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Proposal of regulatory framework for Advanced Therapy Medicinal Products in Brazil

Proposta de marco regulatório para os Produtos de Terapias Avançadas no Brasil

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ABSTRACT

Introduction: Advanced Therapy Medicinal Products (ATMP) have been a therapeutic promise for the treatment of several diseases, including those for which there is no therapeutic alternative available on the market. These products, obtained from human cells, were categorized internationally as a new therapeutic class with similar approach as biological medicines, although with different criteria, due to their peculiarities. **Objective:** This article aims to describe the history of the discussions and regulations published for the thematic, and to present the perspectives related to the development of the Brazilian regulatory framework for this new category of product, with the objective of providing a stable and transparent regulatory environment, favorable to the technological development at national level, as well as to attract national and international investments in the field. **Method:** The development of this article was based on the research of the history of normative published about the topic, on the regulatory initiatives implemented by Anvisa as well as on the participation of the authors in forums and discussions towards the theme. **Results:** Basis of the national regulatory framework for PTA to be elaborated, and exposure of the main aspects of the proposal. **Conclusions:** The proposal of regulatory framework for ATMP will cover the regulations for evaluation and approval of clinical trials by Anvisa, Certification of Good Cell Practices for producer establishments and marketing authorization of products.

KEYWORDS: Regulation; Cell Processing Center; Advanced Therapy Medicinal Products; Cell Therapy; Regulatory Framework

RESUMO

Introdução: Os Produtos de Terapias Avançadas (PTA) têm sido a grande promessa terapêutica para o tratamento de diversas doenças, inclusive aquelas para as quais não existe alternativa disponível no mercado. Estes produtos, obtidos a partir de células humanas, foram categorizados em âmbito internacional como nova classe terapêutica para a qual a regulamentação adotada assemelha-se à dos medicamentos biológicos, embora com abordagem e critérios diferenciados devido às peculiaridades dos PTA. **Objetivo:** O presente artigo tem como objetivos descrever o histórico das discussões e regulamentações editadas para a temática e apresentar as perspectivas relacionadas ao desenvolvimento do marco regulatório brasileiro para esta nova categoria de produto, a fim de propiciar um ambiente regulatório estável e transparente, favorável ao desenvolvimento tecnológico em âmbito nacional, bem como ao fomento através de investimentos nacionais e internacionais. **Método:** O desenvolvimento deste artigo baseou-se na pesquisa do histórico de normativos sobre o tema, nas iniciativas regulatórias adotadas pela Anvisa, bem como na experiência dos autores a partir de participação em fóruns e discussões afetas à área. **Resultados:** Fundamentação do marco regulatório sanitário nacional para PTA a ser elaborado, e exposição dos principais aspectos da proposta. **Conclusões:** A proposta de marco regulatório nacional para os PTAs abarcará regulamentos para avaliação e aprovação de ensaios clínicos pela Anvisa, Certificação de Boas Práticas em Células para estabelecimentos produtores e registro de produtos.

PALAVRAS-CHAVE: Regulamentação; Centro de Processamento Celular; Produtos de Terapias Avançadas; Terapia Celular; Marco Regulatório

INTRODUCTION

Law n. 9.782, of January 26, 1999, which created the Brazilian Health Surveillance Agency (Anvisa)[1], established, among the competencies of the Agency, the regulation, control and inspection of products and services that involve risk to the human health. In its art. 8, the Law regards goods and products subject to health surveillance as those that might pose risks to public health, including those obtained through genetic engineering or other related procedures. It is within this context that cellular therapies fit with the purpose of clinical trial or therapeutic use in humans. The first resolution published in the country to regulate the technical and sanitary criteria for the functioning of umbilical cord blood banks, establishments responsible for making available hematopoietic stem cells for transplantation, dates from the year 2003[2]. Even today, this therapeutic procedure, popularly known as bone marrow transplantation, is the only type of cell therapy recognized by the Brazilian Federal Council of Medicine (CFM).

