

REGULATORY CONSIDERATIONS FOR CELLULAR THERAPY

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ABSTRACT

Advanced therapy products can be an alternative treatment for several disease. Manufacturing steps and product release are critical points to avoid unsafe use of products. Quality controls tests, manufacturing practice, safety testing and efficacy trials need to be properly accessed before releasing to patients. Regulatory system for cell therapy products determines guidelines for production, clinical trials and registration, considering risk-benefit ratios. This article aims to discuss main aspects of National Regulatory for advanced therapy products.

Keywords: Regulatory; advanced therapy products; registration; good manufacturing practice

INTRODUCTION

Therapeutic potential of cellular therapy products has been shown in growing number of clinical trials and can be an alternative treatment to improve outcomes of several disease. However, development of this new approach needs to be faced at the risk of unsafe use of products. Quality controls tests, manufacturing practice, safety testing and efficacy trials need to be properly accessed before releasing to patients. These considerations have led to implementation of specific regulatory system for cell therapy products which incorporates consideration of risk-benefit ratios and includes quality controls tests to release products.

REGULATORY FRAMEWORK

In 1999, Brazilian National Agency of Health Surveillance (Anvisa) was established in order to regulate, control and inspect products and services that involve risk to human health^{1,2}.

After approval of studies with embryonic cells, in 2005, Anvisa was designated to create rules for collection and processing procedures, storage, transportation, quality control tests and use of human embryonic stem cells. This initial attribution triggered other regulations to improve development

of cell therapies products and in 2011, Anvisa published Resolution of the Collegiate Board of Directors (RDC) n° 9, which provides guidelines for operation of Cellular Technology Centers (CTC) for clinical research and use in conventional therapy¹. The RDC n° 09/2011 established minimum requirements for provision of cells by CTC, in addition to making sanitary licensing mandatory of these establishments. This regulation determined criteria for quality control and cell safety and also determined that human cells could only be made available for research clinic after approval of research project by Research Ethics Committee/ National Ethics Commission in Research (CEP/ Conep)³.

Similarly, in 2007, the European Medicines Agency (EMA) and the US Food Agency and medicines (Food and Drug Administration – FDA) published their main regulations and guides for production and control of Advanced Therapies Products^{4,5}.

In 2016, Federal Attorney's Office with Anvisa approved registration and commercialization of cell therapy products conditioned to establishment of a normative framework to guarantee ethical use of human cells⁶.

Considering risks involved in production and use of cell therapy products, Anvisa proposed national

regulatory framework based on: 1) Good Practices in Human Cells for Therapeutic and Clinical Research – Resolution of the Collegiate Board of Directors n° 508; 2) Clinical trials with advanced cell therapy products - Resolution of the Collegiate Board of Directors n° 506; 3) Registration of Advanced Therapies Products - Resolution of the Collegiate Board of Directors n° 505; and 4) Certification of Good Practices for producing establishments⁷⁻⁹.

The regulatory framework aims to ensure quality, safety and effectiveness of these new products and, in this way, guarantee safe access for future users. Several guidelines are outlined in these resolutions to provide good manufacturing practice, such as infrastructure, biosafety strategies, waste disposal, validation process, qualification of equipment and reagents and a quality management system.

It is worth highlighting the difference between concept of minimal manipulation and extensive manipulation of cells. First consists of a cell processing technique or tissues that do not significantly alter their biological characteristics, including differentiation and activation state, proliferation potential and metabolic activity. Stem cells processing for bone marrow transplantation purposes is considered minimal cell manipulation. Extensive manipulation, on the other hand, consists of processing of cells and tissues that alters any of their biological characteristics, including state of differentiation and activation, proliferation potential and activity metabolic and will be focus of our discussion¹⁰.

GOOD MANUFACTURING PRACTICES

Good manufacturing practices (GMP) involve all aspects of manufacturing to guarantee quality and safety of products supplied for therapeutic and research use. To achieve these practices, Cell Therapy Center should have qualified and trained personnel; adequate physical infrastructure; equipment, instruments, suppliers and support services qualified and approved; approved computerized systems that guarantees data traceability; materials, reagents and

products for in vitro diagnostics validated and all activities described in operational procedure approved by director of center.

Quality management system is crucial to success of cell therapy centers, monitoring all activities, reviewing release criteria of all products, identifying non-conforming products and determine root cause of non-conformance or error and determine appropriate corrective action. Quality management will be addressed in another chapter.

INFRASTRUCTURE

Cell therapy center must consist of environments for carrying out administrative activities, receiving biological products area, processing lab, including production of gene therapy vectors or the manipulation of genetic modified products, storage area and a quality control lab⁸.

The Cell Processing Center that process Genetic Modified Organisms (GMO) must be certified by National Technical Biosafety Commission (CTNBio). GMO requires dedicated rooms or isolated environments for manipulation, ensuring that structure is adequate to avoid environmental and professional risks in handling products. GMO and vectors risks are classified considering their characteristics, proposed use and adverse effects on human health and on environment¹¹. Cell Therapy Centers must be planned according to which GMO and vectors they will handle, as physical infrastructure is different for each risk group. As an example, Centers that handle class 2 risk products must have an autoclaving system for their waste before disposing of materials handled in this area.

A Clean Room and controlled environments with air particle count is required to minimize risk of contamination during product manipulation. ISO classification of air is given in Table 1. For advanced cell therapy products manipulation, an ISO 5 condition must be maintained surrounded by environment with ISO 8 classification^{8,12}.

