BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

Comments of the Biotechnology Industry Organization (BIO) to the Ministry of Health and Social Protection Colombia

24 April 2012

Re: The Sanitary Registry Regime for Drugs of Biologic Origins

The Biotechnology Industry Organization (BIO) is grateful for the opportunity to respond to the draft decree concerning the Sanitary Registry Regime for Drugs of Biologic Origins, hereafter referred to as "the Registry Regime".

About BIO and the Biotechnology Industry

BIO is a trade association representing more than 1,100 companies, academic centers and research institutions involved in the research and development of innovative biotechnology products and services. Our members are primarily 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, and numerous other serious diseases and conditions. Another 400 biotechnology medicines are in the pipeline. In the agricultural field, biotechnology innovations are increasing food supplies, conserving natural resources of

land water and nutrients, increasing farm income, and growing the economy worldwide. Within the field of industrial biotechnology, biotech companies are leading the way in creating both conventional and next generation advanced biofuels, which can be produced from forest residues, algae, municipal solid waste, or other renewable sources of biomass, without compromising the environment. Renewable chemicals and biobased product platforms are also providing real opportunities to create green jobs, reduce dependence on foreign oil, increase energy security, and reduce greenhouse gas emissions.

Colombia is a growing market for biotechnology products and with the pending implementation of the U.S.-Colombia Trade Promotion Agreement (TPA), it promises to become an even bigger market. Moreover, Colombia's efforts to link biodiversity to sustainable development[1] and its recent law which provides tax incentives for science and technology investments[2] cast it as a country with interest in developing its biological resources.

BIO's Overall Views on the Regulation and Approval of Drugs of Biologic Origin

BIO commends the government of Colombia's Ministry of Health and Social Protection in its endeavor to create a pathway for the approval of biological and biotechnological products. This is particularly important in view of Colombia's influence as a reference country in Latin America with respect to regulatory issues. Before making specific comments on the proposed Registry Regime, it is important to first understand BIO's general views on the regulation of biological products. As the government of Colombia considers legislation in the approval of biological and biotechnological products, BIO believes that it is important to ensure that patient safety is not compromised and that incentives for innovation are preserved.

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[1] http://www.scidev.net/en/news/colombia-to-commercialise-its-biodiversity.html 6 July 2011
[2] Law 29 of 1990 Rules Pursuant to Articles 70 and 71 of the Colombian Constitution; see also http://www.mondaq.com/article.asp?articleid=10062

Patients should not have to accept greater risks or uncertainties in using a biological products whether a follow on drug of biological origin or an innovator's product. The Draft Registry Regime provides that clinical trials are optional in the registration process for biotechnological products and leaves this decision to the discretion of the Reviewing Commission (Comisión Revisora- Advisory Group). For patient safety, the Clinical Comparative Trials should be mandatory and not optional. Moreover, it is important to recognize the scientific differences between small molecule drugs and drugs of biologic origin. Biologics are much more complex than small molecule chemical drugs. They include many of the latest breakthrough medical therapies for serious and life-threatening illnesses, such as cancer, multiple sclerosis, diabetes, and HIV/AIDS, as well as many serious rare diseases. Due to their size and complexity, biologics generally cannot be scientifically characterized to the same degree as small molecule chemical drugs. This has been recognized by the World Health Organization (WHO) in their guidelines for the evaluation of similar biotherapeutic products and may serve as a starting point for the consideration of the government of Colombia.[3]

In particular with respect to approval of biological products that follow the drug of biologic origin, it is important to ensure that intellectual property and other legal rights are respected. This is especially important in view of Colombia's interest in developing its own biotechnology sector. In this regard, it is essential that substantial non-patent data exclusivity is provided which prevents manufacturers of a follow on product from relying on any health authority's prior approval of the original biologics to support approval of their own products. Such data exclusivity is necessary to prevent unfair competition in the market, which in turn incentivizes innovation within Colombia's nascent biotechnology sector. The test data required by governments for approval of innovator biologic products requires massive investment and is proprietary and thereby deserving of adequate protection. Such investment is less likely to be made if there is little or no

[3]http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

protection for it. The fledgling nature of the biologics industry, its heavy dependence on access to significant amounts of high-cost public and private investment capital, and the high risks and costs involved in the development of new biologic medicines all warrant a substantial period of exclusivity. In the United States, for example, the term of such protection for data is 12 years measured from the date of marketing approval. Moreover, a similar biological product should not be approved until after all statutory protections, including data exclusivity and patent protections, are no longer available for the approved innovator product. In this regard, it is important to ensure that there is appropriate implementation of "patent linkage" provisions set forth in Article 16.10.2 of the U.S.-Colombia TPA, so that innovators may resolve patent disputes prior to marketing approval of products relying on innovator's clinical trial data.

