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This text does not replace the one published in the Federal Official Gazette.

BOARD OF DIRECTORS RESOLUTION - RDC No. 214, DATED FEBRUARY 7, 2018

(Published in the Federal Official Gazette No. 36 dated February 22, 2018)

It provides on the Good Practices on Human Cells () for therapeutic use and clinical research, and other provisions.*

() The expression “Good Practices on Human Cells”, translated from the version in Portuguese, is equivalent to “Good Cell Practices and Good Manufacturing Practices for Advanced Therapy Medicinal Products”, in English.*

The **Board of Directors of the Brazilian Health Surveillance Agency**, in the use of the attribution conferred to it by art. 15, III and IV allied to art. 7, III and IV of Law 9,782, dated January 26, 1999, and to art. 53, V, §§ 1 and 3 of the Internal Regulation approved in accordance with Annex I of the Board of Directors Resolution (RDC, in Portuguese) No. 61, dated February 3, 2016, decided to adopt the following Board of Directors Resolution, as resolved at a meeting held on January 30, 2018, and I, Chief Executive Officer, determine its publication.

Art.1 The Good Practices on Human Cells for therapeutic use and clinical research are established under the terms of this Resolution.

CHAPTER I
INITIAL PROVISIONS

Section I
Purpose

Art.2 The Good Practices on Human Cells for therapeutic use and clinical research are standardized by establishing the minimum technical-sanitary requirements related to the production cycle of cells and of Advanced Therapy Medicinal Products (ATMP), aiming at the safety and quality of these products.

Sole Paragraph. Cells or ATMP that do not comply with the provisions hereunder are disqualified for therapeutic use and clinical research.

Section II
Scope

Art.3 The provisions hereof apply to the Cell Processing Centers and other establishments involved in the production cycle of cells and of ATMP, according to articles 4, 5 and 6 hereof.

§1 Bone marrow and peripheral blood processing laboratories, umbilical cord blood banks and cell technology centers are hereinafter referred as Cell Processing Centers.

§2 The establishments in the main clause of this article can be public or private.



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Art.4 This Resolution covers activities with:

I - hematopoietic progenitor cells for conventional transplantation purposes;

II - ATMP;

III - human cells that do not fall under the conditions listed in art. 5 hereof.

Art.5 This Resolution does not apply to procedures:

I - that cumulatively meet all the following requirements:

a) collection of cells from 1 (one) individual and transplantation, infusion or implant of the material in the same individual (autologous use);

b) during the same surgical or the same therapeutic procedure;

c) with minimal manipulation; and

d) intended for homologous use.

II - related to blood and blood components for transfusion and non-transfusion purposes regulated by specific legislation;

III - related to reproductive cells or tissues for assisted human reproduction; or

IV - related to the cells for basic research purposes.

Art.6 For the purposes of this Resolution are considered as ATMP:

I - Advanced Cellular Therapy Products;

II - Tissue Engineering Products; and

III - Gene Therapy Products. (amended by RDC No. 260, dated December 21, 2018)

Section III
Definitions

Art.7 For the purposes of this Resolution, the following definitions are adopted:

I - Packing: a process by which cells, ATMP or biological samples are placed in packages and labelled with the aim of transportation or storage, in order to protect the material, the people and the environment;

II - Environment: physically delimited space, specialized to the development of certain activity(ies), characterized by different dimensions and facilities, and can be constituted by a room or an area;

III - Clean Environment: a room or an area with defined environmental control in terms of contamination by viable and non-viable particles, designed, built and used in such a way as to reduce the introduction, generation and retention of contaminants in its interior, in which other relevant



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parameters, such as, for example, temperature, humidity and pressure, are controlled as necessary;

IV - Biological Samples: blood, cells, tissue fragments, smears, washes, among others from donors, recipients or from the product that will be intended to perform laboratory tests or quality control tests;

V - Air lock: enclosed space with two or more doors, interposed between two or more adjoining rooms of distinct air cleanliness standards, with the objective of controlling the air flow between them, when they need to be accessed; the air lock is designed to be used for people, materials or equipment;

VI - Area: delimited, open environment, without walls in one or more than one of the faces, that has specific environmental conditions; the biological safety cabinet is included in this definition;

VII - Good Practices on Human Cells: part of the Quality Assurance that ensures that the cells/ATMP are consistently handled and controlled, with quality standards appropriate for the intended use;

