise as defined in Article 2. Some classes***

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	Biotherapeutic Products (SBPs) (at §3 Scope): "This guideline applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins." Therefore, Article 6 should contain language constraining the application of the pathway to products that can be well characterized.	***of biomedicines as defined in Article 2 may not be amenable to a comparison of quality attributes. In order to permit a rigorous comparison of the quality attributes, the RBP and the product subject of the exercise should be well-characterized biotherapeutic products."***
Article 6: Comparability Pathway	The draft decree does not provide an overarching criterion by which a comparability exercise could account for the safety and efficacy attributes mentioned in Article 3. Specifically, to the degree that a sponsor seeks to rely on prior findings of safety and efficacy for a RBP in order to account for the attributes mentioned in Article 3, it is necessary not just that the comparability exercise should be completed, but that it must show that the product subject to the exercise and the RBP are highly similar. As stated in the **WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)** at §5 (Scientific Considerations). "The ability for the SBP to be authorized based on reduced non-clinical and clinical data depends on proof of its similarity to an appropriate RBP through the comparability exercise." And **WHO Guidelines on Evaluation of Similar**	Add to Article 6, following Paragraph 1: ***"Reliance in any part on prior findings of safety and efficacy of a RBP for the purposes of accounting for the attributes mentioned in Article 3 will be contingent on proof of the similarity of the biomedicine that is the subject of the evaluation to the RBP, including that the biomedicine is shown to have highly similar quality attributes when compared with the RBP."***

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	Biotherapeutic Products (SBPs) at §6 (Comparability Exercise) "The comparability exercise for a SBP is designed to show that the SBP has highly similar quality attributes when compared to the RBP."	
ARTICLE 7		
Article 7: Abbreviated Pathway	There are no precedents in any region of the world for this approach, and thus, there is no clear benchmark upon which to establish any comparison. Neither the level of "global evidence" nor the "complexity" of the potential biosimilar drug justify a pathway that seems to depend on source data that is poorly controlled and dependant almost exclusively on the sponsor's views, and that also lacks clear definitions. Both the "Full Dossier" and the "Comparability" pathways encompass all the spectrum of biologics subject to this Decree and as it is, in this "Abbreviated" pathway there's no adequate control, and above all, any reasonable certainty, that a product approved following it indeed has an adequate benefit-risk profile for the Colombian population.	*At minimum, there is a need for explicitly defining:* 1. *What constitutes "global evidence" (i.e. What number of products need to be available in the global market? What number of years of PV data suggest safety? What is an acceptable Severe Adverse Event (SAE) profile?, etc.).* 2. *Clear limits for what constitutes simple biological medicines.*
ARTICLE 8		
Article 8: Common Information	This Article basically describes the CMC/Quality attributes necessary for the 3 different proposed pathways.	

ARTICLE	COMMENTS	PROPOSED CHANGE
	To avoid the gaps in preclinical data, as mentioned in comments on Articles 6 and 7, it would be necessary to include preclinical data explicitly in this list, if not included for the respective Articles.	
Article 8: Common Information "Immunogenicity Tests"	Please refer to Comment on Article 3.	
Article 8: Common Information "Risk Management Plan"	Risk Management Plan is only one component of a comprehensive PV plan. BIO suggests using the wider term and not limiting to only RMP/REMS.	***"Pharmacovigilance, including a*** Risk Management Plan"
Article 8 : Common Information "Standards and Specifications"	This language in Article 8 implies that standards and specifications from the accepted pharmacopeia are both necessary and sufficient for control of biomedicines in marketed in Colombia. While it is appropriate for INVIMA to determine if compliance with a recognized pharmacopeia is necessary, it is not scientifically justified to conclude that such standards are sufficient for quality control of biomedicines. Per **WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)** at §8.3 (Specifications): "As for any biotherapeutic product, specifications for a SBP should be set as described in established guidelines and monographs, where these exist. It should be noted that pharmacopoeial monographs may only provide a minimum set of requirements for	"The standards or specifications and analytical methods to produce this information ***shall, at a minimum, comply with*** those included in the pharmacopeias accepted in paragraph 1 of Article 22, Decree 677 of 1995. ***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.*** Standards or specifications of biomedicines whose monographs are not included in these pharmacopoeias shall be provided by the applicant and established using validated techniques."