General Comments on the proposed Registry Regime

The scope of the draft decree as set forth in Article 1 is very broad and appears to include all biological products. Thus, while the Registry Regime does not clearly distinguish between an innovator drug of biological origin and one that is a follow on product (i.e., biosimilars), it appears to include such follow on or similar products within its scope. For example, sections 2.7, 2.11 and Article 7 all refer to "comparability exercises" or "drug of reference," which indicate an intent to regulate approval of biosimilars.

Instead of such a broad and vague approach, BIO recommends the development of specific regulations for different types of biological products (e.g. well characterized drugs of biological origin, plasma derived products, immunological drugs, and biosimilars) that address the specific considerations of these distinct product types. For example, registrations for biosimilars require a clearly defined regulatory pathway in order to both provide adequate patient safety provisions and enable scientifically justified abbreviation.

In addition, BIO has several concerns relating to some of the terms used in the draft text. For example, it is unclear what exactly is meant by the "drug of reference" in section 2.7

and how, if at all, it differs from the "drug of biologic origin of first entrance". To clarify, we suggest that the guidelines clearly define a reference drug as a product registered with complete information including a full registration dossier as required for a new medicine. In addition, the Registry Regime should be explicit that: (1) the same reference drug must be used throughout development; (2) the dosage form, route of administration and strength should be the same between the biosimilar and reference drug; (3) no biosimilar may be used as a reference product, and (4) INVIMA accrual of adequate safety and efficacy data on the reference drug be a prerequisite for use in a biosimilarity exercise.

The use of the terminology "comparability" implies a comparison between two products. However, this concept is not adequately explained in the proposed Registry Regime. In this regard, it is important to recognize that similarity and comparability are distinct concepts. For example, in the United States, manufacturers of innovator products are permitted to make post-approval manufacturing changes to their products based upon a showing of comparability between the two products. This is viewed as being appropriate because innovator manufacturers possess a thorough and robust body of knowledge about the process used to manufacture the original product, which can be applied in support of subsequent modifications to the manufacturing process. In contrast, the sponsor of a product of biologic origin which is not the innovator product, but purports to be similar would not have access to the cell line or the critical manufacturing processes that are essential to production of the innovator product. As a result, new clinical data will be needed to support similarity to an innovator product. Furthermore it will be necessary to perform a complete analytical comparison with the innovator's product in support of approval of the similar product.

In addition to the particular issues concerning scope and terminology, BIO also notes that several topics of importance do not appear to be reflected in the proposed Registry Regime. These include the recognition of the issues relating to interchangeability or substitution and indication extrapolation. Because of the complex science involved with

manufacturing biosimilar medicines, many advanced regulatory agencies[4] have indicated that the generic drug approval pathway is not appropriate for complex biologics. The World Health Organization's guidelines referenced above may serve as a starting point for any scientifically based regulatory approval pathway for biologics.[5]

BIO's Specific Areas of Interest

With respect to Article 6, the criteria as written are not standards or characteristics on which a determination can be made. Therefore, the regulation is discretional and non-obligatory, which is insufficient in terms of requirements for biologics and biosimilars. Instead, criteria should be developed that articulates standards or characteristics on which a determination can be made (e.g. approved under an ICH biosimilars pathway). The Registry Regime also should clarify the accountability of the applicant and INVIMA in accruing the necessary data for evaluation. Moreover, as noted in the general comments, the definition of a drug of "first entrance" and other terminology should be clarified so that Article 6 is not read to permit a biosimilar to be considered a Reference product under this section. In addition, rather than simply refer to countries in sections 6(a) and 6(b), the Registry Regime should specify the information to be gathered (e.g., efficacy, pharmacovigilance data etc.) and thereby clarify the intent of differentiation between local marketing approvals and experience and 'world market' experience.

The data categories of Article 7 should be included in the "basic information" of Article 6, rather than the "additional information" category. In addition, as noted in the General Comments, the language should confirm that comparability is the assessment of the impact of observed differences on safety and efficacy and can include pre-clinical and clinical confirmation. For biosimilars, the need for pre-clinical and clinical data is

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[4] The U.S. Food and Drug Administration, European Medicines Agency, Canadian Health Authority, Australian Medicines Agency, Japan's Ministry of Health, Labor and Welfare have all confirmed that the small molecule regulatory system is inappropriate for biosimilar approval.

