

PUBLIC CONSULTATION No. 706, AUGUST 26th, 2019

The Collegiate Board of Directors of the Brazilian National Health Surveillance Agency, according to the attributions provided by art. 15, III and IV allied to art. 7, III and IV, of Law No. 9,782, dated January 26, 1999, and by art. 53, III, §§ 1 and 3 of Anvisa's Collegiate Board of Directors Resolution (RDC) No. 255, dated December 10th, 2018, resolves to submit to public consultation, for comments and suggestions from the public in general, proposal of normative act, as approved at meeting held on August 20th, 2019, and I, the Head of the Collegiate Board of Directors, do hereby determine its publication.

Art. 1 The period of forty-five (45) days is hereby established for the submission of comments and suggestions to the text of the proposal of Collegiate Board of Directors Resolution on *the marketing authorization of advanced therapy medicinal products of human origin, and other provisions*, according to the attachment.

1. The term established in this article shall begin seven (7) days counted of the date of publication of this Public Consultation in the Federal Official Gazette.

Art. 2 The proposal of normative act will be available in full on Anvisa's website and suggestions should be sent electronically upon filling the electronic form, available at: http://formsus.datasus.gov.br/site/form.php?id_aplicacao=49682).

1. The contributions received will be considered as publicly released and will be available to any interested person by means of the tools contained in the electronic form, menu "result", including during the consultation procedure itself.

2. After filling the electronic form, the protocol number related to the respective participation shall be available to the interested person, who is not obligated to send physical documents to the Agency by letter or by means of presential protocol.

3. In case the citizen has a limited access to electronic resources, he/she may send and receive written suggestions, by physical means and during the Consultation period, to the following address: Agência Nacional de Vigilância Sanitária (Anvisa)/ Gerência de Sangue, Tecidos, Células e Órgãos - Division of Blood, Tissues, Cells and Organs (GSTCO), SIA, Trecho 5, Área Especial 57, Brasília-DF [Federal District], CEP [Postal Code] 71.205-050.

4. International contributions may be exceptionally forwarded by physical means, to the following address: Agência Nacional de Vigilância Sanitária, International Affairs Office - Assessoria de Assuntos Internacionais (AINTE), SIA, Trecho 5, Área Especial 57, Brasília-DF, CEP 71.205-050.

Art. 3 After the term provided by art. 1, Anvisa shall analyze the received contributions and, once this procedure is concluded, publish the result of the public consultation on the Agency's website.

1. The Agency may, as necessary and taking into account convenience and opportunity, contact bodies and entities involved with the subject of the aforementioned public consultation, as well as stakeholders who have expressed interest in the matter, in order to support further technical discussions and the respective final deliberation to be held by the Collegiate Board of Directors.

WILLIAM DIB
Head of the Collegiate Board of Directors

ATTACHMENT
PROPOSAL UNDER PUBLIC CONSULTATION

Procedure No.: 25351.494647/2015-91

Subject: Proposal of Resolution of Anvisa's Collegiate Board of Directors on the marketing authorization of advanced therapy medicinal products of human origin, and other provisions

Regulatory Agenda 2017-2020: Issue 10.4- Marketing Authorization Application of advanced therapy medicinal product

Responsible Technical Team: Division of Blood, Tissues, Cells and Organs - GSTCO.

Rapporteur: Fernando Mendes Garcia Neto - Director

Anvisa's Resolution of the Collegiate Board of Directors, RDC n.____, mm/dd/yyyy.

Resolution on the marketing authorization of advanced therapy medicinal products of human origin, and other provisions.

The Collegiate Board of Directors at the National Health Surveillance Agency, authorized by art. 15, items III and IV, and art. 7, items III and IV, of the Law No. 9,782, dated January 26th, 1999, and art. 53, items V, §§ 1 and 3, of the Anvisa's Resolution of the Collegiate Board of Directors - RDC No. 255, dated December 10th, 2018, decides to adopt the following Resolution, as approved at the meeting held on mm/dd/yyyy, and I, the Head of the Collegiate Board of Directors, do hereby determine its publication.

CHAPTER I
INITIAL PROVISIONS

Section I
Objectives

Art. 1. This Resolution aims to establish minimum requirements for the marketing authorization of advanced therapy medicinal products, with the objective of ensuring the quality, safety and efficacy of regularized products within the Brazilian market.

Section II

Scope

Art. 2. This Resolution applies to advanced therapy medicinal products of human origin subject to marketing authorization applications before Anvisa.

1. For the purposes of this Resolution, the advanced therapy medicinal products subjected to marketing authorization before Anvisa are:

- I- Somatic cell therapy medicinal product;
- II- gene therapy medicinal products; and
- III - tissue engineered therapy medicinal products.

Art. 3. This Resolution does not apply:

I - to procedures involving progenitors hematopoietic cells employed in conventional transplantations, as provided by the Anvisa's Resolution of the Collegiate Board of Directors (RDC) no. 214, dated February 7th, 2018, or its updates; and

II – to procedures that cumulatively meet all the requirements listed below:

- a. the collection of cells from an individual and the corresponding transplantation, infusion or implantation of the related material in the same individual (autologous use);
- b. during the same surgical or therapeutic procedure;
- c. with minimal manipulation; and
- d. with the purpose of performing the same biological function.