Subsequently, in 2005, with the publication of Law n. 11.105[3], of March 24, Brazil took an important step in the field of cellular therapies. The use of embryonic stem cells for research and therapy was approved by this law. Decree n. 5.591, of November 22, 2005[4], which regulated the law, attributed to Anvisa, in its art. 65, the competence to create norms for the procedures of harvest, processing, laboratory testing, storage, transportation, quality control and use of human embryonic stem cells. This attribution given to Anvisa was important for the beginning of the internal discussion processes within the Agency regarding the need to improve the regulation on cellular therapies. Especially the therapies employing stem cells that, from then on, were being used in several fields and different approaches in basic research, with promising prospects for the development of clinical trial and therapeutic use, in Brazil and in the world. There is special emphasis on researches in the fields of central nervous system repair, treatment of diseases of genetic, immunological and metabolic natures, as well as restoration of tissues and organs with lesions and the promising induced pluripotent stem cells[5].

In 2007, the European Medicines Agency - EMA[6] and the United States Food and Drug Administration - FDA[7] published their main regulations and guidelines for production and control of the so-called Advanced Therapy Medicinal Products (ATMP), which received this name and were placed in a new therapeutic class, no longer understood as a medical procedure, but as a product.

European legislation[6,8] divides the ATMP into three categories:

a) Somatic cell therapy medicinal products, those consisting of cells or tissues intended for therapeutic, preventive or diagnostic purposes through their main metabolic, pharmacological and/or immunological mode of action for autologous or allogenic use in humans. They are more than minimally manipulated and/or perform in the recipient a distinct function from that performed in the donor. Carticel® (culture of autologous chondrocytes) is an advanced cell therapy medicinal product currently approved by the EMA for the repair of symptomatic cartilage defects caused by acute or repetitive trauma in patients who have presented an inadequate response to arthroscopy or other procedures.

b) Tissue engineered products, consisting of cells organized in tissues or organs that have the properties for, or are used in or administered to human beings with a view to regenerating, repairing or replacing a particular human tissue or organ, in the presence or not of structural support consisting of biological or biocompatible material, which have undergone substantial manipulation; and/or perform in the recipient a distinct function from that performed in the donor. Holoclar® is a tissue engineered product, also with current marketing authorization issued by the EMA, which consists of culture of autologous corneal epithelial cells in fibrin matrix, indicated for the repair of corneal damages.

c) Gene therapy medicinal products, *in vivo* or *ex vivo*, defined as those containing an active substance that includes or consists of recombinant nucleic acid, used or administered in humans, for the purpose of regulation, repair, substitution, addition or suppression of a specific genetic sequence. Their therapeutic effects are related to the recombinant nucleic acid sequence they contain or to the gene expression product of that sequence. An example of gene therapy product is Kymiriah®, autologous genetically engineered T cells indicated for the treatment of patients with refractory or relapsed acute lymphoblastic leukemia.

It is worth highlighting the difference between the concepts of minimal manipulation and extensive manipulation of cells[6,8]. Minimal manipulation consists of a cell or tissue processing technique that does not significantly alter its biological characteristics, including differentiation and activation status, proliferation potential, and metabolic activity. Minimal manipulation techniques include cutting, separating, centrifuging, immersing or preserving in antibiotic solutions, concentrating, purifying, filtering, freeze-drying, irradiating, freezing, cryopreserving or vitrification, among others that meet the definition presented. The processing of stem cells for the purpose of conventional transplantation is considered an act of minimal manipulation of cells. The extensive manipulation, in turn, consists of cell or tissue processing that alters any of its biological characteristics, including differentiation and activation status, proliferation potential, and metabolic activity. In this context, all types of cell culture are considered as substantial manipulation.