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	a particular product and additional test parameters may be required."	
ARTICLE 10		
Article 10: Criteria for Evaluation "Global Evidence"	Articles 10 and Article 11 refer to medicines that contain the "same active ingredient" as the biomedicine that is the subject of the application. BIO understands that the term "same active ingredient" refers to a medicine manufactured by another sponsor. If such is the case, BIO finds it problematic -- given the nature of biologics -- to refer to the drug substances made by two different manufacturers as containing the same active ingredient. BIO would suggest alternate text that would align with the scientific principles for evaluation of biologic and biosimilar (also known as "subsequent biologic product – SBP" or "Follow-on biologic -FOB") medicines as expressed in international guidelines, namely that the active ingredients for biologic medicines manufactured by different processes can be highly similar, but are not the same.	**a) Global Evidence**: it refers to the efficacy and safety profile, to the pharmacovigilance information available worldwide, to the countries where the medicine is marketed and to the marketing time of the biomedicine which is the subject matter of the evaluation, ***as well as those containing a highly similar active ingredient as determined in a comparability exercise with the medicine that is the subject matter of the evaluation.***
Article 10: Criteria for Evaluation "Global Evidence"	Global Evidence of the safety and efficacy profile is said to include pharmacovigilance information available worldwide and the respective marketing time of the biomedicine subject matter of the evaluation. While pharmacovigilance data from regions with strong national systems for safety reporting and monitoring may be considered supportive of the safety and efficacy profile of a	**Add as a new paragraph to Article 10 (a):** ***"Global Evidence of efficacy and safety should derive primarily from well-controlled clinical studies, supported as necessary by data from uncontrolled (open***

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	biomedicine, this type of evidence is not considered to be as substantive as data from well controlled clinical studies. Moreover, even in a region with strong pharmacovigilance systems, data from passive pharmacovigilance as gathered from unsolicited case reports is not as convincing as data from active pharmacovigilance studies such as might be obtained from patient registries, well-designed observational studies, or post-approval (open-label) clinical studies. We recommend that Article 10 should include a requirement that only data from well controlled clinical studies or from active pharmacovigilance programs in countries with strong safety reporting systems could be considered substantive evidence of the efficacy and safety profile.	***label) clinical studies or from active pharmacovigilance of the medicine subject matter of the evaluation. Pharmacovigilance data can be considered reliable evidence only in countries with a well-established regulatory framework and principles, as well as considerable experience of evaluation of biotherapeutic products and post-marketing surveillance activities, and alone is not sufficient. The lack of unexpected adverse event reports as a result of passive surveillance cannot be considered evidence of product safety and efficacy."***
ARTICLE 11		
Article 11: Approval of Indications	"A generic medicine contains the same active pharmaceutical ingredient as and is bioequivalent to an originator (comparator) medicine." - WHO Similar Guideline on the Evaluation of Similar Biological Products at §4. "Demonstration of structural sameness and bioequivalence of the generic medicine with the reference product is usually appropriate to infer (conclude) therapeutic equivalence between the generic and the reference product. However, *the generic approach is not suitable for the licensing of SBPs since biotherapeutic products usually consist*	Approved indications for the drug that is the subject matter of the evaluation shall be***, as appropriate, those claimed and proven by the applicant and / or those listed in The New Indication List for another biological medicine containing an active ingredient that is highly similar to the active ingredient contained in said drug as determined in a comparability exercise with the medicine that is the subject matter of the***

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	of relatively large and complex entities that are difficult to characterize." (Emphasis added) - WHO Guideline on the Evaluation of Similar Biological Products at §5. "The active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product." - EMA Guideline on Similar Biological Medicinal Products. -- Approval of indications. The approval of indications must always be supported by evidence of their safety and efficacy through clinical trials. The biosimilar cannot apply for an indication different from the originator product (Health Canada). Extrapolation of indications may be allowed if the biosimilar applicant performs a head to head equivalence study with the most sensitive population. Please follow the WHO, EMA or FDA guideline on extrapolations of indications.	***evaluation.***
ARTICLE 13		
Article 13: Good Manufacturing Practices	See earlier comment.	While the Ministry of Health issues the guideline mentioned in Article 23.c) the recommendations issued by the World Health Organization in its technical reports shall apply always in

