Biotechnology Industry Organization

June 5, 2013

MINISTÉRIO DA SAÚDE
Secretaria de Atenção à Saúde
Departamento de Ações Programáticas e Estratégicas
Área Técnica de Saúde da Pessoa com Deficiência
SAF/Sul, Trecho 2, Edifício Premium, Torre 2, bloco F, térreo, sala 11
CEP: 70070-600– Brasília/DF

Re: Public Consultation N°7 of April 10, 2013: Standards for Enabling Specialized Care Services and Reference Centers for Rare Diseases in the Unified Health System (SUS) and Guidelines for Integral Care for People with Rare Diseases in the SUS

Dear Mr. José Eduardo Fogolin Passos:

The Biotechnology Industry Organization (BIO) thanks the Brazilian Ministry of Health (MoH) for the opportunity to submit comments on the proposed *Standards for Enabling Specialized Care Services and Reference Centers for Rare Diseases in the Unified Health System (SUS)* and *Guidelines for Integral Care for People with Rare Diseases in the SUS*.

About BIO and the Biotechnology Industry

BIO is a not-for-profit trade association representing more than 1,100 companies, academic centers and research institutions in over 30 nations worldwide involved in the research and development of innovative biotechnology products and services. Ninety percent of our members are small and medium sized enterprises (SMEs) working to develop and commercialize cutting-edge products in the areas of healthcare, agriculture, energy, and the environment. Simply put, this global industry would not exist without a stable, predictable and transparent intellectual property system that enables researchers and their sponsors to manage the risks of biotechnology innovation.

Developing a biotechnology product is a lengthy and expensive endeavor. In the health sector, on average, it takes US$1.2 billion over a period of more than a decade to bring a new biopharmaceutical to market; for agricultural biotechnology it takes hundreds of millions of dollars and over a decade to develop a new product. Biotechnology companies, whether in the United States or in Brazil, choose to make this investment when there is a reasonable expectation of a return on investment.

Government policies that support innovation are critical as the biotechnology industry seeks to develop innovative healthcare, agricultural, industrial and environmental biotechnology products and provide them to users all around the world. Innovation requires not only scientific research and commercial expertise, but also supportive and dynamic governments that help facilitate the expensive and risky process by which that science is turned into new products. Brazil has recognized the value of innovation in maintaining a robust, diversified economy that can compete in the 21st century, and declared biotechnology a national priority. A symbiotic relationship between Brazil and

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the biotech industry results in high paying jobs, a healthier, more productive workforce, and positive externalities benefiting society as a whole. While Brazil has made significant strides over the last decade and established ambitious goals, opportunities abound for additional policies to further support the ecosystem of innovation and put the country at an even stronger competitive advantage in the global economy. With this background, BIO respectfully submits comments for the consideration of the Brazilian Ministry of Health on the proposed texts.

General Comments:

Countries across the globe are realizing the significant impact rare diseases are having on their populations, and responding by putting national policies in place to address these unmet medical needs. BIO commends the government of Brazil for taking steps towards developing regulatory requirements to ensure patients suffering from rare diseases have access to treatment through certified reference centers, for putting forth a validated and accepted definition of rare disease, and for prioritizing access to diagnostic and therapeutic resources. At the same time, policies that help to support and advance orphan drug development, approval and access should also be considered in the formulation of a national rare disease policy. Thus, significant strides in the treatment of rare diseases are possible by leveraging and coordinating Brazil's existing services and capabilities—improving the organization of assistance to these patient populations, providing for earlier diagnosis, and developing well-trained, assessable provider networks—as well through more efficient and broader access to appropriate medicines. Below, we have provided additional areas for your consideration.

