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Ministry of Health & Social Protection
Cra 13 # 32-76
Bogotá DC, Colombia

February 22, 2013

Dear Minister Alejandro Gaviria Uribe:

CC: Ms. Nancy Huertas, Director of Medicines
Ms. Claudia Vaca
Mr. Rodrigo Moreira

*Re: Draft Colombian Biologics Regulations*

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) appreciates the opportunity to submit comments on the proposed biologics regulations. IFPMA is a global, non-profit, nongovernmental organization that represents the research-based pharmaceutical industry, including companies engaged in the biotechnology and vaccine sectors. We applaud the efforts of the health authorities in Colombia to create a comprehensive set of regulations for biologics, and we respectfully submit the following comments.

In the implementation of a regulatory pathway for innovative biologics and biosimilars, the paramount consideration should be patient welfare. Biologics are very complex molecules and are often challenging to characterize and to manufacture with consistency. It can be difficult to determine whether seemingly minor differences in structure or manufacturing process will result in clinically meaningful differences between two different versions of a biological product. At the same time, many biologics are intended to treat patients with serious diseases. The consequences of unanticipated immunological or other adverse events can be grave. And the consequences of diminished efficacy can be just as devastating to a critically ill patient. Given this context, we urge INVIMA to follow the path of other health authorities and global organizations and evaluate all biologics, including biosimilars, based upon the best available science, including analytical characterization and appropriate clinical data.

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Our most significant concern with the draft regulations is the lack of explicit approval standards for biosimilar medicines. Without robust approval standards for these products, the safety and efficacy of medicines in Colombia may not always be guaranteed. Inconsistency in approval standards could threaten patient safety and lead to a lack of confidence in biological medicines. Applications submitted through the full dossier pathway should be approved only if the applicant establishes that the biologic is clinically safe and effective. Consequently, a product should be approved through the comparability pathway only if the applicant establishes that it is "highly similar" to its reference product.

*A. Eliminating the "Abbreviated" Pathway*

We have particular concerns about the suggestion of a third pathway, for "abbreviated" applications. In our view, biological medicines should be approved *either* on a stand-alone basis with a full dossier of supporting CMC (Chemistry, Manufacturing & Control), preclinical, and clinical evidence, *or* on the basis of a robust analytical, preclinical, and clinical comparison with a reference biologic previously approved on the basis of a full dossier. This approach protects patients while building confidence in biological medicines, including biosimilars.

As it stands, the draft provisions concerning the abbreviated pathway do not provide sufficient assurance that products approved via this pathway will be safe and effective. In particular, the final regulations should include more information regarding the types of analytical, preclinical, and clinical data that should be included in such an application. This would facilitate consistency with WHO standards and provide Colombian patients with high quality and clinically safe and effective biosimilars. It is not clear, however, how such a pathway (with these requisite data requirements) could be distinguished from the comparability pathway described in the current draft.

The regulations should also state that the information submitted to INVIMA must be data from testing the actual product that is the subject of the application, as opposed to data solely related to other, potentially similar products. Similarly, in the absence of data establishing the similarity of the proposed product to a reference biological product, it would be scientifically inappropriate for the sponsor or INVIMA to rely on prior findings of safety and efficacy from another product.

*B. Clarifying Some of the Terminology and Provisions in the Draft*

We also have some concern regarding the terminology used in the proposed regulations. The regulations repeatedly use the term "comparability." We recommend that the final regulations be clarified to distinguish this approval pathway from the term "comparability exercise," which is used to evaluate changes introduced in the manufacturing process of a given product as outlined by the ICH Q5E Guidelines. Distinguishing between the two exercises would also clearly reflect the fact that the data necessary to seek approval of a biologic product (even under a biosimilar pathway) are different and that, in most cases, significantly more robust data are needed for a biosimilarity exercise than when an existing manufacturer makes a process change. We would suggest adding a clarification in Article 2 as follows: "'Comparability' is defined here only for the purpose of establishing similarity to a reference biological product, and should not be confused with an exercise designed to justify a manufacturing change by the same sponsor."

Also, Article 10 defines global evidence as information available worldwide for the product that is the subject of the application or "those containing the same active ingredient." Because of the complexity of biologics, it is currently not possible for two unrelated manufacturers to produce two products having the "same" active ingredients. This language should therefore refer to other products that are "highly similar" to the product that is the subject of the application.

Article 10 also appears to include "pharmacovigilance information available worldwide" in the set of information that constitutes "global evidence." Although this information may be helpful support in determining whether to approve a product, passive collection of data should not be a substitute for generating clinical safety data, active pharmacovigilance (such as patient registries), or other active pharmacoepidemiological methods. A collection of voluntary case reports from passive pharmacovigilance is not substantial evidence of safety and efficacy. There is no assurance that safety issues will be consistently reported in an accurate and timely manner. Accordingly, the final regulations should be amended to clarify that data pulled from passive pharmacovigilance databases around the world are not a substitute for a more robust safety data set.