This stage was set in 2007, when the main international regulatory agencies included cellular therapies in the logic of products. However, the same did not happen in Brazil, because the local legal understanding at the time was fully based on the rule established in art. 199, §4, of the Brazilian Federal Constitution of 1988[9], which prohibits any type of trade of organs, tissues and parts of the human body, including products derived from them. With that, in Brazil, the cellular therapies were categorized by

the regulatory bodies under the same rationality of blood for transfusion purposes and the cells and tissues for conventional transplantation, that is, products that cannot receive marketing authorization. Sanitary regulations for these products have therefore been established as minimum requirements for the functioning of establishments responsible for donor selection, harvest of cells, processing, storage, laboratory controls, release for therapeutic use and transport of biological material.

In 2011, Anvisa published the Resolution of the Collegiate Board of Directors (RDC) n. 9, of March 14, 2011, which provides the rules for the functioning of Cellular Technology Centers (CTC) for the purposes of clinical trial and therapy[10]. This RDC was the result of the discussions of a Working Group (WG) composed of specialists in the field of cellular therapies, formally appointed by the Agency. The WG was formed by members of the Brazilian Association of Cell Therapy (ABTCEL), members of Anvisa and the Brazilian Ministry of Health. RDC n. 9/2011 established the minimum requirements for the provision of cells by the CTC, in addition to making the sanitary licensing of these establishments mandatory by the competent Health Surveillance body. Furthermore, in its art. 7, the RDC determined that human cells could only be made available for clinical trial after approval of the trial project by the Research Ethics Committee/National Research Ethics Committee (CEP/Conep). If they were to be made available for therapeutic purposes, the therapies should be recognized by the CFM or the Federal Council of Dentistry (CFO), as applicable. Thus, in 2011, sanitary regulation established criteria for quality control and cell safety, provided by RDC n. 9/2011, although the approval of procedures for therapeutic use involving cellular therapies remained the responsibility of Professional Councils.

It should be noted that, as explained above, both EMA and the FDA in 2007 already considered this new therapeutic category - the ATMP - as a product, whose clinical trials are subject to evaluation and approval by health authorities, prior to its initiation, as well as require approval and marketing authorization before they can be made available to the population.

In this sense, Anvisa's participation in forums, meetings and international meetings focused on the discussion of ATMP, especially in the meetings of the regulators' group of Pharmaceutical Inspection Co-operation Scheme (PIC/S)[11], challenged the regulatory standard established by Brazil, since the model initially adopted was completely different from the models adopted by the main international regulatory agencies. In addition, foreign companies have questioned the Agency about the possibility of evaluating clinical trials and marketing authorization of products of this type.

Considering these discussions and the desire that Brazil would adopt a regulatory model closely harmonized with international regulation for products and services related to health surveillance, Anvisa also held in 2011 the National Seminar on Regulation in Cell Therapies[12], with strong participation of representatives of the regulatory bodies, among which the Ministry of Health, the Ministry of Science and Technology, the National Institute of Industrial Property (INPI), Professional Councils, Associations, Universities and the regulated sector. The purpose of this Seminar was to promote a broad and democratic discussion about the various aspects that involve the area of cellular therapy, considering scientific, ethical and legal approaches, and to disseminate the state of the art of cellular therapies, as well as the prospects in this field, the public funding of research in Brazil, as well as refering on the subject of intellectual property. Regarding the latter, presentations were made on the international patent regime and the flexibility of the health sector, national legislation on intellectual property, the impact of health patents and the development of products consisting of or based on cells and human tissues with a focus on obtaining patents. Finally, the last panel of the Seminar focused on the debate on bioethical and legal aspects, sessions on bioethics in the face of the development of cellular therapies, the interpretation of article 199 of the Brazilian Federal Constitution from the point of view of these products and the guarantee of access to cellular therapies. In this panel, there were reflections on the reinterpretation of the Constitution over time, considering the technical-scientific progress and the urgency to ensure compliance with the basic constitutional rights of the Brazilian citizens. These discussions were vital to boost the processes of reinterpretation of the veto to the marketing of products of human origin by the Federal Constitution and elaboration of the proposal of a new health and safety reagulatory framework.