Definition of Rare Disease:

Although the World Health Organization's (WHO's) definition of rare diseases may be a valid metric to quantify the disease areas that may qualify for classification as a rare disease, BIO recommends that the MoH instead adopt the European Union (EU) definition of rare disease as it is the definition commonly used by numerous countries who have already developed rare disease policies. Specifically, the EU's definition of a rare disease is one that affects no more than 5 per 10,000 persons in the EU.[1] In addition to its use across European countries, this definition also has been adopted by other Latin American countries, including Chile and Mexico. By adopting a definition more commonly used throughout the world, Brazil will be better aligning its rare disease policy efforts with those already well-established in other countries. In addition, many global decision-makers, including the National Institute for Health and Care Excellence (NICE) in England[2] and the All Wales Medicines Strategy Group (AWMSG) in Wales[3],

[1] Definition outlined in recommendation published by The Council of the European Union on June 8, 2009. Available at http://ec.europa.eu/health/rare_diseases/policy/legal/index_en.htm.
[2] NICE. 2004. Citizen Council Report on Ultra-Orphan Drugs. Available at http://www.nice.org.uk/niceMedia/pdf/Citizens_Council_Ultraorphan.pdf.
[3] Reference to AWMSG definition included in NHS document entitled "Overview of Current Policy for Orphan Drugs" published in June 2008. Page 31.

have made efforts to further stratify rare diseases and identify a subset of rare diseases that should be classified as "ultra-rare." For example, NICE considers a disease ultra-rare if it affects no more than 1 out of 50,000 persons.[4] Several EU Member States and expert groups have begun developing or are already using their own definition of ultra-rare diseases in the absence of a common EU definition, and have evoked the need for a European reference for this specific ultra-rare patient population. We encourage Brazil to continue this momentum and adopt the NICE's definition of an ultra-rare disease as part of its comprehensive rare disease policy.

Rare Disease Stratification:

The development of integrated healthcare treatment networks with access to appropriate diagnostic and therapeutic resources is critical, particularly for the treatment of patients with rare diseases, but does not appear to be directly correlated with, or require the further stratification, by the type of rare disease. To date, worldwide rare diseases policies have focused on a definition based largely on disease prevalence and severity, and have not sought to further categorize such diseases based on their etiology, as this may further decrease patient access to treatment for diseases that do not fit into the pre-specified disease categories. Therefore, the MoH's attempt to create different "assistance axes" to categorize rare diseases seems unnecessary and overly complicated, and could lead to unintended restrictions in patient access to needed care. Based on the current stratification proposed within the Public Consultation document, it appears that not all rare diseases, based on the proposed disease prevalence definition, would have an appropriate group in which to be classified. As such, we recommend the MoH follow other countries' rare disease policies in which diseases are not categorized into different types.

Regulatory Considerations:

Patients with rare diseases face many challenges including misdiagnosis and lack of effective therapy. Drug developers also face challenges of limited knowledge about the disease, hard-to-find patients, and problematic return on investment. Providing orphan drug status for medicines to treat rare diseases is an important component of a viable rare disease policy.

Speeding the development and availability of drugs that treat serious diseases is in everyone's interest, especially when the drugs are the first available treatment, have advantages over existing treatments, or provide therapeutic alternatives for patients who have exhausted currently available therapeutic options. In particular, the current EU regulations that provide for three different types of "Authorization" depending on public health need, recognizes and accounts for the challenges of developing drugs for

[4] NICE. 2004. Citizen Council Report on Ultra-Orphan Drugs. Available at http://www.nice.org.uk/niceMedia/pdf/Citizens_Council_Ultraorphan.pdf.

rare diseases, especially in very small patient populations. The EU Authorization mechanisms, first laid out in the European Parliament Directive 2001/83/EC Annex I, Part II, provide for three approval pathways: full approval/authorization; conditional marketing authorization; and authorization under exceptional circumstances.