III – to procedures related to blood and blood components aiming at transfusion, as provided by Anvisa's Resolution of the Collegiate Board of Directors (RDC) No 34, dated June 11th, 2014, or its updates;

IV – to procedures related to cells and germinative tissues aiming at assisted human reproduction, as provided by Anvisa's Resolution of the Collegiate Board of Directors (RDC) No 23, dated May 27th, 2011, or its updates; and

V – to biological products, as defined by Anvisa's Resolution of the Collegiate Board of Directors (RDC) No 55, dated December 16, 2010, or its updates;

VI – to medical products, as defined by Anvisa's Resolution of the Collegiate Board of Directors (RDC) 185, dated October 22nd, 2001, or its updates.

Section III

Definitions

Art. 4. For the purposes of this Resolution, the following definitions are adopted:

I – Therapeutic alternative: therapies, products or medicines indicated for the same therapeutic or clinical purpose, which potentially have the same therapeutic effect;

II – serious debilitating condition: disease or condition associated with irreversible morbidity or high probability of death, unless the course of the disease is interrupted;

III - active component: cells, nucleic acid sequence or substances that have a necessary effect for the intended therapeutic activity, used in the production of the advanced therapy medicinal product;

IV - National Biosafety Technical Commission (CTNBio): multidisciplinary advisory and deliberative collegiate board established to provide technical support to the federal government on the formulation, update and implementation of the National Biosafety Policy on Genetically Modified Organisms (GMO) and its derivatives, as well as on the establishment of technical safety standards and on the formulation of technical

opinions related to the authorization of activities involving research and commercial use of GMOs and their derivatives (construction, testing, cultivation, handling, transportation, commercialization, consumption, storage, release and disposal), based on the risk assessment of GMOs to animal health, human health and the environment;

V - emerging or reemerging diseases: new health conditions, usually with infectious origin, or conditions already described, that acquired or regained epidemiological significance in public health;

VI - neglected diseases: diseases that are not economically attractive in terms of the development of products or medicines, or that predominantly affect developing countries' populations;

VII - rare disease: a disease that affects up to sixty-five people every 100,000, as defined by the "Política Nacional de Atenção Integral às Pessoas com Doenças Raras" (National Policy for the Unabridged Attention to People with Rare Diseases", based on official national data or, where none available, on published scientific data;

VIII – Public health emergency: situation that demands the urgent adoption of measures aiming at preventing, controlling and combating risks, damages and losses to public health, in situations that may be epidemiological (outbreaks and epidemics), disasters or that involve lack of assistance to entire populations;

IX – primary or internal package: package that is in direct contact with the final advanced therapies medicinal product, constituting a container, casing or any other form of protection, whether it is removable or not, destined to fill, to keep, to cover or to package;

X - excipient: any component of the final product, intentionally added to its formulation, other than the active component, impurities and packaging material;

XI - impurity: any component present in the final advanced therapy medicinal product that is not an excipient or active component.

XII - minimal manipulation: the processing of cells or tissues that does not significantly alter their biological characteristics, including state of differentiation and activation, potential of proliferation and metabolic activity. It is considered minimal manipulation, cutting, separating, centrifuging, immersing or preserving in antibiotic solutions, concentrating, purifying, filtering, lyophilizing, radiating, freezing, cryopreserving or vitrifying, among other acts that meet the present definition;

XIII - extensive manipulation: the processing of cells and tissues that alters any of their biological characteristics, including state of differentiation and activation, potential of proliferation and metabolic activity. Every form of processing cells and tissue that does not constitute minimal manipulation. All types of cultivation of cells are considered extensive manipulation;

XIV - Starting material: material used in the production of the advanced therapy medicinal product and part of the final product, including those of biological and non-biological origin. Examples of starting materials are cells or tissues removed from a donor, bases and matrixes or biomaterials combined with engineered cells;

XV - raw material: any substance, whether active or inactive, used in the production of the active component and not intended to be an integral part of the final product. Examples of raw materials are: culture means, growth factors, accessory cells and nucleic acids;

XVI - Advanced Therapy Medicinal Products: Somatic cell therapy medicinal product, gene therapy medicinal products and tissue engineered therapy medicinal products;

XVII - Advanced Therapy Medicinal Product - Class I: Somatic cell therapy medicinal product that undergoes minimal manipulation and performs in the recipient a different function than that in the donor;

XVIII - Advanced Therapy Medicinal Product - Class II: somatic cell therapy medicinal product undergoing extensive manipulation, tissue engineered therapy medicinal products and gene therapy medicinal product;

XIX - tissue engineered therapy medicinal products: biological product consisting of human cells organized in tissues or organs that have properties that allow the regeneration, reconstitution or replacement of a human tissue or organ, in the presence or absence of structural support consisting of biological or biocompatible material, and (a) has undergone extensive manipulation; and / or (b) performs in the recipient a function different from that in the donor;