In 2012, Anvisa instituted its 1st Committee for Advanced Cell Therapies (CAT), inspired by the European version[13]. The CAT currently employs consultants of well-known technical expertise in cell and gene therapy and has the following attributions: to assist in the elaboration of regulations that define the technical-sanitary criteria for the evaluation of clinical trials and marketing authorization, to issue recommendations on clinical trials, on the safety and efficacy of ATMP and on the regulatory framework of these products for the purpose of subsidizing decisions of the technical area and the Anvisa Collegiate Board of Directors (Dicol).

In addition to the contextualization presented in 2013, the international WG on gene and cell therapy, made up of representatives of the major international regulatory agencies - the International Pharmaceutical Regulators Forum (IPRF) - published a summary[14] on the regulatory prospects for the ATMP categories, which concluded:

a) cells which have undergone substantial manipulation in the laboratory or which perform in the recipient a function other than that performed in the donor pose high intrinsic risks to the health of the users. Therefore, the related clinical investigations as well as their therapeutic use require evaluation and prior approval by regulatory agencies;

b) the origin of the cells - whether autologous (from the individual him/herself) or allogeneic (obtained from a donor) - represents less impact on the risk assessment than the degree of manipulation to which the cells are subjected;

c) there is a striking difference between the regulatory framework of cells subjected to minimal manipulation for use in the same function and the regulatory framework of cells submitted to minimal manipulation but have a distinct function in the recipient than in the donor. The latter denotes evaluation of efficacy of the therapy;

d) some regulatory authorities exempt products of autologous origin from being subject to regulatory rules applied to other ATMP, provided that they are processed at the "bedside" in a hospital context.

Ultimately, in 2016, due to the discussions about the access of the Brazilian population to the ATMP, and considering the national regulatory context that was outlined in view of the legal compliance at the time, the Anvisa's Federal Attorney's Office, through Legal Opinion[15], was favorable to the possibility of marketing authorization of ATMP based on the principle of human dignity and fundamental rights to life and health, conditioned to the construction of a strict infraconstitutional regulatory framework to ensure that substances of human origin to be used in ATMP are free of charge, collected unselfish free, spontaneous and informed donation, in order to avoid the risk of any abuse. This rereading of the constitutional content paved the way for the development of the regulatory framework to be elaborated by the Agency. The figure shows the early days of the national regulatory framework affecting the area, culminating in the decision for the possibility of marketing authorization of ATMP.

METHOD

A broad search was carried out in Brazilian and international published regulations on the topics of "cell therapy", "advanced therapy medicinal products" and "stem cells", without time delimitation.

We evaluated the official documents published by the Food and Drug Administration (FDA) of the United States, and the European Medicines Agency (EMA) of the European Community, as well as by the Japanese Agency for Products and Medicines (PMDA), available on their websites in pages dedicated to advanced therapy medicinal products. The personal contributions of the authors, obtained through their participation in specific forums on the subject, of a regulatory and scientific nature, between the years 2005 and 2017, contributed to the enrichment of this article.

RESULTS AND DISCUSSION

Considering the health risks involved in the production and use of an ATMP, Anvisa chose to follow, in its best conception, the regulation established by Europe as the conceptual axis guiding the proposal for a national regulatory framework. In the meantime, the Agency was faced with the need to adapt the ATMP concept accepted by EMA to fit its internal structure. With that in mind, Anvisa adopted the following definitions: ATMP are products consisting of cells of human origin or their derivatives not chemically defined and are categorized into three types: advanced cell therapy medicinal products, tissue engineered products and gene therapy medicinal products. This last category includes, according to the definition suggested by Anvisa, only the *ex vivo* products of gene therapy. The category of *in vivo* - gene therapy products in which the final product corresponds to the nucleic acid sequence to be infused directly into the patient, in order to obtain therapeutic, preventive or diagnostic property, without the mediation of *ex vivo* - transfected carrier cells - was then considered a type of classical biological product, and should follow the specific regulatory framework for this class of medicines. According to the definition adopted by the current national regulations, the product containing chemically defined molecules with known biological activity is now classified as a biological medicine[16].

