Regulation of Tissue Engineered Devices in some Latin American Countries: Development and External Influences*

Reglamentación de dispositivos de ingeniería tisular en algunos países Latinoamericanos: desarrollo e influencias externas

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ABSTRACT

***Background*:** Emergence of new technologies and advances in tissue engineering strategies to treat diseases are shifting the conventional conception of medical devices. Tissue engineered products, manufactured as a combination of biomaterials, cells, and/or bioactive factors, are intended to temporarily restore an organ or tissue function, and induce the generation of newly site-appropriate functional tissue. Regulatory pathways for tissue engineered products require grouping policies controlling each of the components: materials, human cells, and active molecules. ***Purpose*:** To review current regulatory policies for medical devices (and within this, tissue engineered products), in a subset of Latin American countries, and to analyze the influence of international organizations and technological world power countries on policies of that subset. ***Methods*:** Top-down and horizontal diffusion models were employed to identify how regulatory policies have moved to Brazil, Colombia, Ecuador, Mexico, and Peru. ***Results*:** There are differences in technological appropriation to comprehensively define and classify medical devices. None of the countries have a definition of tissue engineered products. A top-down diffusion pattern was found to be associated with the current regulations. A horizontal diffusion is being applied as a regional effort to facilitate commercialization of medical products within Latin America. ***Conclusion*:** The concept of tissue engineered products is slowly arriving into the evaluated Latin American countries. Each country has the potential to take advantage of local institutions and regional and inter-regional coalitions to improve current guidelines and prepare the health system to the introduction of tissue engineered products.

Keywords

classification; commercialization; Latin America; medical devices; product; public policy; regulation; tissue engineering

Thematic fields

health regulatory policies; public policy studies; tissue engineered product

RESUMEN

***Antecedentes*:** El surgimiento de estrategias de ingeniería tisular para tratar enfermedades está cambiando la definición tradicional de dispositivos médicos. Los productos de ingeniería tisular, fabricados a partir de la combinación de biomateriales, células y factores bioactivos, remplazan temporalmente un órgano o tejido e inducen la producción de nuevo tejido. Los mecanismos de reglamentación de productos de ingeniería tisular necesitan agrupar las políticas que controlan cada uno de sus componentes: materiales, células humanas y moléculas activas. ***Objetivo*:** Revisar las políticas de reglamentación actuales para dispositivos médicos (y entre estos, los productos de ingeniería tisular), en un grupo de países latinoamericanos, y evaluar la influencia que organizaciones internacionales y países con poder tecnológico mundial ejercen en las políticas locales. ***Métodos*:** Se utilizaron modelos de difusión *top-down* y horizontal para identificar cómo las políticas de reglamentación han llegado a Brasil, Colombia, Ecuador, México y Perú. ***Resultados*:** La apropiación tecnológica empleada para clasificar los dispositivos médicos de manera integral difiere entre los países. Ninguno define el concepto productos de ingeniería tisular. Se encontró un patrón de difusión *top-down* asociado a las reglamentaciones empleadas. Se está aplicando una difusión horizontal como esfuerzo regional para facilitar la comercialización de productos médicos. ***Conclusión*:** El concepto de producto de ingeniería tisular está llegando lentamente a los países latinoamericanos. Cada país tiene el potencial de aprovechar las

instituciones locales y las coaliciones regionales e interregionales para mejorar la regulación actual y preparar al sistema de salud para la llegada de productos de ingeniería tisular.

Palabras clave

América Latina; clasificación; comercialización; dispositivos médicos; ingeniería tisular; política pública; producto; reglamentación

Áreas temáticas

estudios de políticas públicas; políticas de reglamentación en salud; producto de ingeniería tisular

INTRODUCTION

With the emergence of tissue engineering applications as an alternative treatment to restore, repair or replace damaged organs in the human body, new medical devices and implantable materials are being produced (1). Research, development, and clinical applications of tissue engineered products have been mostly made in post-industrialized countries like the United States of America, the United Kingdom, some members from the European Union, and Japan. In parallel to product development, these countries have concentrated their efforts in the establishment of new regulatory policies aimed at not only controlling the commercialization of tissue engineered products, but also defining their path from the bench to the bed side, evaluating risks and benefits, and ensuring efficacy of the treatment and security of the patients.