XX - Somatic cell therapy medicinal product: Biological product consisting of human cells or their non-chemically defined derivatives, which has the purpose of obtaining therapeutic, preventive or diagnostic properties through its main mode of action, of metabolic, pharmacological and / or immunological nature, for autologous or allogeneic use in humans, which (a) has undergone extensive manipulation; and / or (b) performs in the recipient a function different from that in the donor;

XXI - gene therapy medicinal product: a biological product whose active component contains or consists of recombinant nucleic acid, in order to modify (regulate, repair, replace, add or delete a gene sequence) the expression of a gene, aiming at a therapeutic, preventive or diagnostic outcome;

XXII - Final Advanced Therapies Medicinal Product: the final product in its primary package after completing all the production phases.

CHAPTER II GENERAL PROVISIONS

Section I

Art. 5. Marketing authorization applications related to advanced therapy medicinal products shall be assessed based on the requirements stated by this Resolution, as well as by the applicable legislation.

Art. 6. When applying for the marketing authorization, the applicant, a legal person, shall, in the act of filling the application, prove the payment of the corresponding sanitary inspection fee, as well as inform if the application form refers to:

I – the marketing authorization of an Advanced Therapy Medicinal Product - Class I, as established by Chapters III and IV of this Resolution;

II - the marketing authorization of an Advanced Therapy Medicinal Product - Class II, as established in Chapters III and V of this Resolution; or

III - the marketing authorization of an Advanced Therapy Medicinal Product – Class I or Class II, with conclusive clinical safety studies and incomplete efficacy studies regarding the proposed therapeutic indication, as established in Chapter VI of this Resolution.

Art. 7. The applicant is entitled to submit the information requested by this Resolution in accordance with the Common Technical Document (CTD), as established by the Guidance M4 of the International Council on Harmonization (ICH).

Art. 8. All companies involved in the manufacturing of an advanced therapy medicinal product shall comply with Good Manufacturing Practices, as provided by the Anvisa's Resolution of the Collegiate Board of Directors (RDC) No 214, dated February 7th, 2018, and its updates.

Art. 9. The holder of a marketing authorization related to an advanced therapy medicinal product expired or cancelled for reasons other than efficacy or safety issues may re-submit the same product following a simplified documentation review.

1. For situations not covered by the chapeau of this article, the marketing authorization holder shall re-initiate the procedures stated by this Resolution, in order to re-obtain the respective marketing authorization.

Art. 10. All therapeutic indications requested in a marketing authorization application related to an advanced therapy medicinal product shall be stated and documented through clinical and non-clinical studies reports constituting the application dossier, as established by this Resolution herein.

1. All clinical trials performed in Brazil with advanced therapy medicinal products shall be previously approved by Anvisa, as established by Anvisa's Resolution of the Collegiate Board of Directors (RDC) No. 260, dated December 21st, 2018, or its updates.

2. A company applying the marketing authorization of an advanced therapy medicinal product intending to use information from clinical trials performed in Brazil prior to the publication of the Anvisa's Resolution of the Collegiate Board of Directors (RDC) No. 260, dated December 21st, 2018, shall demonstrate compliance with the technical requirements stated by the aforementioned Resolution, as well as with Good Clinical Practices.

Art. 11. Anvisa may at any time, upon technical grounds and justification, require additional evidences related to the identity and the quality of the components constituting the advanced therapy medicinal products, or require further studies aiming at demonstrating clinical efficacy and safety, in case of new facts justifying supplementary assessments, even when these facts take place afterwards the granting of the respective marketing authorization.

Art.12 No advanced therapy medicinal product involving GMOs may be made available for use or consumption in the Brazilian market without CTNBio's prior consent, as provided by Law No. 11.105, dated March 24th, 2005, or its updates.

Art. 13. The advanced therapy medicinal product produced non-routinely, for a specific patient, under the responsibility of a medical professional, and prepared in accordance with quality and safety requirements, as established by Chapter VII of this Resolution, is exempted from marketing authorization.

1. Such condition only applies to patients whose therapeutic indication relates to the treatment of diseases with no therapeutic alternative available in the country and that are facing imminent life-threatening condition.

2. The therapeutic indication related to this article must be assessed and approved by the medical professional for each patient and for each therapeutic indication, and shall

be notified to Anvisa, when related to advanced therapy medicinal product – class I, somatic cell therapy product and tissue engineered therapy product.

3. In case of gene therapy product, besides the assessment and approval performed by the patient's medicinal professional, the use of the product itself shall be previously authorized by Anvisa.

4. The provisions stated by the chapeau of this article do not apply to patients participating in expanded access, compassionate use and post-study provision programs, and shall follow, in respect to access to medicines, the established by Anvisa's Resolution of the Collegiate Board of Directors (RDC) No 38, dated August 12th, 2013, or its updates.