Currently, the ATMP under development in Brazil should follow the same ritual applied to conventional therapies, and the clinical trials are analyzed only by the CEP/Conep System responsible

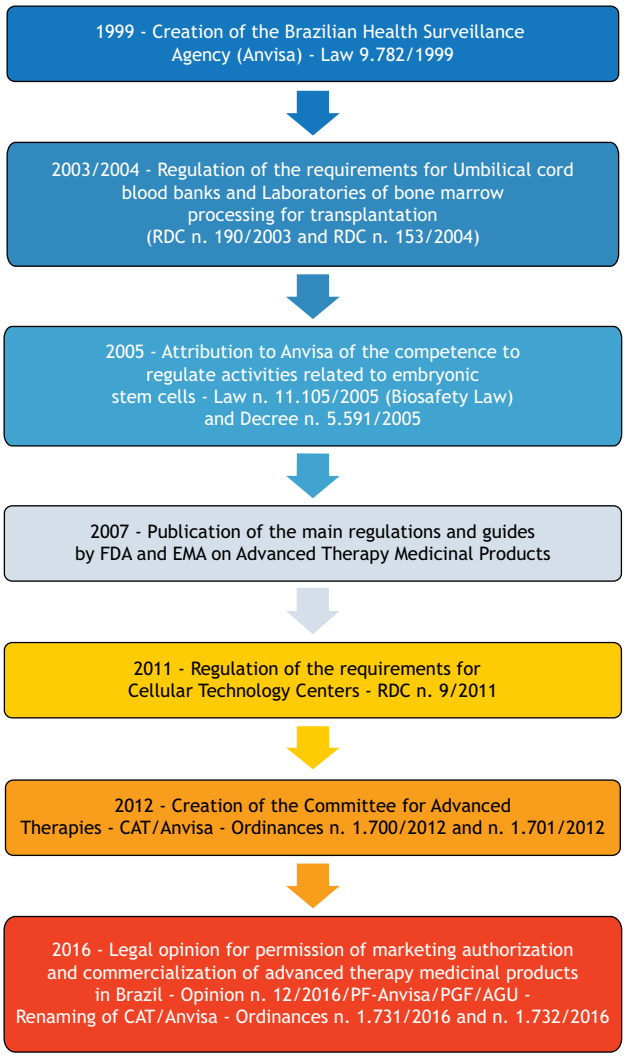

Figure. Timeline: the early days of the sanitary regulatory framework related to Advanced Therapy Medicinal Products in Brazil.

for evaluating and approving studies involving human beings, in a way that takes into account the relevant ethical and scientific foundations[17]; and the therapeutic use of the products being recognized by CFM or CFO.

However, recognizing ATMP under the umbrella of therapeutic products implies that Anvisa takes responsibility for evaluating their quality, safety and efficacy, as determined by Laws n. 6.360, of September 23, 1976[18] and n. 9.782/1999[1]. In view of that, Anvisa should begin to issue the marketing authorization of such products prior to their commercialization or availability to the population.

Given this context, in order to understand the national regulatory framework for ATMP to be elaborated, the Table summarizes the respective proposal, as states Anvisa's Regulatory Agenda 2017-2020[19].

Good Cell Practices for therapeutic use and clinical trial purposes

The RDC that will address the Substituir por Good Cell Practices for therapeutic use and clinical trial composes the proposal of regulatory framework for ATMP in Brazil, together with the regulations that will regulate clinical trials, registration and Certification of Good Practices of producing establishments.