As a result of the high investment and technological resources needed, advances in tissue engineering applications in Latin American countries are lower when compared with developed countries. Even though the clinical applications of tissue engineered products seem to be far from the reality, in part due to elevated costs and lack of coverage by health systems, some initial efforts are being applied for the development of alternative treatments to injuries that otherwise could not be treated by conventional means (2,3). In light of the limitations that emerge from applications that are new in health care systems, it is analyzed here whether the concept of tissue engineering is conceivable within the regulation for research and development of medical and implantable devices in a subgroup of Latin American countries: Brazil, Colombia, Ecuador, Mexico, and Peru. Additionally, an evaluation of the influence exerted by international public and private organizations upon the existing policies for tissue engineering applications in the studied Latin American countries is included.

TISSUE ENGINEERING: DEFINITION, COMPONENTS, AND FACTORS

The field of tissue engineering has emerged as an interdisciplinary area that combines efforts from biology, medical sciences, and engineering, to design and produce functional substitutes of damaged tissues/organs that due to their extent cannot be repaired by the own biologic system (4). Tissue engineering applications are of particular interest as an alternative to organ donation strategies, which have been associated with disadvantages in terms of long-life immunosuppression and a limited number of organ donors, among others. Tissue engineered products are intended as temporary substitutes that provide mechanical and functional support while inducing the reparative process within the tissue. For instance, they are ideally composed of

a degradable scaffold material to bring the required three-dimensional structure, an adequate source of cells, and bioactive molecules, all of which are employed individually or in combination (1). For this reason, tissue engineering applications can have cell-based approaches, as occur with stem cell injections (5), whereas other applications have scaffold-based approaches, in which an *in vivo* cell infiltration is expected (6). More complex applications involve the implantation of already cell-seeded scaffold materials (7).

Each constituent of the tissue engineered product has important considerations that should be taken into account and that should be a matter of strict regulation to ensure successful clinical applications. First, scaffold materials which can be produced from synthetic (i.e., polymers), biosynthetic (i.e., polyhydroxyalcanoates), or natural (i.e., xenogeneic or allogeneic extracellular matrix-derived scaffolds) sources, are chemically and structurally different, and therefore could positively or negatively be associated with distinctive responses within the body (8). Factors such as the host response to the implanted scaffold material and the biocompatibility should be evaluated before any intended clinical application (9). The host response in general and in particular the plasticity of macrophages interacting with the scaffold materials, are the determinant factors defining long term outcomes of site appropriate functional tissue remodeling vs. foreign body reaction (10). The term biocompatibility refers to the ability of the implanted scaffold material to perform a tissue-specific function without eliciting a detrimental immune host response, characterized by chronic inflammation and development of a foreign body reaction, which ultimately can influence the failure of the tissue engineered product (10-12).

Second, it has to be recognized that inclusion of cells within the tissue engineered product increases the complexity of the clinical approaches. When cells are seeded on the scaffold material prior to implantation, an adequate cell source (i.e., autologous vs. heterologous stem cells), the mechanisms for vascularization, and the risks of cell manipulation, are among the factors that should be considered (13). Lastly, addition of bioactive molecules like cytokines, growth factors, or differentiation-stimulating factors, which are needed to promote cell migration, and differentiation, also require a detailed attention. The use of high doses and their release in the circulatory system might have adverse effects in other tissues, raising questions about the safety of the patient receiving the implant (14).

Based on the combinatorial options of tissue engineered components, the required regulatory pathways to commercialize tissue engineered-derived products might vary considerably. Whereas products containing cells require extra controls and highly trained personnel, less complex products (composed solely by the scaffold material) might provide more versatility as they can have a defined and longer shelf life, be shipped, and manipulated without requiring advanced training.