CHAPTER III

THE MARKETING AUTHORIZATION OF ADVANCED THERAPY MEDICINAL PRODUCTS

Section I

The Administrative Documentation Required for Advanced Therapy Medicinal Product – Classes I and II

Art. 14. At the moment of the protocol of an application requesting the marketing authorization of an advanced therapy medicinal product, the applicant shall submit the following documents:

I – duly completed application forms;

II - original proof of the payment receipt of the sanitary surveillance inspection fee, or proof of exemption, when applicable;

III - description of the product characteristics and of its package;

IV – copy of the company's operation certificate (AFE), for each one of the companies involved in the product manufacturing, in case of national production;

V - protocol requesting inspection before Anvisa, aiming at the issuing of a Certificate of Good Manufacturing Practices, for all companies involved in the manufacturing chain of the advanced therapy medicinal product;

VI - copy of the Good Manufacturing Practices Certificate issued by the competent health authority of the country where the companies involved in the manufacturing chain of the advanced therapy medicinal product are located, when applicable;

VII - assessment report issued by competent health authorities in charge, in other countries, for granting marketing authorizations to advanced therapy medicinal products, when appropriate;

VIII - copy of the package leaflet approved by the competent health authority of the country where the product was manufactured, when applicable;

IX - leaflet models to be adopted in Brazil, as well as the models for primary and secondary packages; and

X - updated post-marketing authorization monitoring data obtained from clinical and non-clinical studies, and from the commercialization of the product in other countries, where applicable, as well as the proposed Risk Management Plan for the product in Brazil.

Section II

General Information about Advanced Therapy Medicinal Product - Classes I and II

Art. 15. At the moment of the protocol of the application requesting the marketing authorization of an advanced therapy medicinal product, the applicant shall submit technical reports to Anvisa with the following information:

I - summary of the general characteristics of the product, such as:

- a) form and presentation;
- b) complete formulation, with all its components specified by their technical names and synonyms, in accordance with the International Common Name (DCI) or Brazilian Common Name (DCB), when applicable;
- c) routes of administration;
- d) indications, purpose or intended use;
- e) contraindications;
- f) side effects;
- g) adverse reactions;
- h) restrictions or cautions that should be considered;
- i) precautions and warnings;
- j) use during pregnancy and lactation and pediatric use;
- k) drug and food interactions;
- l) changes in laboratory tests;
- m) shelf life;
- n) storage conditions, including storage temperature;
- o) storage temperature;
- p) transport temperature;
- q) material specifications regarding the primary package.

II- summary containing information on the mechanism of action and the clinical use of the advanced therapy medicinal product;

III- summary of quality information, in order to highlight the critical parameters of the product's quality;

IV- summary and critical analysis of non-clinical aspects of the product;

V- summary and critical analysis of the clinical aspects of the product.

CHAPTER IV

SIMPLIFIED MARKETING AUTHORIZATION OF ADVANCED THERAPY MEDICINAL PRODUCT - CLASS I

Art. 16. In addition to the provisions of Chapter III, Sections I and II, of this Resolution, the applicant of a simplified marketing authorization, applicable to advanced therapy medicinal products – class I, shall submit to Anvisa a complete report of all non-clinical studies and clinical trials performed with the product.

Art. 17. The principles underlying the non-clinical development of the product and the criteria used to select relevant *in vitro* and *in vivo* species and models shall be analyzed and technically grounded by the occasion of the critical analysis of non-clinical data.

Art. 18. The report on non-clinical studies with advanced therapy medicinal products shall contain:

I - studies required to demonstrate the intended therapeutic effect and effective dose, based on the type of product and frequency of administration;
II- studies on the interaction of the product with other tissues, with evaluation of potential side effects;
III- studies to determine the parameters of feasibility, shelf life, distribution, metabolism and excretion of advanced therapy medicinal products;
IV- toxicity studies of the product, including the cellular component, excipients and any impurity related to the process;
V- studies to determine potential immunogenic effects; and
VI- studies on the tumorigenic potential of the advanced therapy medicinal product.

1. If any of the studies listed in this article is not performed, the marketing authorization applicant shall provide the corresponding justification, based on risk management approach and scientific evidence, observed the type of advanced therapy medicinal product implied.

Art. 19. The report on clinical studies with advanced therapy medicinal product shall contain:

I - safety studies that address aspects related to biodistribution and grafting, shelf life, ectopic graft, oncogenetic transformation and cell line stability; and
II - clinical efficacy studies.

1. The strategy adopted in clinical studies aiming at assessing the long-term efficacy of the advanced therapy medicinal product shall be submitted to Anvisa by the marketing authorization applicant.

2. If any of the studies listed in this article is not performed, the marketing authorization applicant shall provide the corresponding justification, based on risk management approach and scientific evidence, observed the type of advanced therapy medicinal product implied.

Art. 20. Upon receipt of the documentation related to a simplified marketing authorization application of advanced therapy medicinal product - class I, Anvisa will have 365 (three hundred and sixty-five) days to conclusively review the respective claims, as stated by Law No. 6360, dated September 23rd, 1976, and its updates

1. If the advanced therapy medicinal product - class I is intended to rare, neglected, emerging or reemerging disease, to emergencies in public health or serious debilitating conditions, and under situations where no therapeutic alternative is available, its marketing authorization application shall be addressed in the priority category, and Anvisa will have 120 (one hundred and twenty) days to conclusively review the respective claims.