Full approval is considered when there is comprehensive data to assess benefit-risk balance. Conditional marketing authorization is considered when comprehensive clinical data are not yet available but the benefit-risk balance is positive. This is a provisional authorization and once data required for full authorization is provided, it may become a "full authorization". Conditional authorization may apply for orphan products as well as products intended for seriously debilitating or life-threatening diseases and products intended for use in emergency situations such as in response to qualified public health threats. Conditional authorization can only be granted for medicines satisfying an "unmet medical need", and it is therefore important patients have early access to the medicine concerned. Authorization under exceptional circumstances recognizes that in some cases, comprehensive clinical data cannot be provided because a condition is too rare, or due to the present state of medical knowledge or collection of such information would be contrary to medical ethics. Exceptional Circumstances is an alternative to a full authorization when comprehensive data cannot be provided. Approval under exceptional circumstances is widely used, and is nearly always applied for treatments for ultra rare diseases/conditions.

Another regulatory approach that has facilitated earlier access to drugs in the United States is the US Food and Drug Administration's accelerated approval regulation. Accelerated approval regulation is designed to facilitate the development of drugs to treat serious diseases and fill an unmet medical need on the basis of a surrogate endpoint followed by post-market confirmatory studies. The purpose is to get important new drugs to the patient earlier.[5] It should be noted that successful accelerated approval regulation does not compromise the standards for the safety and effectiveness of the drugs that become available through this process. Priority review mechanisms to expedite the regulatory review of drugs that offer major advances in treatment can also help improve patient access to new, novel therapies and can help ensure Brazilian patients have prompt access to novel medications that may be recommended for treatment according to each rare disease, based on clinical protocols and therapeutic guidelines.

In some countries, tax credits (US) for research and development (R&D), fee waivers and reductions (US/EU) and market exclusivity (US/EU) have helped companies bring more rare disease therapies to patients. BIO recommends such policies for consideration as the Brazilian government works to enable specialized care services for

[5] US FDA Fast Track, Accelerated Approval and Priority Review. Retrieved 2 May 2013 from: http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm.

rare diseases. Indeed, BIO believes these incentives have been an essential part of the success of the orphan programs in these countries.

Early Access:

Even following accelerated or conditional approval, reimbursement negotiations can delay access for patients who need the medicine. It may take longer to negotiate reimbursement for an orphan drug than it does for a traditional drug. To address the problems caused by access delays in the face of urgent unmet medical needs, and to allow for the easy transition from approval to rapid commercial use, Brazil could consider creating funded early access and compassionate use programs for orphan drugs, as a means to provide patients with needed therapies as quickly as appropriate. Such programs should be structured in a way that promotes timely reimbursement following regulatory approval and maximizes incentives to render reimbursement decisions as efficiently as possible. Furthermore, there should be clear guidance as to how patients would be transitioned to commercial reimbursement once marketing authorization is granted. The current "Temporary Authorization for Use" (ATU) program in France[6] is an example of a best practice enabling early access to patients for potentially life-saving new drugs. Such guidance should also clarify post-study access to medication for all clinical trial participants who received a benefit and for those the study physician recommends continuation of treatment. At the end of a study, all patients participating should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified in by the study up until the product is commercially available. Following approval, access will be available through the normal channels for supply of approved products.

An additional consideration is the balance between accelerating patients' access to treatments, and the need to make the best possible assessment of the risks and benefits of new medicines. This is important to ensuring that patients suffering from rare diseases are entitled to the same quality of care and access to treatments as those suffering from more common diseases.

Establishment of Coordination Center for Rare Diseases within MoH:

As is the case for other diseases and public health issues such as blood products, neonatal screening, and immunizations, we recommend that a dedicated "Coordination Center" be established within the MoH for rare diseases. The Coordination Center for Rare Diseases should be similar in structure to those that already exist within the MoH's Department of Specialized Care (DAE)/ Secretary of Health Assistance (SAS) such as the General Coordination of Blood and Blood Products (CGSH) and the National Neonatal Screening Program (PNTN). Other Coordination Centers include those for the General Coordination of the National Program of Immunization (CGPNI) and the General Coordination of Communicable Diseases (CGDT) within the Secretary of Health

[6] French regulation on ATU available through http://agence-tst.ansm.sante.fr/html/pdf/5/atu_eng.pdf.