INTERNATIONAL REGULATORY FRAMEWORKS FOR MEDICAL DEVICES AND TISSUE ENGINEERED PRODUCTS

The development of a common regulatory framework for assurance of effectiveness and safety of medical devices in a global perspective started in 1992, when a group of medical device regulatory authorities from the European Union, the United States of America, Canada, and Japan formed the

Global Harmonization Task Force (GHTF), now identified as the International Medical Device Regulators Forum, IMDRF. The objective of the GHTF was to generate a regulatory consensus for medical devices and practices involving medical devices (15). Likewise, an original aim was to provide assistance in the regulatory process for medical devices in developing countries (16). The harmonized guidelines include a definition of medical devices as "*any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article:*

a) Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- *Diagnosis, prevention, monitoring, treatment or alleviation of disease… or an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices, providing information for medical or diagnostic purposes by means of in vitro, examination of specimens derived from the human body; and*

b) *which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means."* (17).

Additionally, this guideline provides the final agreement of classification of medical devices based on risk assessment, which means, the probability of that device to generate damage and the evaluation of the severity of the harm produced. The classification system proposes four different risk-based categories (Table 1), and within each one, a comprehensive sub-classification according

to invasiveness, bioactivity, and time of contact with the body. The classification and sub-classification systems allow for a straightforward searching to determine the risk level of a specific medical device (17).

The harmonization does not explicitly include tissue engineered products, which are the focus of this work; however, they do present options where these products could fit in a regulatory analysis. Specifically, they would be included into the group D, since they would contain animal- or human-derived cell or tissue components, bioactive components, and degradable materials.

REGULATION OF TISSUE ENGINEERING PRODUCTS THROUGHOUT LATIN AMERICAN COUNTRIES

The following section will focus on the identification of the tissue engineering term among the regulations for development, manufacturing, and commercialization of medical devices in a subset of Latin American countries: Brazil, Colombia, Ecuador, Mexico, and Peru. The sections will also provide information regarding the mechanisms of classification of medical devices according to the factors identified for tissue engineered products in these countries.

Brazil

In Brazil, the entity in charge of regulating manufacturing, packaging, imports, and commercialization of medical devices is the National Health and Surveillance Agency (ANVISA, *Agência Nacional de Vigilância Sanitária*). Under the Resolution RDC No. 185 of 2001, ANVISA provides the orientations for registering, validating, and modifying the commercial rights of

medical products in the country. According to this entity, a medical product is defined as any equipment, material, or system used to prevent, treat, or rehabilitate patients. Medical products cannot exert their main function through pharmacological, immunological, or metabolic means. The medical products are classified from I to IV, according to the intrinsic risk that they represent for the patients using them (18). Both risk classification and sub-classification are similar to the guidelines established by the GHTF.

Based on the proposed system of classification and considering the definition of tissue engineered products, those medical devices intended to accomplish functions of tissue repair would belong to class IV devices. The resolution includes the cases of biologic derived materials and combined materials with bioactive molecules (drugs); however, it does not consider regulatory mechanisms of complex tissue engineering applications where the cellular components are included.

TABLE 1
CLASSIFICATION OF MEDICAL DEVICES IN THE HARMONIZATION CONSENSUS FROM THE GHTF (17)

Factor / Class	Risk Level	Invasiveness	Intended use
A	Low Risk	Non-invasive	Products that do not have contact with the patient or contact only the intact skin. Devices for channeling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body. Devices that come into contact with injured skin if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates. Devices are manufactured from or incorporate non-viable animal tissues or their derivatives that come in contact with intact skin only.
		No surgically invasive (used through body orifices)	Devices not intended for connection of an active medical device or connected to a class A device, for a transient use.
		Surgically invasive	Reusable surgical instruments.
B	Low-Moderate Risk	Non-invasive	Devices connected to a medical device in class B or higher. Devices for storing or channeling blood or other body liquids or for storing organs, parts of organs or body tissues. Devices for filtration, centrifuging or exchanges of gas or of heat of blood, other body liquids or other liquids intended for infusion into the body. Devices that come into contact with injured skin devices principally intended to manage the microenvironment of a wound.
		No surgically invasive (used through body orifices)	Devices not intended for connection of an active medical device or connected to a class A device, for short term use. Devices that are intended to be connected to an active medical device in class B or a higher class.
		Surgically invasive	Devices intended for a transient or short-term use and designed for a single use. Implantable devices, and long-term surgically invasive devices intended to be used in the teeth.

