

Brazil breakthrough in advanced therapy Regulations: a boost for cell-based clinical trials and market approval in the region?

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Brazil just laid the regulatory path for advanced therapies with the recent publication of the regulatory framework by Anvisa, the national regulatory agency linked to the ministry of health. The new regulation had different objectives including, fostering clinical development and consequently, speeding Market approval of gene and cell products by optimizing the risk-based authorization process. This is also thought to prevent the use of unproven treatments in the country.

The technical framework that regulates the clinical trials with products of advanced investigational therapies in Brazil has just been published and details are available on the [agency website \(02/01/2019\)](http://portal.anvisa.gov.br/noticias/-/asset_publisher/FXrpx9qY7FbU/content/aprovadas-regras-para-estudos-de-terapias-celulares/219201?p_p_auth=Tm6XVs6i&inheritRedirect=false&redirect=http%3A%2F%2Fportal.anvisa.gov.br%2Fnoticias%3Fp_p_auth%3DTm6XVs6i%26p_p_id%3D101_INSTANCE_FXrpx9qY7FbU%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26p_p_col_id%3D_118_INSTANCE_veHKmkDUo2dN_column-2%26p_p_col_count%3D2):http://portal.anvisa.gov.br/noticias/-/asset_publisher/FXrpx9qY7FbU/content/aprovadas-regras-para-estudos-de-terapias-celulares/219201?p_p_auth=Tm6XVs6i&inheritRedirect=false&redirect=http%3A%2F%2Fportal.anvisa.gov.br%2Fnoticias%3Fp_p_auth%3DTm6XVs6i%26p_p_id%3D101_INSTANCE_FXrpx9qY7FbU%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26p_p_col_id%3D_118_INSTANCE_veHKmkDUo2dN_column-2%26p_p_col_count%3D2

An exclusive interview with Anvisa representative, Mr. João Silva, manager of Blood, Tissues, Cells and Organs Office of Anvisa, shed more light on the impact of such step for the advance of the regenerative medicine field in the country.

What is the actual regulation for cell therapy in Brazil?

The Federal Constitution of Brazil (1988) establishes that donation of parts of the human body (blood, tissues, cells and organs) must be voluntary and without marketing purposes. This premise determines the voluntary donation of the starting material for the production of cells in cell therapy, and forbids its commercialization. Based on this constitutional premise, there are laws that define the national transplantation policy and Good Practice guidelines of Anvisa for conventional cellular therapies, for example hematopoietic progenitor cell transplants.

What are the main highlights of the recently unveiled regulation?

RDC 214/2018 is the current Anvisa technical standard that defines Good Cell Practices for two types of products:

Conventional therapies: defined as minimally manipulated product for homologous biological use; this product will also require an additional approval of the clinical procedures of the Professional Councils and Ministry of Health in the context of Public Transplantation Policies (for example, in the case of transplantation of hematopoietic progenitor cells in bone marrow transplants).

Advanced therapies defined as substantial manipulated or minimal manipulated product with non-homologous application. The advanced cell therapy, gene therapy and tissue engineering must prove quality, safety and efficacy before obtaining conditional market authorization following registration and approval by Anvisa.

This means that Anvisa distinguishes 2 distinct categories for advanced therapies?

Yes, indeed, advanced therapies products were classified into two types according to risk:

Class I (*minimal manipulation, for non-homologous use or different biological function*) and **Class II** (*substantial manipulation - tissue engineering, gene therapy, cell production / laboratory*).

For **Class I** products, the documentary process is simplified and the initiation of the clinical trial is granted after submission of the documents to the Agency under monitoring, while for **Class II** products, clinical trials can only be initiated after approval by Anvisa.

What was the Brazilian scientific community reaction?

This initiative started in Brazil in 2012, with countless discussions and national and international forums. Initially there were many questions and debates about the peculiar nature of the cellular products, the difficulty of defining criteria for control of the final product, the differences between autologous and allogeneic products and the legal issues of commercialization of a product derived from the human body. The discussions evolved with the development of proposals for regulatory frameworks with the participation of researchers from both academic and from the private sector including small start-ups and large companies interested in contributing to the regulatory frame. This interaction has been very positive for defining the national guidelines allowing the investor to know with clarity the regulatory requirements.

What was the methodology followed by Anvisa? Other neighboring countries are also looking at regulating this field, any recommendation for the regional regulatory agencies?

Anvisa relied on a direct dialogue with the regulation sector. The transparent discussion between regulator and industry has been fundamental since the beginning of this process. Another fundamental factor was the creation of a Technical Committee formed by experts in the subject connected to Brazilian Universities, under the coordination of Anvisa. Also, the merge of two regulatory models in Brazil, the regulation of blood, tissues, cells and organs for transplants or transfusion and the expertise in regulation of biological medicines was fundamental. These two models allowed revisiting traditional regulation to propose a specific and innovative mechanism.

Where do ANVISA policies stand in comparison with global regulations such as the European, Japanese or US. FDAs?

The overall technical requirements defined by Anvisa are convergent with the ones defined by Europe, USA and Japan. The agencies of these countries have gained a great amount of experience in the subject through the important number of applications they received. Anvisa's regulatory model is obviously different due to the distinct research environment in Brazil. For readers to better understand the situation in our country, there are models of public health policies that interrelate

with private health plans. Likewise, there is public and private funding for research centers and biotechnology companies that must be inter-acting in a different reality from other countries.

For advanced therapy products, we use a regulatory model that provides a pre-market assessment with the possibility of conditional authorization, while focusing on the risk-based monitoring assessment. The model is well developed for conventional blood, tissue and cell banks in Brazil and has appeared to be useful with some amendments to adapt it to advanced therapies, specifically for efficacy, safety, and quality reviews of clinical trials and marketing authorization. Moreover, the approach of monitoring the entire product life cycle from development stage to its clinical use by patients is critical. Another point that deserves attention in the Brazilian model was the definition of advanced therapy products as a new class of therapeutic product other than medicine and health products, for example. This proposal gives opportunity for the development of innovative regulatory mechanisms.

What would be the average reviewing timeframe for a specific application?

It depends on the product and the development phase. For example, a highly complex gene therapy product (Class II) maximum reviewing time was set for 180 days from filing to a first decision. Advanced therapy products of less complexity such as Class I products, initiating research can be done immediately after submission of the documentation to the Agency, while the reviewing deadline is reduced to 30 days before issuance of the export and import authorization, if necessary.

It is hoped that these initiatives will promote the research and development of advanced therapies in Brazil, and perhaps, to serve as a model for the rest of the countries in the region. It is also important that such regulatory frame serves as a barrier for the misuse of cell therapy while encouraging legitimate scientific and clinical advancements in the region. The final intention of such initiative among others is to move the stem cell field from a medical buzzword to clinical evidence.