TABLE 1 – ISO class number based on particle concentration¹²

ISO class number	Maximum Allowed Concentration Particles Equal Or Greater Than The Considered Size					
	0,1µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	10					
2	100	24	10			
3	1.000	237	102	35		
4	10.000	2.370	1.020	352	83	
5	100.000	23.370	10.200	3.520	832	
6	1.000.000	237.000	102.000	35.200	8.320	
7				352.000	83.200	293
8				3.520.000	832.000	2.930
9				35.200.000	8.320.000	29.300

Clean environments must perform microbiological monitoring regularly. The limits expressed in colony forming units (CFU) in operation are described in Table 2.

TABLE 2 – Limits of microbiological monitoring in clean environments⁸

	Sedimentation Plate (90 MM; CFU/4 HOURS)	Contact Plates (55 MM; CFU/ PLATE)	Air Sampling (CFU/M ³)
ISO 5	<1	<1	<1
ISO 8	50	25	100

BIO SAFETY

Cell Therapy Center must keep procedures to assure occupational and environmental safety, including waste disposal and transportation of biological material.

Cell Processing Center must have an advice regarding classification of the biosafety level of Environments, as well as the hygiene rules and necessary personnel protective equipment at entrance of each sector.

Transportation of biological products and samples must be packaged in a way that preserves their integrity and stability during transport, as well as guarantees safety of personnel involved in this process. GMO and its samples have and additional rule for transportation and center that will receive these products have to be certified to handle GMO class risk^{13,14}.

Reagents and products for in vitro diagnostics

All materials used in advanced cell therapy must be regularized with Anvisa and suppliers must be qualified by center. Materials used in collection and

processing cells must be sterile, non-pyrogenic and, when applicable, non-cytotoxic, of pharmaceutical grade and for single use. Centers must respect the manufacturer’s recommendations for use, conditions of preservation and storage and the expiration dates. Products of animal origin must be avoided^{8,15}.

Growth factors, measures of identity, purity and potency must be established, to ensure reproducibility of the characteristics of the cell culture that will be addressed in other chapter⁸.

Qualification and Validation

Qualification and validation are necessary to prove that all processes defined as critical are under control, providing security to products and users.

Qualification program should include: 1) Project qualification; 2) Installation qualification; 3) Operation qualification; 4) Performance qualification.

Project qualification provides evidence for acquiring, installing, and operating a new equipment or system have met initial requirements. Installation Qualification requires: 1) identification of installed items; 2) maintenance and calibration requirements; 3) list of

operating and work instructions given by supplier; 4) cleaning requirements. Operation Qualification corresponds to the evaluations or studies of critical parameters of operation of an equipment or system, with objective of evidencing, through documents, that all the functions of the equipment/system are in accordance with the manufacturer's manual. Performance Qualification must provide documented evidence that the equipment or systems and all your components can work consistently with your specifications and routine of work¹⁶.

Validation aims to demonstrate that critical processes, using specified materials and equipment, systematically achieve their goals, ensuring that consistent results are obtained, and final products are safe and of good quality. Validation can be based on evidence obtained through testing (prospective and concurrent validation) or on analysis of data accumulated over a given period (retrospective validation). Whenever possible, prospective validation should be opted for, since retrospective validations are no longer recommended¹⁶.

Quality control tests

In order to release final advanced therapy products for patient use there are tests that must be performed to guarantee quality and safety. This issue will be addressed in specific chapter.

CLINICAL TRIALS

All clinical trials with advanced therapy products must have Anvisa and respective ethics committees the CEP/CONEP approval.

Advanced therapy products are classified in two types: 1) Class I product: advanced cellular therapy product that undergoes minimal manipulation and performs a different function in recipient from that performed in donor; 2) Class II product: advanced cell therapy product subjected to extensive manipulation, tissue engineering product and gene therapy product. ⁽⁷⁾ In class I products trial, Anvisa approval will be based in documents about clinical investigation plan, containing description of the product and a summary description of indications, outcomes and population to be studied; and product's critical parameters of processes and critical attributes of quality that will be analyzed.

In class II products trial, documents with extensive description of product, including composition; biological and toxicological effects on animals and hu-

mans; information on safety and efficacy in humans; and possible risks and adverse events related to use of investigational product should be added to documents described in class I product trial for Anvisa approval⁷.

Clinical trials should be registered on clinical trial database of the "International Clinical Trials Registration Platform/World Health Organization" (ICTRP/WHO), the Brazilian Registry of Clinical Trials (ReBEC) or another entity⁷.

Cell Therapy Products Registry

Commercialization of advanced therapy products after efficacy and harmlessness are proven is possible by registration in Brazil. Requirements for registration for a class I product are: 1) studies to prove therapeutic effect and effective dose; 2) studies on the interaction of product with other tissues, with evaluation of potential side effects; 3) studies aimed to determine parameters of viability, shelf life, distribution, metabolism and excretion of the advanced therapy product; 4) product toxicity studies, including cellular component, excipients and any impurities related to process; 5) studies to determine potential immunogenic effects; 6) studies on tumorigenic potential of the product; 7) safety studies, which address aspects related to biodistribution and grafting, shelf life, oncogenetic transformation and cell line stability; and 8) clinical efficacy studies⁹.

Registration of class II product will be necessary to include documents with product manufacturing, containing: 1) information on starting material, material and excipients; 2) information about active component and final advanced therapy product; 3) Information about manufacturing steps; 4) protocol and report of stability studies performed; 5) additional comparability studies, considering possible changes in the advanced therapy product manufacturing process; and 6) description of storage of final advanced therapy product⁹.

CONCLUSION

National regulatory framework for advanced cell therapy products aim to ensure quality, safety and effectiveness of these new products and promote health of the population. Good manufacturing practices, clinical trials approval by Anvisa and registration of advanced therapy products guarantee safe access for future users and create a stable and transparent regulatory environment, to promote technological development.

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