Factor / Class	Risk Level	Invasiveness	Intended use
C	Moderate-High Risk	Non-invasive	Non-invasive devices intended for modifying the biological or chemical composition of blood, other body liquids or other liquids intended for infusion into the body. Non-invasive devices which come into contact with injured skin intended to be used principally with wounds which have breached the dermis and can only heal by secondary intent.
		No surgically invasive (used through body orifices)	Devices not intended for connection of an active medical device or connected to a class A device, for long term use.
		Surgically invasive	Transient or short-term devices intended to supply energy as ionizing radiation. Transient devices intended to have a biological effect or be partially/totally absorbed. Short term devices intended to have chemical changes in the body. Transient or short-term devices intended to deliver medicines. Implantable devices, and long-term surgically invasive devices.
D	High Risk	Non-invasive or invasive	All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and which is liable to act on the human body with action ancillary to that of the devices. All devices manufactured from or incorporating animal or human cells/tissues/derivatives thereof, whether viable or non-viable
		Surgically invasive	Transient, short term, or long-term devices intended to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body. Short term or long-term devices intended to have a biological effect or be partially/totally absorbed. Short term devices intended for use in direct contact with the central nervous system. Implantable and long-term devices intended to be life supporting or life sustaining. Implantable and long-term devices intended to administer medicines. Implantable and long-term devices intended to have chemical changes in the body.

Resolution RDC No. 56 of 2010 provides regulations for cell banks working with hematopoietic stem cells derived from bone marrow, peripheral blood, umbilical cord, or placenta, for autologous or allogeneic transplants (19). The use of hematopoietic stem cells is restricted to the correction of defects of the bone marrow or restoration of the hematopoiesis after chemotherapy processes involving damage of the myeloid and lymphoid precursors. The isolation of other cell types (e.g., mesenchymal stem cells) for therapeutic use in tissues other than blood, is not considered within the regulation, and therefore its application in tissue engineered approaches is limited.

In 2010, following an international trend in bio-therapeutic products lead by the World Health Organization (WHO) (20), ANVISA released the Resolution RDC No. 55 to regulate the registration process of biological and biotechnological products in the country for marketing purposes. It includes both products manufactured in Brazil and imported from approved companies to commercialize them in the country. The final goal of the resolution is to guarantee quality and efficacy of biologic medicines, therefore ensuring safety of the patients (21). For instance, the regulation provides mechanisms to control hormones, growth factors, and bioactive molecules that could be used for tissue engineering applications.

Colombia

Colombia has a regulatory system similar to the one described in Brazil. The regulation for licensing for the production, processing, packaging, storage, commercialization, import/export, and maintenance of medical devices for human use is found in the Decree No. 4,725 of 2005. Under this Decree, the National Institute of Surveillance of Medicines and Food (INVIMA, *Instituto Nacional de Vigilancia de Medicamentos y Alimentos*) is given the administrative power

to execute the regulatory functions. INVIMA is also assigned the faculty to perform technical studies and analysis required to verify quality of medical devices, as well as evaluation of compliance of good manufacturing practices (GMP). Likewise, the Decree defines the classification of medical devices according to the potential risk (I: low, IIa: moderate, IIb: high, III: very high) associated with its use (22). Each of the categories is also divided in a sub-classification system based on invasiveness of the medical device, comparable with the guidelines provided by the GHTF.