The RDC draft of Good Cell Practices is aligned with the international regulatory framework of Good Manufacturing Practices (GMP)[20] and comprises the conceptual basis and handling conditions required for ATMP, according to their categorization of risk by determining that:

a) all activities developed at the cellular processing center are clearly defined and systematically reviewed;

b) it be provided with all necessary resources to carry out the expected activities, including qualified and trained personnel; physical infrastructure; equipment, instruments, computerized systems, suppliers, support services and, where applicable, outsourced services; materials, reagents and diagnostic products *in vitro*; and protocols approved and in force;

(c) the necessary validations, qualifications and calibrations are carried out;

(d) the traceability of the products is maintained and the records show that all stages of the production process have been followed and that the quantity and quality of the product obtained are in line with what is expected;

(e) records allowing the traceability of ATMP are archived in a safe, organized and easily accessible manner;

f) a system capable of collecting any nonconforming product should are implemented; and

g) appropriate actions are taken and registered with respect to non-compliant ATMP and, when applicable, measures to prevent recurrences are adopted.

Clinical trials with advanced therapy medicinal products

The regulatory model guiding the present RDC proposal was based on RDC n. 9, of February 20, 2015[21], which provides for the regulation for conducting clinical trials with drugs in Brazil. Both models are aligned with the Good Clinical Practices: Document of the Americas[22] - a set of standards and ethical and scientific guidelines aimed at the design, conduct, records and dissemination of clinical trial results, although the proposed regulation of trials should take into account the specificities of these products, since the final product considered is, in synthesis, viable cells, not chemically defined molecules.

Regarding clinical trials, the main objectives of the regulatory proposal are:

a) to ensure the safety and rights of participants in clinical trials;

b) to ensure that such tests are properly conducted by qualified investigators;

c) to request review and approval of the clinical trial protocol by scientific commissions;

d) to require modification of the protocol and/or interruption of the tests, when necessary; and

e) enable on-site inspections to confirm the quality and reliability of the data obtained[21].

Chart. Proposed regulatory sanitary framework for Advanced Therapy Medicinal Products in Brazil.

Regulation - Anvisa (Addresses)	Objective
Good Cell Practices for therapeutic use and clinical trial purposes	To standardize Good Cell Practices for therapeutic use and clinical trial, by establishing technical and sanitary requirements related to the production cycle of cells and advanced therapy products, aiming at the safety and quality of these products.
Clinical trials with advanced therapy medicinal products	To define the procedures and regulatory requirements for conducting clinical trials with advanced therapy medicinal products in Brazil, including the Clinical Product Development Dossier to be submitted to Anvisa for consent.
Marketing authorization of advanced therapy medicinal products	To establish the requirements for the registration of advanced therapy products, in order to guarantee their quality, safety and efficacy.
Certification of Good Practices for producing establishments	To define the administrative procedures for granting the Certificate of Good Practices, which will ensure that the Cell Processing Center complies with the requirements of Good Cell Practices, according to specific regulation.

In accordance with the proposal, the trial sponsor or sponsor-researcher, as the coordinator of the clinical trial protocol, shall organize the product development plan in dossier format and collect the data on aspects of quality of the investigational ATMP, in order to aggregate information to mitigate possible risks to the participants of the clinical trials. Thus, the proposed regulation of clinical trials to be developed with investigational ATMP should be based on aspects related to product quality, as well as on safety information, in order to complement the evaluation of bioethical precepts, done by the CEP/Conep System.

Registration of Advanced Therapy Medicinal Products

The main objective of the regulation that deals with ATMP authorization will be the establishment of legal-administrative and technical-scientific criteria concerning the production, marketing, and therapeutic use of ATMP.

The ATMP authorization proposal, as well as the regulation of the clinical trials of these products, should take into account their particularities. Consideration should be given, for example, to questions on:

a) donor selection (clinical, physical, social and laboratory screenings);

(b) the type and origin of the product, whether autologous or allogeneic;

(c) the rarity of the disease to be treated, ie the scarcity of patients available for clinical trials;

d) difficulties in conducting controlled studies;

e) the complexity of monitoring quality parameters related to the final product made available for use; and

(f) guarantee of the homogeneity of batches of cells.

