INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

10 October 2019

President William Dib
Agência Nacional de Vigilância Sanitária (ANVISA)
International Affairs Office - Assessoria de Assuntos Internacionais (AINTE), SIA,
Trecho 5, Área Especial 57, Brasília-DF, CEP 71.205-050

Dear President Dib,

On behalf of the International Society for Stem Cell Research (ISSCR), I write to share our comments regarding ANVISA's proposed regulations for advanced therapy medicinal products (Public Consultation No. 706). The ISSCR is the leading professional organization of stem cell scientists and represents more than 4,000 members in Brazil and around the world. Our members are scientists, clinicians, ethicists, and educators dedicated to the responsible advancement of stem cell research and its translation to the clinic.

Our experience in other countries shows that it is critical to test the safety and effectiveness of new therapies before they are marketed to patients. We are deeply concerned that ANVISA's proposed regulations will promote the premature commercialization of stem cell-based interventions before they are proven safe and effective. We urge you to consider revising the draft regulations to promote the development of safe and effective new treatments, protect the public health, and harmonize them with the evolving international standards.

Safety and Efficacy Testing Before Commercialization

The regulatory review process for new treatments must be designed to rigorously evaluate the safety and effectiveness of each potential therapy before it is marketed to patients. Accordingly, the ISSCR Guidelines (Recommendation 3.5.1) urge national governments to "maintain rigorous review pathways to ensure that stem cell-based products conform to the highest standards of evidence-based medicine." We are concerned that ANVISA's proposed conditional marketing authorization (Chapter VI) fails to meet that standard and will allow products to be

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marketed to patients without adequate testing of safety and effectiveness.

The premature commercialization of regenerative medicine products threatens the development of scientifically validated therapies and places unnecessary economic burdens on healthcare systems and the public. When new products are sold to patients before their effectiveness is fully tested, government and private healthcare payers are often compelled to reimburse for the products without knowing whether they work, and physicians with inadequate expertise are left on their own to evaluate the safety and efficacy of products for individual patients. For example, Japan's conditional approval pathway has come under increasing scrutiny for the conditional approval of regenerative medicine products based on a presumption of efficacy. Their national health system is currently reimbursing for a product that was conditionally approved based on an open-label clinical trial with seven patients. Another speculative and controversial treatment for spinal cord injuries received conditional approval earlier this year.

Multiple other international regulators have created better mechanisms to accelerate the development of new treatments while ensuring the safety and efficacy of new products. For example, in the United States, the Food and Drug Administration (FDA) has several programs to expedite the approval of new therapies for serious or life-threatening diseases. The FDA's accelerated approval pathway enables them to fast track new therapies by using surrogate endpoints that are "reasonably likely to predict clinical benefit" or "clinical endpoint[s] that can be measured earlier than irreversible morbidity or mortality" (21 U.S.C. 256 (c)). The FDA also has several programs that provide product developers with early advice throughout the development process to expedite the approval of new therapies. Similarly, the European Medicines Agency's (EMA) PRIME program enables early engagement with product developers to accelerate the development of new products. The EMA also has a conditional marketing authorization pathway that allows them to approve products if the "risk-benefit balance" is positive and the "benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk" (EC No 507/2006). We encourage ANVISA to consider the FDA and EMA as models for revising the proposed conditional approval pathway.

Clarify the Definition for Minimal and Extensive Manipulation

In many countries, unscrupulous businesses marketing unproven products as stem cell-based "treatments" have abused ambiguous product definitions to evade regulators. In response, governments have begun to strengthen and clarify the regulatory pathway for stem cell-based products. We welcome ANVISA's commitment to improving the regulation of stem cell-based products in Brazil with the proposed regulations. These guidelines must be carefully drafted to allow common medical procedures like skin grafts and breast reconstructions to continue while ensuring that complex and more speculative therapies are more stringently regulated.

While we appreciate that the ANVISA's proposed definitions for minimal and extensive manipulation are broadly similar to the definitions used by the FDA and the EMA, we recommend including specific examples to explain that the manipulation of cells and tissues can change their biological characteristics and physiological functions. Examples regarding adipose tissue are particularly important, as adipose tissue is often used as a source for mesenchymal stromal cells (sometimes improperly referred to as mesenchymal stem cells), which is one of the cell types most commonly advertised by clinics marketing unproven stem cell-based interventions. We urge you to include an example that clarifies that the processing of adipose tissue by centrifugation and enzymatic digestion to isolate the stromal vascular fraction is considered extensive manipulation. This would harmonize your guidance with the FDA's guidance regarding minimal manipulation (example 14-1) and EMA's classification of advanced therapy medicinal products (2.2.4 a) substantial manipulation).

Distinction Between Class I and Class II Advanced Therapy Medicinal Products

We encourage ANVISA to regulate minimally manipulated somatic cell therapy products for non-homologous uses (Class I products) as stringently as Class II products, including extensively manipulated cell therapy products, tissue-engineered products, and gene therapy products. The use of cell therapies for non-homologous treatments is complex, speculative, and has been shown to have risks, including tumor growth and blindness. Furthermore, all cell therapy products come with processing and contamination risks that need to be evaluated by regulators and minimized by product developers. Due to the inherent risks of somatic cell therapy products for non-homologous uses, we believe it is important to require the same level of information (including the quality dossier) for Class I and Class II products to enable a rigorous evaluation of the safety and efficacy of each potential new therapy. This would also harmonize your regulations with the FDA and the EMA, which regulate cell therapy products for non-homologous uses as stringently as extensively manipulated products.

Experimental Therapies for Life-Threatening Conditions

Patients understandably seek experimental therapies when they have no other treatments for incurable diseases or conditions. Many countries enable patients to access experimental treatments through well-regulated programs that require prior authorization from national regulators. The FDA's Expanded Access Program enables patients to access experimental treatments through a process that provides important checks and balances to ensure patient safety, facilitates drug development, and preserves the integrity of clinical trials. Similarly, the EMA's Compassionate Use Program enables experimental therapies to be "made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials." We encourage you to revise Chapter VII, Article 33 to require prior authorization for every advanced cell therapy medicinal product. While we appreciate that ANVISA proposed regulations will require prior

authorization for Class II products, we believe it is also justified for Class I products due to the product's inherent risk as previously mentioned.

Thank you for considering our recommendations as you continue to develop regulations for advanced therapy medicinal products. If the ISSCR can clarify any of these views or be of assistance, please contact Eric Anthony, ISSCR's Director of Policy at eanthony@isscr.org.

Sincerely,

Deepak Srivastava, MD
President, ISSCR
President, Gladstone Institutes