2. The request for classification in the priority category shall be submitted at the moment of the protocol of the marketing authorization application, and the company shall attach documents able to demonstrate the fulfillment of the criteria provided by paragraph 1 of this article.

Art. 21. The marketing authorization of an advanced therapy medicinal product - class I is valid for 5 (five) years, and may be renewed based on risk assessment grounded on reports declaring the inexistence of ineffectiveness as well as significant adverse events, and other applicable regulatory requirements.

1. After the second renewal, the marketing authorization shall be valid for 10 (ten) years.

CHAPTER V

MARKETING AUTHORIZATION OF ADVANCED THERAPY MEDICINE PRODUCT – CLASS II

Art. 22. In addition to the provisions stated by Chapter III, Sections I and II, of this Resolution, the applicant of marketing authorization of an advanced therapy medicinal product - class II, shall submit the quality dossier of the product, as well as a complete report of all non-clinical and clinical studies developed with the product.

Art 23. The quality dossier of the advanced therapy medicinal product – class II shall contain:

I- Information on starting material, raw material and excipients:

- a. a list of all starting materials used in the production of the advanced therapy medicinal product, including, in case of gene therapy medicinal product, the materials required to produce vectors as well as to perform the genetic manipulation of the cells;
- b. data on genetic modification, sequence analysis, attenuation of virulence, tropism for certain tissue or cell types and cell cycle dependence, in case of microorganisms or viruses;
- c. a list of the raw materials used in the production of the advanced therapy medicinal product, including the name of the material, manufacturer, quantity employed in the process, pharmacopoeia recommendations, or material or technology in-house specifications, including documentation of the quality controls adopted;
- d. list of equipment employed in the manufacturing process;
- e. information on the selection of the starting materials donors and human-sourced materials, including clinical and social screening, physical evaluation, laboratory screening and other applicable assessments, as provided by Anvisa's Resolution of the Collegiate Board of Directors (RDC) No 214, dated February 7th, 2018, or its updates;
- f. Documentation regarding the control of transmissible spongiform encephalopathies (TSE), as stated by Anvisa's Resolutions of the Collegiate Board of Directors RDC No 214, dated February 7th, 2018, and RDC No. 305, dated November 14th, 2002, or their updates;
- g. specification of excipients, description of possible chemical interactions with the active component, description of physicochemical properties, microbiological properties and other quality controls;
- h. information on bases, matrixes and devices employed, including tests performed, in terms of safety, biocompatibility and durability, in accordance with Anvisa's Resolutions of the Collegiate Board of Directors RDC No. 185, dated October 22nd, 2001, and RDC No 51, dated April 6th, 2001, or their updates.

II- Information on the active component and the final advanced therapy medicinal product:

- a. characterization of the active component, including, as appropriate, its identity, quantity, purity, feasibility, potency, cariology and sterility;
- b. description of the validated analytical methodologies adopted for the characterization of the active component;
- c. general description of the final advanced therapy medicinal product, including, as appropriate, information on composition and characterization, including identity, quantity, purity, feasibility, potency, cariology and sterility;
- d. qualitative and, as possible, quantitative information about the impurities related to the process and the product, and the determination degree of the impurities shall be reasoned.

1. If any of the aforementioned tests cannot be performed with the final product, but only with intermediate products and/or as process controls, or is not considered applicable to a specific product, and, therefore, potentially subject of exemption, this situation shall be appropriately justified and technically grounded by the applicant.

III- information on the manufacturing process of an advanced therapy medicinal product:

- a. detailed description of all manufacturing steps of the advanced therapy medicinal product, including the steps of selecting the cell population of interest, cell culture, transformation by physicochemical and / or biological agents;
- b. detailed description of all production steps of vectors, when appropriate;
- c. detailed description of all production steps of excipients, when appropriate;
- d. validation report of critical process steps aiming at ensuring batch and process uniformity, as well as functional integrity of cells during all manufacturing steps;
- e. identification and safety mechanisms able to ensure product traceability.

IV- protocol and report of the stability studies performed; and

V - description of the storage conditions of the final advanced therapy medicinal product.

Art. 24. The principles underlying the non-clinical development of the product and the criteria used to select relevant *in vitro* and *in vivo* species and models shall be analyzed and technically grounded by the occasion of the critical analysis of non-clinical data.

Art. 25. The complete report of non-clinical studies developed with advanced therapy medicinal product – class II shall contain:

- I - studies required to demonstrate the intended therapeutic effect and effective dose, based on the type of product and frequency of administration;
- II - studies on the interaction of the product with other tissues, with the assessment of potential side effects;
- III - studies aimed at determining the parameters of feasibility, shelf life, distribution, metabolism and excretion of advanced therapy medicinal products;
- IV - biodistribution studies on gene therapy medicinal product shall address the risk of transmission in the germ line;

V - product toxicity studies, including the cellular component, excipients and any process-related impurities, in case of gene therapy medicinal product, studies on the product integration to the cell genome shall be submitted;

VI - studies to determine potential immunogenic effects;

VII - studies on the tumorigenic potential of the advanced therapy medicinal product.