Currently, the regulations state that – according to the English translation - "[t]he approval of indications must always be supported by evidence of their safety and efficacy." They also add that "[a]pproved indications . . . shall be those claimed and proven by the

applicant and / *or those mentioned in the "Pharmacological Normals" for the active ingredient contained in said drug*" (emphasis added). Although we do not fully understand the impact of these provisions, we believe that they may relate to the issue of indication extrapolation (i.e., the use of clinical data from one indication to support approval of another indication). If INVIMA intends to allow applicants to extrapolate clinical data, it should set forth factors that it will consider in determining whether doing so is warranted in individual cases (e.g., whether the mechanisms of disease are the same, whether the biologic's mechanism(s) of action and/or receptor(s) are well-defined and common to all indications, whether the indications share the same patient disease state and population, and whether clinical safety, efficacy, and immunogenicity have been studied in the most sensitive disease state and/or population). In addition, we have concerns regarding the reference to the "Pharmacological Normals." Because biologics with similar active ingredients can have different clinical effects, the fact that an indication and active ingredient are listed together in a compendium is not sufficient evidence standing alone for approval of any particular biological medicine for that indication. In sum, approved indications should be limited to either those established via a robust data set by the sponsor (for the full dossier pathway), or by appropriate extrapolation based on a more limited data set (for the comparability pathway).

Article 25 of the English translation of the draft regulations suggests that immunogenicity data "may" be required of an applicant. It is not clear whether this is the intended interpretation. Article 8 of the draft regulations would require all applicants, regardless of the pathway chosen, to submit immunogenicity testing data. We are concerned that Article 25 could be misinterpreted as an exception to this important requirement. Article 25 should be clarified to ensure appropriate evidence concerning immunogenicity is submitted by all applicants. We strongly believe that no biologic should be approved in Colombia without some premarket clinical evidence of immunogenicity of the specific product that is the subject of the application. Even well-characterized biologics can have immunogenicity profiles that are unexpected based on analytical and preclinical data alone.

In our view, the information provided in Article 21 'Amendment to sanitary licenses for biomedicines' does not adequately describe the processes for application, evaluation and approval of modifications to licensed products clearly enough. We suggest the addition of further details related to the exact processes and timelines.

C. *Limiting the Scope of the Comparability Pathway*

INVIMA should ensure that the comparability pathway is limited to products that can be well-characterized, according to the criteria set forth by the WHO in its guidelines for similar biological products. The draft regulations currently do not have any such limits. Further, as we understand the regulations, vaccines could be approved via the abbreviated or comparability pathways. If that is the case, we urge the Ministry of Health to reconsider this approach and exclude vaccines from these pathways. Vaccines should be approved only after a robust approval program that includes extensive analytical, preclinical, and clinical studies because of their complexity and heterogeneity, as well as their unique risk/benefit profiles (e.g., they are often administered to healthy populations or to children). Abbreviated testing programs intended for biosimilars are not appropriate for vaccines.

D. *Ensuring Robust Chemistry, Manufacturing and Control (CMC) Standards*

Article 25 requires the authorities to establish a guideline on stability testing for biological products. INVIMA should ensure that this guideline is consistent with the guidelines in ICH Q5C (Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products), in particular regarding the requirements for establishing long-term stability. Article 13 of the draft regulations suggests that the WHO guidelines on good manufacturing practices for biologics will apply. The final regulations should also explicitly require validation of manufacturing methods.

E. *Addressing Naming, Labeling, and Substitution of Biosimilars*

The proposed regulations do not address naming and labeling conventions for biologics. We understand that, by default, the rules that are currently applicable to non-biological drugs would apply to biologics as well. Given the significant differences between non-biological drugs and biologics, however, we do not believe this is appropriate. In particular, because a biosimilar (or comparable biologic) will not be the "same" as the reference product, the biosimilar product should not automatically have the same labeling as the innovator (which is the case for generic drugs). Product labeling should be used to inform healthcare professionals and patients about any potential differences between the products, as well as the testing that was actually performed on the biosimilar product (as opposed to on an innovative product). Moreover, a biosimilar should have a name that is distinct from that of the reference product. This will ensure that all stakeholders, including healthcare professionals, recognize that these products are only highly similar to (not the same as) their reference products. Furthermore, unique

naming facilitates the pharmacovigilance process and supports the ability to generate a product specific safety profile. As biosimilar products can by definition be only highly similar to their reference products, the ability to analyze product-specific safety data is critical to ensuring the best information is available for physicians and their patients. Distinct names will facilitate this process by ensuring that adverse events can be traced to the responsible product (rather than inadvertently being attributed to the incorrect product).

The proposed regulations also do not address the interchangeability or substitution of biologics. Currently, there is no scientific or medical consensus on the standards for approval of an interchangeable biologic.[1] Therefore, we suggest that INVIMA explicitly state that biologics should not be automatically substituted for one another unless scientifically justified through adequately designed clinical trial(s).

*F. Protecting Existing Incentives for Innovation*

The proposed regulations do not currently discuss data protection. We understand that Colombia grants five years of regulatory data protection to innovative drugs and biologics alike (i.e., five years during which a biosimilar applicant cannot rely on approval of the prior innovative drug or biologic in order to receive a shortcut to approval). We request that the final regulations note that a product may not be approved via any pathway not requiring a full dossier until five years after the reference product (or any innovative product used to support the application) is approved. This five-year period will help to ensure that there is an opportunity for sponsors to recoup their investment and to protect incentives for companies to develop innovative new therapies.

Finally, Article 27 of the proposed guidelines provides that the minutes of the Review Commission "shall be published and shall gather all scientific discussions and supports used for decision-making." Although we support efforts to ensure that the Review Commission's decision-making process is transparent and consistent, this provision should be amended to state that trade secret and confidential commercial information submitted to the Review Commission will not be released. This will help to preserve incentives for pharmaceutical companies to undertake robust development programs for new medicines.

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[1] We note that the law in the United States, the Biologics Price Competition and Innovation Act of 2009, is structured such that any finding of interchangeability between a follow-on biologic (biosimilar) and a reference product would require a higher scientific standard than the biosimilarity "highly similar" exercise.