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		their latest version, ~~provided they do not contradict this Decree and other current sanitary regulation~~ (DELETE).
ARTICLE 20		
Article 20: Renewal of Sanitary Licenses	What will happen with currently registered biological medicines that do not meet the criteria as specified in the present decree? The regulation and INVIMA need to establish a procedure for these products.	
ARTICLE 21		
Article 21: Amendments to Sanitary Licenses	What will happen with currently registered biological medicines that do not meet the criteria as specified in the present decree? The regulation and INVIMA need to establish a procedure for these products.	
ARTICLE 22		
Article 22: Nomenclature of Sanitary Licenses	BIO takes the position that, in order to accommodate the subsequent advent of new biosimilars, each biological medicine should have a distinct International Non-proprietary Name (INN) to permit tracing an event to the product administered. A standardized naming system for the nonproprietary name with distinguishing prefix and suffix should be considered. While a distinct INN could consist of the same stem name as the innovator plus a unique suffix (such as "-alpha" or "-beta" or the manufacturer's name), distinguishing also by prefix provides more apparent traceability. Due to the potential for incorrect naming based only on non-proprietary name, both proprietary and non-proprietary names should be collected on adverse	

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	experience reports.	
ARTICLE 23		
Article 23: Unregulated Aspects	Among these non-regulated aspects of this Decree, **interchangeability/substitution and labeling are critical, especially for those products registered through the "Comparability" and the "Abbreviated" pathways.** Decree 677 does not address these issues with their peculiarities inherent for biosimilars, and as such Colombia's Ministry of Health and INVIMA **should update the respective decrees with specific provisions for products approved through these pathways that follow internationally accepted standards**. Specific labeling guidance for these products must be provided. Either via an article in this guidance, modification of 677 or through the development of a specific decree for biologics. This may have clear implications on Colombia's public health, especially regarding potential safety/efficacy/immunogenicity issues when inadequately alternating (i.e. repeatedly switching) between a reference product and its biosimilar(s) or even among biosimilar(s).	
ARTICLE 24		
Article 24: Adoption of Guidelines		**Adoption of guidelines.** The Ministry of Health and Social Protection shall ~~adapt and~~ (DELETE) adopt the latest

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		versions of the following guidelines within 6 months following the date of entry into force of this Decree: **(ADD:)** ***g) WHO Recombinant DNA products.***[2]
ARTICLE 25		
Article 25: Preparation and Issuance of Guidelines	BIO applauds the MoH's transparency in the drafting process thus far and would appreciate the opportunity to continue to engage as guidelines are developed.	
Article 25: Preparation and Issuance of Guidelines "Immunogenicity"	This decree appears to constrain the scope of the required immunogenicity guideline to acute sensitivity or immunotoxic effects. INVIMA should also be concerned about potential for loss of efficacy for biomedicines used in the long term as this can impact the efficacy profile. We suggest that the guideline should also require evaluation of neutralization of effect in addition to "immunotoxic" events.	Modify Article 25 (a) as follows: "Guideline for the evaluation of immunogenicity of the medicine which is subject matter of the application. It shall include general criteria for the sequence of in - silico /in vitro preclinical and clinical tests which may be required according to the characterization and molecular complexity of the active ingredient, its

[2] http://www.who.int/biologicals/publications/trs/areas/vaccines/rdna/WHO_TRS_814_A3.pdf

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		formulation, excipients, container, packaging and clinical use, in order to establish any potential hypersensitivity, autoimmune reactions and other immunotoxic events**, *and potential for loss of efficacy due to immunological neutralization of effect.*** (Three months from issuance of this Decree)
ARTICLE 31		
Article 31: Pharmacovigilance	In this Article there is no distinction as per the PV requirements approved through the different pathways as established in Articles 5, 6 and 7. Especially for the latter two (i.e. those approved through the "Comparability" and the "Abbreviated" pathways), which are products that rely on dossiers that are less extensive than those products approved through Article 5 (i.e. "Complete Dossier" pathway), PV may necessarily vary to that required from their reference products. As such, it must be clearly stated that: 1. PV is necessary for all biologics, including biosimilars, to continually define the product's benefit:risk profile; 2. For products approved through the "Comparability" and the "Abbreviated" pathways, robust post-marketing requirements that are at least equivalent to that of their reference product, or higher in	

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	selected cases, should be implemented. 3. To effectively track-and-trace potential adverse events for biotherapeutic products post-approval, as many **unique identifiers** as possible should be encouraged when reporting adverse events, including distinct non-proprietary names which becomes even more critical where drug prescription and dispensing is done using only INN, as in Colombia through Decree 2200, Chapter IV, Article 16.	