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GUIDE FOR MANUFACTURE AND QUALITY CONTROL OF ADVANCED CELL THERAPY PRODUCTS

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1. INTRODUCTION

In veterinary medicine, the number of commercial laboratories that offer therapies based on autologous or allogenic mesenchymal stem cells and their derivatives has been growing considerably.

For the purpose of this guide, the products originating from the manipulation of these cells and their derivatives will be called advanced therapy products.

Clinical studies show that cell therapy have efficient and safe results in the treatment of diseases in animals, among which is the chronic kidney disease (Lee et al., 2017), neurological disorders (Zhang et al., 2005; Marconi et al., 2013), medullary lesion (Jung et al., 2009; Kim et al., 2016), hip dysplasia, osteoarthritis (Diekman et al., 2013; Davatchi et al., 2016) and corneal ulcers (Yao et al., 2012; Di et al., 2017).

The stem cells, in these cases, have immune-mediation, anti-inflammatory and tissue regeneration functions.

To ensure the safety and quality of the advanced therapy products provided for therapeutic use in animals, it is necessary to specify minimum technical-health requirements for the functioning of the laboratories that manipulate stem cells.

1. OBJECTIVES

The purpose of this guide is to provide technical guidance for the manufacture and quality control of advanced cell therapy products.

For the purpose of this guide, advanced therapy products are biological products constituted by animal cells or their non-chemically defined derivatives, with the purpose of obtaining therapeutic, preventive or diagnostic properties through their main mode of action of metabolic, pharmacological and/or immunological nature, for autologous or allogenic use in animals, provided that tissues/cells:

I –have been subjected to minimum manipulation and act with a function different from that performed in the donor tissue; or

II – have been subjected to extensive manipulation;

The provisions of this guide do not apply to any type of cells or tissues that are genetically manipulated.

3. DEFINITIONS

3.1 Packing: process by which the cells, advanced therapy products and biological samples are placed in packages for transportation or storage purposes, aimed to protect the material, people and the

environment.

3.2 Biological samples: blood, cells, fragments of tissues, smears, lavage, among others, from donors or recipients and that will be used to conduct laboratory tests or quality control tests;

3.3 Autologous cells: these are cells that are collected and administered to the same animal; the donor and recipient is the same individual;

3.4 Allogenic cells: these are cells that are collected from one donor animal and used in another recipient animal of the same species: the donor and recipient are not the same individual;

3.5 Stem cells: these are cells able to divide indefinitely and differentiate into distinct types of specialized cells, not only morphologically, but also functionally.

3.6 Batch of advanced therapy product: specific quantity of the final product, originated from a single donor, which is intended to have uniform qualities, within specific limits, produced according to a single processing protocol during the same processing cycle;

3.7 Minimum manipulation: it is the processing of cells that does not involve cell cultivation;

3.8 Extensive manipulation: it is the processing of cells that involves cell cultivation;

3.9 Autologous use: the implantation, transplant, infusion or transfer of cells back to the animal from which the cells were recovered;

4.0 Allogenic use: the implantation, transplant, infusion or transfer of cells from a donor animal to another recipient animal of the same species;

4. THE QUALITY CONTROL OF ADVANCED THERAPY PRODUCTS

The advanced therapy products can only be released for therapeutic use only after the observation of the predefined determinants or criteria related to the selection of the donor, quality controls of the production process and the finished products specified below:

I – For processes considered minimally manipulated:

a) count of the total number of cells;

b) cell viability test;

c) microbiological tests for fungi and bacteria research.

When it is proved that it is not possible to carry out one or more tests described in the item I, they may be dispensed.

II – For processes considered as extensive manipulation:

a) count of the total number of cells;

b) cell viability test;

c) immunophenotyping appropriate for the cell therapy product and quantification of the cell populations present;

d) dosing of endotoxins;

c) microbiological tests for fungi, bacteria and mycoplasma research.

f) karyotyping test;

g) confluence analysis:

The karyotyping test must be conducted in case the production process requires a number of passes greater than 4;

The confluence analysis must be conducted before each pass and before freezing.

The certificate of release for each batch of advanced therapy product must contain the identification code of the donor in addition to what is required by the applicable effective legislation.

5. THE PHYSICAL INFRASTRUCTURE

The physical infrastructure of the establishment that manipulates advanced therapy products must consist of, at least, environments for the execution of the following activities:

I – administrative;

II – receiving of biological material;

III – processing of advanced therapy products;

IV – storage of advanced therapy products; and

V – quality control.

The ISO 5 "operational" condition should be maintained in the area around of cells and Advanced Therapy Products, as well as materials and reagents that will come into direct contact with cells and Advanced Therapy Products, whenever exposed to the environment or when removing aliquots or samples for quality control or diagnosis.

6. THE LABORATORY SCREENING OF THE DONOR

6.1 Preliminary donor assessment:

The cell donations must mandatorily be preceded by the blood test with results within the reference ranges.The performance of the laboratory screening tests is not mandatory for autologous use, provided the therapy does not cause the potentiation of a previously existing disease.

The laboratory tests must be conducted on each cell donation, for autologous or allogenic use, regardless of the results of the previous donations.

During each collection of biological tissue, blood or serum samples must be collected to conduct laboratory tests to:

- Detect the main infectious diseases of concern each donor species:

I – Canine Species: canine distemper, parvovirus and leishmaniasis;

II – Feline Species: feline immunodeficiency virus (FiV), feline leukemia virus (FelV), toxoplasmosis and coronavirus;

III – Equine Species: Infectious equine anemia; and

For other animal species, the regulatory agency must establish the tests to be conducted.

- Detect endemic diseases in the region where the donor lives;

For allogenic transplants, only animals with results in compliance with the aforementioned laboratory tests can be the donors.

6.2 Requirements for processing donor samples

The performance of serological tests must not be allowed in the pool of blood samples of donor animals.

The use of pool of blood samples of donor animals is allowed for nucleic acid tests (NAT), according to

the recommendation of the manufacturer of the diagnosis kit used.

In case of the performance of the NAT tests in pool, the group of samples with positive result must be dismembered and their samples tested individually to identify the infectious agents in question or dispose of all the materials originated from those donors involved in the pool.

6.3 The following are exclusion criteria of the cell donation candidate for allogenic or autologous use:

I – Nonconformity results of the laboratory screening tests;

II – the presence and history of malignant neoplastic disease; and

III – clinical condition that places the donor's health at risk;

In the allogenic treatment, in case the laboratory tests results are inconclusive, the donor must be excluded.

In the autologous treatment, in case the laboratory tests results are inconclusive, the risk-benefit of the application must be evaluated.

7. THE PACKING, LABELING AND TRANSPORTATION OF BIOLOGICAL SAMPLE

The labeling of products must be as determined by the effective legislation applicable in addition to containing:

I - donor identification;

II – in case of autologous transplant, the information "Only for autologous use" and the data of the recipient.

The identification of the donor must necessarily be written on the label, and the information contained in item II can be contained in the package insert.

For cryopreserved products, the date of manufacture must be considered as the day of freezing.

For products used "fresh", the date of manufacture must be considered the day of removal of the cultivation cells and preparation for shipment.

The establishment must define and validate the temperature conditions of the biological materials and biological samples during transport in order to preserve the integrity and stability of the

transported material.

8. THE FINAL AND TEMPORARY PROVISIONS

Any Quality Control documentation related to the records of a batch, including the documentation of the donor, must be kept for one year after the expiry date of the batch.

The applicable determinations of the effective legislation related to Good Manufacturing Practices must be observed.

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