1. If any of the studies listed in this article is not performed, the marketing authorization applicant shall provide the corresponding justification, based on risk management approach and scientific evidence, observed the type of advanced therapy medicinal product implied.

Art. 26. The complete report of clinical studies developed with advanced therapy medicinal product – class II shall contain:

I - studies that address aspects related to biodistribution and grafting, shelf life, ectopic graft, oncogenetic transformation and cell line stability, and, when gene therapy medicinal product is concerned, additional studies on excretion and changes in the genomic sequence; and

II - clinical efficacy studies.

1. The strategy adopted in clinical studies aiming at assessing the long-term efficacy of the advanced therapy medicinal product shall be submitted to Anvisa by the marketing authorization applicant.

2. Additional studies on comparability may be required, based on possible changes in the manufacturing process of the advanced therapy medicinal product.

3. If any of the studies listed in this article is not performed, the marketing authorization applicant shall provide the corresponding justification, based on risk management approach and scientific evidence, observed the type of advanced therapy medicinal product implied.

Art. 27. Upon receipt of the documentation related to a marketing authorization application of advanced therapy medicinal product - class II, Anvisa will have 365 (three hundred and sixty-five) days to conclusively review the respective claims, as stated by Law No. 6360, dated September 23rd, 1976, and its updates.

1. If the advanced therapy medicinal product - class II is intended to rare, neglected, emerging or re-emerging disease, to emergencies in public health or serious debilitating conditions, and under situations where no therapeutic alternative is available, its marketing authorization application shall be addressed in the priority category, and Anvisa will have 120 (one hundred and twenty) days to conclusively review the respective claims.

2. The request for classification in the priority category shall be submitted at the moment of the protocol of the marketing authorization application, and the company shall attach documents able to demonstrate the fulfillment of the criteria provided by paragraph 1 of this article.

Art. 28. The marketing authorization of an advanced therapy medicinal product - class II is valid for 5 (five) years, and may be renewed based on risk assessment grounded on reports declaring the inexistence of ineffectiveness as well as significant adverse events, and other applicable regulatory requirements.

1. After the second renewal, the marketing authorization shall be valid for 10 (ten) years.

CHAPTER VI

MARKETING AUTHORIZATION OF ADVANCED THERAPY MEDICINAL PRODUCT REQUIRING ADDITIONAL DATA AND EVIDENCES OF CLINICAL EFFICACY

Section I

General information on marketing authorization of advanced therapy medicinal product requiring additional data and evidence able to demonstrate clinical efficacy

Art. 29. Anvisa may exceptionally grant marketing authorization concerning advanced therapy medicinal product that requires additional data and evidence able to demonstrate clinical efficacy, provided that the applicant's product cumulatively meets all the requirements listed below:

I - be indicated to serious debilitating condition;

II - be utilized in situations in which there is no comparable therapy, product or alternative medicine for the same stage of the disease; and

III – there is evidence demonstrating that the product significantly improves the patient's evolution or enables the remission of the disease.

Art. 30. At the moment of the protocol of an application aiming the marketing authorization of an advanced therapy medicinal product - class I or II, which requires additional data and evidences of clinical efficacy, the applicant shall submit the following information:

I – in case of an advanced therapy medicinal product - class I, the documentation stated by Chapter III, sections I and II, and Chapter IV, art. 18, of this Resolution;

II – in case of an advanced therapy medicinal product - class II, the documentation stated by Chapter III, sections I and II, and Chapter V, arts. 23, 24 and 25, of this Resolution;

III - report of clinical studies already performed with the product, as well as the respective conclusion schedules;

IV - description of the disease the product will be indicated to; and

V - evidence of the relevance of the product, considering the treatment, diagnosis or prevention of the disease, according to the criteria defined in Article 29.

1. If Anvisa's technical analysis does not confirm the product as qualified for the assessment under art. 29 of this Resolution, the respective marketing authorization application shall be summarily dismissed.

2. Anvisa will have 180 (one hundred and eighty) days to conclusively review the claims arising from these applications.

Art. 31. The marketing authorization, as provided in art. 29 of this Resolution, shall only be granted upon the signature of a Performance Commitment Agreement, according to the applicable template provided in Annex I of this Resolution, and shall address at least the following obligations:

I - the applicant shall submit, within the term defined by Anvisa's competent authorities, a clear and complete schedule of clinical studies to be developed, whose results will be the basis of the benefit-risk re-evaluations of the advanced therapy medicinal product.

II - the package leaflets, packages and any other medical information shall highlight the fact that the product is authorized for clinical use, under monitoring conditions and further production of additional data and evidences able to demonstrate clinical efficacy.

1. The conditions imposed to the marketing authorization holder of an advanced therapy medicinal product, by means of the Performance Commitment Agreement, will be made public, along with the terms and dates related to their implementation, through Anvisa's website.