The parameters for manipulation of human tissues are established within the Decree No. 2,493 of 2004. INVIMA is again the surveilling entity evaluating methods of isolation, preservation, processing, storage, transportation, transplantation and/or implantation in the recipient patients. The regulations include bone marrow and tissues other than blood. The institutions in charge of processing and storing the tissue samples are authorized tissue and bone marrow banks (non-profit institutions), which should guarantee GMP. The tissue and bone marrow banks are coordinated in a network centralized from the Health Ministry and that directly communicate with Health Service Institutions, the parties performing the surgical procedures to the patients (transplants or implants) (23).

More recently, under the Decree No. 1,782 of 2014, the country gave a step forward in the recognition of the importance of biotechnology in the development of new medical products and stipulated the regulation for production and commercialization of biologic and biotechnological medicines. Biologic and biotechnological medicines include all cytokines, growth factors, and hormones, among others, that can be used to improve the performance of implanted biomaterials

(24). The Decree is further reinforced with guidelines for the evaluation of immunogenicity of biologic medicines (Resolution No. 4,490 of 2016) (25), and a guideline for the evaluation of the stability of biologic medicines (Resolution No. 3,690 de 2016) (26). The regulation of biologic and biotechnological medicines, however, does not include products that "*contain or are exclusively formed by cells and/or non-viable human or animal tissues and that do not exert a function primarily pharmacologic, immunologic, or metabolic.*" (26) This exclusion, however, disclaims the bioactivity of naturally produced scaffolds, which have been shown to promote constructive remodeling of the tissue, as it has been shown by Sicari *et al*. (27). In fact, even though these are not "biologic medicines" as stated in the Resolution, they are composed mainly by proteins that are be recognized by host cells inducing an immune response.

Ecuador

In Ecuador, the regulation for medical devices and biologic products is centralized through the National Regulatory, Control and Surveillance Health Agency (*Agencia Nacional de Regulación, Control y Vigilancia Sanitaria*). Under the Official Registry No. 573 of 2009, the regulation for commercialization of medical devices is provided. As indicated in the original document, these parameters were established following international norms, such as those from the Food and Drug Administration (FDA), the International Council for Harmonization (ICH), the WHO, and the International Organization for Standardization (ISO) (28).

As seen for the other countries described, the medical devices are defined as articles, instruments, devices, or artifacts, for use in diagnosis, treatment, or prevention, to replace or modify the anatomy or physiological processes in the body. They are classified according to their use

(therapeutic or diagnostic), invasiveness (non-invasive or invasive), and risk level (I: very low, II: moderate, III: high, IV: very critical) (28). The regulation, however, does not provide a comprehensive association between the classification criteria (use and invasiveness with risk level).

Additionally, the regulation does not have input about what is considered low, moderate, high, or critical risk, as well as the specific applications, uses, or considerations that should be analyzed to classify a medical device within each of the established parameters. Within the regulation, factors such as degradability of materials, combination of medical devices with drugs, and biologic materials are not considered either, and therefore tissue engineered devices cannot be easily identified/classified within the local regulatory system.

The official Registry No. 21 of 2013 provides the regulation for commercialization of biologic medicines both locally and with other countries. Like in the other described countries, the present regulation contains the framework for vaccines, biotechnological medicines, among others. Moreover, contrasting with the other countries, the Ecuadorian regulation includes a guideline for tissue engineering under the Official Registry No. 745 of 2012. The regulation indicates that the National Institute of Donation and Organ Transplantation (INDOT, *Instituto Nacional de Donación y Trasplante de Órganos*) has the regulatory functions associated to organ donations and transplantations, and includes the topics of cell therapy, tissue engineering, and xenotransplantation. INDOT is also provided with the faculty to modulate activities of research in the field (29). Even though a general framework is included in the regulation, additional definitions

framing the terms of tissue engineering and cell therapy, as well as the mechanisms by which research in the area is going to be focused, are needed.

Mexico

In Mexico, regulations are distributed between three entities: the Federal Commission for the Protection against Risks in Health (COFEPRIS, *Comisión Federal para la Protección contra Riesgos Sanitarios*), the National Center for Transplants (CENATRA, *Centro Nacional de Trasplantes*), and the National Center for Transfusion of Blood (CNTS, *Centro Nacional de Transfusión Sanguínea*), all derived from the Health Ministry (30).