Surveillance (SVS). The creation of such Coordination Centers has been extremely useful to allow for comprehensive and coordinated management of these programs and the patients that they serve. The purpose of the Coordination Center for Rare Diseases should include oversight of implementation of the rare disease policy adopted by the MoH, including focus on ensuring patients with rare and ultra-rare diseases have access to needed medical care, including treatment at rare disease reference centers. In addition, the Coordination Center for Rare Diseases should be responsible for determining metrics to evaluate the care provided to patients with Brazil with rare diseases. Finally, the Coordination Center should focus on developing programs to educate health professionals about the unique nature of rare and ultra-rare diseases and the challenges that such patients are likely to face.

Health Technology Assessment (HTA), Pricing and Funding of Rare Disease Treatments:

The small number of patients with each rare disease means that new orphan medicines typically have high acquisition costs per patient and are launched with evidence drawn from smaller patient populations and less extensive clinical trials. This can cause problems in evaluation and reimbursement, particularly if government agencies apply standards and processes developed for common conditions (e.g., cost-effectiveness analysis) to rare diseases, or expect levels of evidence that are unattainable at time of launch.

Decision-making about availability and access to rare disease treatments does not benefit from a closed technical process of cost-effectiveness evaluation. The basic arithmetic is that drug development costs must be weighed against small patient numbers, with a consequent high cost per quality adjusted life year (QALY) gained. In addition, efficacy/effectiveness information can only be based on small numbers of subjects making statistical analyses difficult since small changes in patient data cause large fluctuations in final results. The low number of affected patients ensures a limited budgetary impact to the system, so using traditional cost-effectiveness analyses to evaluate treatments for rare and ultra-rare diseases may create access problems for patients in need of life-saving treatments. As such, it is suggested that CONITEC creates a special technical subgroup for rare diseases, as it already exists for (I) clinical protocols and therapeutic guidelines (PCDT), (II) revision of RENAME list (national list of essential medicines), and (III) medical devices.

The involvement of patients, clinicians, and companies in setting the framework for assessment of a new orphan medicine is essential. These wider groups are needed to properly include values such as lack of alternative treatments, equity of care, fairness of process, and society's willingness to pay more for therapies affecting rare catastrophic diseases. All these values need to be factored into decisions on reimbursement and access.

Unique orphan drug-specific evaluation processes are not effective unless paired with a corresponding process for funding. When such a paired system does not exist, a positive

centralized review of orphan drugs may lead to funding challenges at the hospital or regional level. If responsibility for funding treatments for a rare disease falls on one or two centers of excellence, then the budget impact of a concentration of rare disease patients can overload the local health budget and provision of a high standard of care can be compromised. Countries which have provided central funds to resource rare disease treatments in their specialist hospitals[7] tend to be more successful in generating sustainable and high-quality levels of care. Brazil's most successful disease programs in terms of coordination and patient outcomes—such as those for hepatitis B, HIV, hemophilia, and Gaucher's Disease—have historically received financing from the Federal level, which has ensured equitable access to treatment for all patients suffering from these conditions. In order to ensure the development and implementation of a successful and equitable rare disease policy for all of Brazil's population, explicit financial support and budget development from the federal government must be planned and enforced.

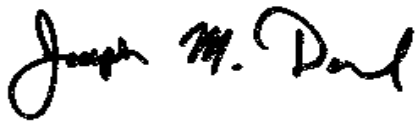
Multi-Stakeholder Approach:

The development of national rare disease policy should involve input from all rare disease stakeholders. Foundations, patient groups, academia, industry, and others are vital for developing accurate knowledge about different rare diseases, research challenges, treatments options, and the burden of disease, which are all considerations for Brazil's rare disease policy.

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/health-care.

Respectfully submitted,



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[7] Examples include Japan's Intractable Disease Fund, http://www.nanbyou.or.jp/english/nan_kenkyu_45.htm; and Australia's Life Saving Drugs Program- http://www.health.gov.au/lsdp.