Art. 32. The marketing authorization of an advanced therapy medicinal product - class I or II, which requires additional data and evidences of clinical efficacy, shall be valid for 1 (one) year and may be renewed annually for a maximum period of 5 (five) years, upon quality assessment of the compliance of the Performance Commitment Agreement implicated, and the benefit-risk balance of the product, until the definitive marketing authorization is granted.

1. The holder shall submit, within sixty (60) days before the expiry date of the marketing authorization of an advanced therapy medicinal product - class I or II, which requires additional data and evidences of clinical efficacy, the due documentation able to demonstrate compliance with the terms of the respective Performance Commitment Agreement, as well as sufficient data enabling the assessment of the benefit-risk balance of the product.

2. Anvisa has 45 (forty-five) days, counted of the respective application, to assess the information mentioned in this article, as well as to issue its decision on the extension of the marketing authorization.

3. Failure to comply with obligations established by the Performance Commitment Agreement, as well as requests on extension of the terms established for the provision of such information, shall be submitted in written to the Agency, upon reasoning.

CHAPTER VII

CRITERIA FOR NOTIFICATION AND PRIOR AUTHORIZATION OF ADVANCED THERAPY MEDICINAL PRODUCT EXEMPTED FROM MARKETING AUTHORIZATION

Art. 33. The advanced therapy medicinal product exempted from marketing authorization, as defined in art. 13 of this Resolution, is subject to notification or prior authorization.

1. The notification provided by the chapeau of this article applies to advanced cell therapy medicinal products - class I and II and to tissue engineered products, and shall be performed by the physician previously responsible for the patient.

2. The prior authorization provided by the chapeau of this article applies exclusively to gene therapy medicinal products.

Art. 34. The use of notified advanced therapy medicinal product does not require Anvisa's prior authorization, remaining though subject to other applicable ethical approvals.

Art. 35. The production of advanced therapy medicinal product exempted from marketing authorization shall fully comply with provisions stated by Anvisa's Resolution of the Collegiate Board of Directors (RDC) No 214, dated February 7th, 2018, or its updates.

Art. 36. The commercialization of advanced therapy medicinal product exempted from marketing authorization is forbidden.

Art. 37. Anvisa shall annually publish on its website the updated list of information on advanced therapy medicinal products that have been notified or authorized.

Art. 38. The notification and application for prior authorization related to advanced therapy medicinal products exempted from marketing authorization shall have by the following information:

- I - application form completed and signed by the physician responsible for the patient;
- II - documentation providing the rational of use and the previous clinical experience with the product, when appropriate;
- III- documentation that demonstrates compliance with Good Manufacturing Practices by the company involved in manufacturing the advanced therapy medicinal product.

Art. 39. Upon receipt of the documentation requested by art. 38 of this Resolution, Anvisa will have 30 (thirty) days to conclusively review the request for prior authorization of a gene therapy product.

Art. 40. The person in charge of an advanced therapy medicinal product exempted from marketing authorization shall send to Anvisa therapeutic follow-up reports of each patient, observed the periodicity to be determined by the Agency, according to each specific case.

1. Anvisa will have 30 (thirty) days of the notification of a product to define the periodicity of a patient therapeutic follow-up reports.

2. If Anvisa does not determine within 30 (thirty) days of the notification, the periodicity to be applied to a patient therapeutic follow-up reports, the periodicity of six (6) months is automatically established.

Art.41. Anvisa may suspend or cancel the use of an advanced therapy medicinal product, if the provisions of art. 13 of this Resolution are not complied with.

CHAPTER VIII FINAL AND TRANSITORY PROVISIONS

Art. 42. At the moment of the marketing authorization approval of an advanced therapy medicinal product, Anvisa will disclose information on its webpage, regarding the technical ground for the authorization and the issuance of the respective “Letter of Approval”, observed the due omission of any commercial or confidential information.

1. The information provided by the chapeau of this article shall include a written and accessible summary to a lay person, including a section on the use conditions of the advanced therapy medicinal product.

Art. 43. The marketing authorization of an advanced therapy medicinal product shall only be granted after the issuance of the corresponding Certificates of Good Manufacturing Practices of each company involved in the manufacturing chain of the advanced therapy medicinal product.

1. Anvisa may consider, upon evaluation of the inspection reports to be submitted by the applicant, granting the marketing authorization of an advanced therapy medicinal product whose manufacturing chain is already certified by an international health authority which has similar sanitary regulations and measures to Anvisa’s, as well as a bilateral agreement signed with the Brazilian Agency.

Art. 44. The applicant of a marketing authorization of an advanced therapy medicinal product may contact, prior to the respective submission, the technical team responsible for the process, in order to discuss aspects related to product development, adopting in this regard the mechanisms available within the Agency for this purpose.

Art. 45. Technical panels may be organized by Anvisa, on its own criteria or at the request of the applicant, upon the authorization of the respective supervising director, with the objective of clarifying doubts arising from the assessment of marketing authorization applications related to advanced therapy medicinal products, observed the specific procedure disclosed at Anvisa’s webpage.

Art. 46. The requirements for the importation and exportation of authorized advanced therapy medicinal products will be defined by specific regulation.