COFEPRIS covers medical devices. The institution has established a series of guidelines to provide the regulatory framework for certification of medical devices. Under the regulation, there is not an explicit description for tissue engineered products. A similar system of classification is found in this guideline when compared to the other countries, with the same limitations when intended for tissue engineered products. Three levels of risk assessment (class I, II, and III) are described and combined with the levels of uncertainty (whether the medical device is commonly used in medical applications or has been recently introduced in the market, and whether it is dependent of material variations or dosage concentrations), invasiveness (non-invasive, invasive for less than 30 days, invasive products for more than 30 days) and safety (defined as “proved” or not in patients) (31). Based on the specific descriptions of the intended use, tissue engineered products will be ranked within class III, since it covers invasive materials that will last more than 30 days and that will partially or totally degrade exerting a biologic effect.

Under the regulation of CENATRA, Mexico entered in the international efforts to control biologic medicines (32), within the exact same terms used in Brazil, Colombia, and Ecuador. Additional norms are found for the use of human organs and tissues for therapeutic purposes, specifically for transplants (33).

Lastly, the CNTS is in charge of the norms regulating the acquisition and use of hematopoietic stem cells (34), but directives for other stem cells are not provided, generating a limitation in tissue engineering applications.

Peru

In Peru, pharmaceutical and medical devices are regulated under the Law 29,459 of 2009. The entity in charge is the General Directorate of Medicines, Supplies, and Drugs (DIGEMID, *Dirección General de Medicamentos, Insumos y Drogas*). Herein, a medical device is defined as an instrument, machine, material or any other article to be used in the treatment or alleviation of a disease or lesion. It involves also research, replacement, modification, or support of the anatomy or a physiological process (35). Both definitions could include the objective of a tissue engineered product, but the term was not explicitly stated.

Medical devices are classified according to the risk that they represent. Like in the definitions found for the equivalent regulation in other countries, medical devices are ordered as low, moderate, high, or critical risk potential (35). However, as occur with the regulation in Ecuador, the specific parameters that should define the risk levels are not explained in the Law. The same information is found in Decree 016-2011-SA, which regulates Law 29459, and includes the

consideration of risk level for medical devices as suggested in the GHTF (36), but the exact descriptions are not provided in the document.

The Decree also has the requirements for commercialization of biologic products. No additional information, compared to those found in other countries' regulations, is present here. Peru relies in the information provided by other countries, which the regulation frames as "countries with high sanitary surveillance", such as France, Holland, United Kingdom, United States, Canada, Japan, Switzerland, Germany, Spain, Italy, Belgium, Sweden, Norway, Australia, Portugal, Denmark, and Korea, to get the certificates to import products for commercialization in the country (36).

On the other hand, the National Organization of Donation and Transplants (ONDT, *Organización Nacional de Donación y Trasplantes)* was created as the entity in charge of the regulation of human tissue donation for therapy (approved by Law 28,189 of 2004) (37), bone marrow and hematopoietic stem cells transplants (38).

MEDICAL DEVICES IN LATIN AMERICA: WHERE DOES THE REGULATION COME FROM? AND HOW ARE THEY EVOLVING?

From the information above, it can be perceived the similarity of the regulation for medical devices among the studied countries. The information however is more comprehensive in some countries (Brazil, Colombia, and Mexico) than in others (Ecuador and Peru), showing a lack of reflection in the process of policy adaptation.

A detailed comparison between the framework designed by the GHTF and the ones found in each of the studied countries, allows the identification of fragments of the former into the local ones. Even though they represent a good effort to incorporate the regulation into the public policies of the countries, following a top-down diffusion pattern, important aspects involving complex medical devices, like those comprising the tissue engineered ones, were excluded from almost all the regulatory policies of Ecuador and Peru. For instance, the evolution of technologies in these countries or the importation processes of complex devices could be difficult or impossible.