[5] http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

assumed based on expected product differences resulting from unique cell line, process, purification and container closures system.

BIO notes with appreciation the requirement in Article 7, paragraph 3 for the development of an Evaluation Manual for evaluating the parameters of the information that is requested for sanitary registry of drugs of biologic origin. Nonetheless, in order for the manual to guide industry and to guide INVIMA's decisions in a product specific manner, the Registry Regime should establish appropriate and distinct basic criteria, consistent with WHO guidelines, for well-characterized drugs of biological origin, plasma derived products, immunological drugs and biosimilars, as noted in the general comment. If that is the case, such a manual will be helpful in clarifying many of the requirements for the registry process. It is respectfully requested that to the extent possible, the proposed measures be published in advance and that interested persons and parties be granted a reasonable opportunity to comment on such proposals.

BIO also notes that in Article 7, Paragraph two there is a requirement for the applicant to respond to a decision of the Specialized Chamber within 60 days. In this regard, it is important to consider the requirements in the decision of the Specialized Chamber. As an example, if the decision requires additional clinical trials, a full response may be difficult to present within a 60 day time-frame, whereas additional analytical testing may be more easily achievable. In the former case, applicant should be able to provide a plan for addressing the requirements in the decision within the 60 day time frame. BIO urges that in this regard, the applicant be afforded reasonable opportunity to present facts and arguments in support of their positions prior to any final administrative action.

BIO further notes that in Article 8, there is no recourse for an applicant if the result of the evaluation by the Specialized Chamber is unfavorable. In most regulatory approval regimes, applicant has access to some sort of dispute resolution mechanism or hearing that allows them to air their concerns. BIO recommends that the government of Colombia also consider such a mechanism for drugs of biologic origin. It is instructive to

consider the provisions of Article 19.5 of the U.S. Colombia TPA which require the establishment or maintaining of judicial, quasi-judicial, or administrative tribunals or procedures for the purpose of the prompt review and where warranted correction of final administrative actions.

With respect to Article 9, the Registry Regime should clarify that this Article is not intended for use by biosimilar products and that, in line with the appropriate standards, a product can only become a reference drug through submission of a full registration dossier for each indication.

With respect to "conditioned sanitary registry" in Article 10, the Registry Regime should be amended to articulate criteria of unmet medical need or emergency situation. The use of a biosimilar in these types of situations, especially if approved in non-reference countries with ambiguous regulations, poses safety risks to exposed patients.

In Article 15 of the Registry Regime, BIO notes that there are two different naming schemes for drugs of biologic and biotechnologic origin. This implies that there is a discernible difference between these two types of products. However, there is no reason to believe that such differences exist and that even if they do, they have an impact on the structure and/or function of the biologic product. Moreover, the Registry Regime should articulate a requirement for distinguishable names for biosimilar products for purposes of accurate prescription by health care professionals, to avoid risks of inappropriate substitution, and for traceability and pharamacovigilance.

Article 17 of the Registry Regime, concerning pharmacovigilance, should also require that pharmacosurveillance prerequisites for biosimilars be equal to those of the innovator at the moment the biosimilar is granted registration approval. In addition, attribution measures, to facilitate accurate link of events and outcomes between products (i.e., traceability) should also be required for effective pharmacovigilance.

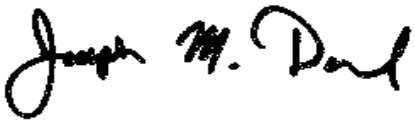
Finally, BIO notes that the time frame for existing holders of sanitary registries to comply with the requirements of the present Decree is shorter than what is considered to be reasonable. Additional requirements for clinical trials, or testing could impact the availability of such products for patients. As often times some of these products are the only ones that are available for use, their absence could create significant access issues for patients.

Conclusion

We commend the Government of Colombia for taking steps towards developing a sanitary regime for drugs of biological origin. We urge that the Registry Regime include a transparent process which ensures patient safety and provides effective protections to incentivize innovation. There should be a transparent statutory and regulatory process which enables manufacturers of first drug of biologic origin to provide full and fair opportunities to engage government authorities and other stakeholders in a meaningful public process. As such, it is urged that all regulations and guidelines, or proposed amendments to such regulations and guidelines, be publicly available and subject to public notice and comment.

We appreciate the opportunity to express our views. 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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