Art. 47. Anvisa may request, when necessary, laboratory analysis of advanced therapy medicinal product to an official control laboratory or to a laboratory designated for such an analysis.

Art. 48. Failure to comply with the conditions, obligations and terms agreed through Performance Commitment Agreements mentioned by this Resolution shall lead to the cancellation of the respective marketing authorization, without prejudice to other applicable civil, criminal and administrative sanctions.

Art. 49. Failure to comply with the provisions established by this Resolution, as well as the submission of false or incorrect data and information which do not correspond to the facts, constitutes a sanitary violation, as stated by Law No. 6,437, dated August 20th, 1977, without prejudice to applicable civil, administrative and criminal liability.

Art. 50. This Resolution enters into force in thirty (30) days of its publication.

WILLIAM DIB
Head of the Collegiate Board of Directors

ANNEX I
PERFORMANCE COMMITMENT AGREEMENT AIMING AT THE SUBMISSION OF
COMPLEMENTARY DATA AND ADDITIONAL EVIDENCE OF CLINICAL EFFICIENCY, APPLIED
TO THE MARKETING AUTHORIZATION OF ADVANCED THERAPY MEDICINAL PRODUCT -
CLASS I OR II

I, _____, the undersigned, bearer of the Identity Card (RG) _____ and enrolled with the Individuals Taxpayer Registration (CPF) under No. _____, in full power of the position of Legal Representative of the institution _____, enrolled with the Corporate Taxpayer Registration (CNPJ) under No. _____, DO COMMIT TO, observed the Schedule mentioned in the Attachment I of this Performance Commitment Agreement, submit the complementary data and additional evidences required by Anvisa by means of the Official Letter _____, in order to complement the clinical efficacy data grounding the MARKETING AUTHORIZATION granted to the advanced therapy medicinal product (CLASS I OR CLASS II) _____, process _____, regarding the following therapeutic indications:

- 1) _____;
- 2) _____.

I DO HEREBY DECLARE, observed art. XX of Anvisa's Resolution of the Collegiate Board of Directors (RDC) X of X of XXX of 2019, which regulates the marketing authorization of advanced therapy medicinal products of human origin, and other provisions, that the complementary data and additional evidences required by Anvisa by means of the aforementioned Official Letter are not currently available, as well as that all data and

evidences regarding the safety and efficacy of the product currently owned or known by the company has been adequately submitted and informed to the Agency.

I FURTHER DO HEREBY DECLARE that all data and evidences submitted to date to Anvisa's technical team are true and properly interpreted, observed their intended purpose, leading to technically and statistically correct inferences and conclusions responsible to repute the concerned product safe and efficient.

I also DO HEREBY COMMIT TO submit the complementary data and additional evidences required by Anvisa by means of Official Letter _____, in a single act, within the term set by Anvisa's technical team for the last action of the proposed SCHEDULE.

I finally DO HEREBY COMMIT TO comply with the obligations established by this Performance Commitment Agreement in accordance with the provisions stated by the Anvisa's Resolution of the Collegiate Board of Directors (RDC) X of XXX of 2019, as well as other applicable normative acts, observing the principle of good faith and the public health interest in Brazil, and MAKING ADDITIONALLY THE COMMITMENT to immediately report to Anvisa any complication that might harm or prevent compliance with the herein provisions.

I DO HEREBY ACKNOWLEDGE that failure to comply with the conditions, obligations and terms provided in this Performance Commitment Agreement shall imply the immediate cancellation of the concerned marketing authorization, without prejudice to other applicable civil, criminal and administrative sanctions.

I ALSO DO HEREBY DECLARE to be aware of the clinical uncertainties and the consequent legal uncertainty that might arise from the marketing authorization of the advanced therapy medicinal product class I or II requiring complementary data and additional evidences able to demonstrate clinical efficacy, so that I DO HEREBY AFFIRM to be aware of eventual risks and civil and criminal liabilities assumed, including the reimbursement of government purchases, in case the advanced therapy medicinal product in question demonstrates to be, when exposed to actual clinical use, clinically unsafe or ineffective, particularly in case of serious personal injury, permanent injury or patient death.

And because it is the expression of the truth, I DO HEREBY SIGN this document, so that its legal and judicial effects may arise.

Attachments:

Attachment I - Copy of the Power of Attorney granting powers to the legal representative in question, as well as of articles of association and minutes of assemblies required to verify the liability chain within the legal entity.

Attachment II - Detailed schedule on the submission of complementary data and evidences, as required by Anvisa, related to the marketing authorization of the advanced therapy medicinal product (class I or II) implied.

_____, ____ of _____ of _____.

Name:

Position:

CPF:

Attachment II

Detailed schedule on the submission of complementary data and additional evidences able to demonstrate the clinical efficacy of an advanced therapy medicinal product (class I or II) object of marketing authorization

Chronological order of submission	Item description, observed the Official Letter issued by Anvisa	Date in which the item shall be available to the company	Date in which the item shall be submitted to Anvisa, through a single act
1.			
2.			
3.			