More recently, and in order to overcome the problems of evaluation of complex medical devices, the region of Latin America has initiated a program of cooperation and technical assistance, where the regulatory agencies of different countries have been articulated to help each other and to share information regarding medical devices introduced in the market of the region. The National Regulatory Agencies of Regional Reference (ARNR, *Autoridades Reguladoras Nacionales de Referencia Regional*) was founded by the regulatory agencies from Argentina, Brazil, Colombia, Cuba, and Mexico, in 2011 to accomplish these functions and help into the development of the region in terms of evaluation of quality and safety of medical devices. Since 2014, the ARNR has received help from the FDA, and Health Canada in order to strengthen the regulatory capability of the region, provide technical cooperation to other regulatory agencies, and improve strategies of communication and diffusion of important material (39). The regional effort generated herein could be analyzed from a perspective of an Advocacy Coalition Framework (ACF) model, where the regulatory entities entered into coalition and strategically are forming learning processes or sharing regulatory information that facilitates the evaluation of medical devices into the region. The coalition helps them to be prepared for the rapid technological changes occurring in medical

devices around the world, and to rapidly answer to alerts generated with specific medical devices in other countries.

The international coalitions seen here have been motivated among other factors, by established trade agreements between the involved countries. For example, the North American Free Trade Agreement (NAFTA) between the United States, Canada and Mexico, makes this last country one of the main markets for imported medical devices coming from the United States (40). Similarly, the Common Market of the South (MERCOSUR, *Mercado Común del Sur)* formed by Argentina, Brazil, Uruguay, and Paraguay, looks for the generation of a harmonized market for medical devices among these countries (41).

Some other strategies of horizontal diffusion have been applied in the region to improve the quality of the regulatory processes regarding medical devices across borders. They can be evidenced for example with the activities that INVIMA is doing since 2013 with other regulatory agencies in Paraguay, Venezuela, Ecuador, Chile, Dominican Republic, Peru, Costa Rica, and Salvador, providing them technical assistance and sharing with them its scientific and regulatory experience (39).

As seen with the topic of medical devices, similar experiences and harmonization of strategies to regulate medicines are being in process worldwide. In face of the challenges that globalization represents, for quality control and safety of the final users of medical devices and medicines, regulatory agencies around the world have congregated in the International Coalition of Medicines Regulatory Authorities (ICMRA) (42). ICMRA was created on 2013, and the active members are

Brazil, Canada, China, European Union, France, Germany, Ireland, Italy, Japan, Korea, Mexico, the Netherlands, New Zealand, Nigeria, Singapore, South Africa, Switzerland, the United Kingdom, the United States, and the World Health Organization. The objective of ICMRA is to help providing direction in regulatory process regarding medicines, traditional and emerging ones, sharing information and with a collaborative focus to globally advance in the research and development of the field (43). Particularly, ICMRA generates harmonized guidelines for regulatory processes regarding biologic and biotechnological medicines, for public access. The utilization of these guidelines is of free decision from each country.

The coalition of countries with the goal of sharing experiences in medicines has not been unique from ICMRA. Since 1997, Iberoamerican Network of Authorities in Medicines (Red EAMI, *Red de Autoridades en Medicamentos de Iberoamerica*) was formed, and now has 22 Iberoamerican countries participating: Andorra, Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panamá, Paraguay, Peru, Portugal Dominican Republic, Uruguay and Venezuela (44).

CONCLUSION

The definition of tissue engineering is broad enough to allow the participation of different biomaterials, cells, and molecules, whose interaction represents a complex, that is difficult to regulate. Immunological, pharmacological, and biocompatibility factors should be evaluated for each tissue engineered device to ensure safety and efficacy when used for clinical applications.

Regulatory mechanisms being applied in the reviewed Latin American countries have a strong influence from international regulations being applied through global coalitions among the regulatory agencies. It is evident however a less restricted, and lower developed system of evaluation policies for tissue engineered products. These differences provide a window of opportunity for applying clinical research that might not provide the safety and efficacy that should be guaranteed to the patients.

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