In view of the peculiarities of the ATMP, the marketing authorization proposal has paid special attention to risk management, as well as to the implementation of mechanisms that allow the Agency to grant a type of temporary sanitary registration to these products, such as the model adopted by the PMDA[23]. These are the main innovations of this regulatory proposal, which seeks to simplify the regulatory process without compromising safety and quality.

The assertion that has been evaluated by Anvisa and CAT, regarding ATMP is summarized as follows:

Issuance of marketing authorization for ATMP submitted to substantial manipulation techniques - classification of the product in the highest risk category: Anvisa must receive complete studies in order to grant the authorization. The studies must include a dossier with information about the quality (material data validation and quality controls, stability, traceability, among others), in addition to the reports of the non-clinical and clinical studies done with the product, in order to prove its safety and efficacy.

Issuance of a simplified authorization, exclusive to ATMP submitted to minimal manipulation techniques and that perform in the recipient a distinct function from the original function performed in the donor. In this case, we assume that the minimal manipulation techniques do not significantly change the biological characteristics of the cells: the dossier to be analyzed by Anvisa should contain only the reports of the non-clinical and clinical studies developed with the product, in order to prove its safety and efficacy.

Issue of authorization or temporary registration - category of analysis as sanctioned by the PMDA - in which a provisional authorization is granted, provided that the clinical trials carried out prove safety and have evidence of efficacy. In this case, patients who make therapeutic use of products certified through this type of authorization should be scientifically informed of such data by signing a specific Consent Form. The clinical centers will have the responsibility of developing rigorous mechanisms for monitoring and follow-up after market[21]. In Japan, this provisional authorization is valid for a specified period and, after that deadline, manufacturers must submit the complete documentation for the definitive registration of the ATMP by the regulatory agency. This proposal has been accepted from the regulatory point of view with good prospects, as it will enable the achievement of the particularities of the ATMP discussed earlier in this article.

Certification of Good Practices for producing establishments

In order to complete the proposed regulatory framework for ATMP, Anvisa envisions the issuance of a Certificate of Good Practices for producing establishments, in order to declare that they comply with the requirements of Good Practices. The administrative process for the purposes of issuing such Certificate still requires in-depth discussion, although it may assume the conditions established under the certification already granted to establishments.

CONCLUSIONS

The absence of a national regulatory framework for ATMP causes uncertainty in the productive sector and negatively affects the interest in the development of researches in Brazil. Furthermore, it hinders the country's achievement of the world technological progress in this area. The proposal to establish the national regulatory framework for ATMP is necessary to overcome the regulatory gap that currently exists and to enable the coordinated and articulated action of the Regulatory Agency. In this context, the role of the Committee for Advanced Therapies (CAT/Anvisa) has been fundamental to the development, together with the Anvisa team, of the national regulatory framework for ATMP, in line with what has been developed by the main international Regulatory Agencies.

The proposed regulatory framework presented in this article aims to ensure compliance with Anvisa's institutional mission - to protect and promote the health of people by intervening in the risks arising from the production and use of products and services

subject to health surveillance. In this sense, the Agency's expectation is that, in the next three years, the national regulatory framework for ATMP will be published in the form of regulations that will define the Good Cell Practices for therapeutic use, the criteria for conducting clinical trials, as well as the marketing authorization and post-authorization approval of these products, in addition to the rules for the Certification of Good Practices for cellular processing centers. This regulatory framework will aim to ensure the quality, safety and efficacy of these new products and, with that, guarantee safe access to future users. Based on regulatory convergence, its intention is to harmonize national and international guidelines and create a stable and transparent regulatory environment, in order to foster technological development at a national level and attract investments to the sector.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.