VIII - Available Cells or ATMP: those released for use, whose availability was communicated to the professional interested in using it or to the National Transplant System responsible body;

IX - Distributed Cells or ATMP: those that left the Cell Processing Center;

X - Cell Processing Center: establishment that has physical infrastructure, equipment, techniques and human resources, and may have as its attributions procurement (donor selection, including clinical, social, physical and laboratorial screening), recovery, identification, transportation, assessment, processing, packaging, storage and availability of cells of human origin or ATMP for therapeutic use, and may also provide cells or ATMP for research, education, training, quality control or processes validation;

XI - Change Control: set of actions aimed at maintaining under control the changes that may have impact on qualified equipment or components of an equipment, as well as over already validated systems, processes or procedures, and may or may not affect the quality of the cells and ATMP provided for therapeutic use or clinical research;

XII - Storage Device: equipment such as refrigerator, freezer, ultra-freezer and container or other storage place defined by the Cell Processing Center;

XIII - Donor: a living or deceased individual whose body is the source of biological material;

XIV - Intermediary or Secondary Packaging: packaging placed between the internal or primary packaging and the external or tertiary packaging, in order to contain the internal or primary packaging;

XV - Primary or Internal Packaging: packaging that is in direct contact with the cells, ATMP or biological sample, constituting a container, wrap or any other form of protection, removable or not, intended for holding, covering or packaging;



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XVI - Outer or Tertiary Packaging: packaging used exclusively for the external protection of the cargo during movement (loading, unloading and transportation) and storage operations;

XVII - Adverse Event: any unfavorable occurrence associated to the productive cycle of a product, from the activity of obtaining human cells, tissues and organs from a living or deceased donor, including evaluation of biological material, processing, storage, distribution and use of the product; adverse reactions are type of adverse event;

XVIII - Quality Assurance: set of organized actions adopted with the objective of ensuring that the available cells and ATMP have the quality required for its therapeutic use;

XIX - Exceptional Release: providing for use of cells or ATMP that do not fully meet the quality and safety criteria defined by the establishment and non-compliant with the provisions in Standard Operating Procedure (SOP);

XX - Batch: specific amount of the final product aimed at having uniform character and quality, within predetermined specifications and limits, produced according to singular process, during the same processing cycle and, where applicable, the same cryopreservation step, avoiding or preventing mix up of products from two or more types or donors;

XXI - Minimal Manipulation: cells or tissues processing that does not significantly change their biological characteristics, including differentiation and activation status, proliferation potential and metabolic activity. Acts of cutting, separating, centrifuging, immersing or preserving in antibiotic solutions, concentrating, purifying, filtering, lyophilizing, irradiating, freezing, cryopreserving or vitrifying are considered as minimal manipulation, among others that meet this definition;

XXII - Substantial Manipulation: cells and tissues processing that change any of their biological characteristics, including differentiation and activation status, proliferation potential and metabolic activity. It is every cell and tissue processing that does not constitute a minimal manipulation. All cell culture types are considered as substantial manipulation;

XXIII - Standard Operating Procedure (SOP): written, properly authorized and controlled instruction or procedure, that establishes detailed instructions for performing specific procedures at the Cell Processing Center and other general nature activities;

XXIV - Tissue Engineering Product: biological product consisting of human cells organized in tissues or organs that have properties that allow regenerating, reconstituting or replacing a human tissue or organ, in the presence or not of structural support consisting of biological or biocompatible material, and a) has been subjected to substantial manipulation; and/or (b) performs in the recipient a function distinct from that performed in the donor;

XXV - Advanced Cellular Therapy Product: biological product consisting of human cells or its non-chemically defined derivatives, with the purpose of obtaining therapeutic, preventive or diagnosing properties, through its main mode of action of metabolic, pharmacological and/or immunological nature, for autologous or allogeneic use in humans, and (a) has been submitted to substantial manipulation; and/or (b) performs in the recipient function distinct from that performed in the donor;



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XXVI - Gene Therapy Product: biological product whose active component contains or consists of recombinant nucleic acid, to modify (regulate, repair, replace, add or delete) a genetic sequence or to modify the expression of a gene, for therapeutic, preventive or diagnostic purposes; (amended by RDC No. 260, dated December 21, 2018)

XXVII - Final Product: consists of the finished product, which has completed all production steps by the Cell Processing Center;

XXVIII - Qualification: set of actions performed to provide documented evidences that all equipment components, materials and critical reagents used for obtaining, manipulating and cryopreserving the cells and ATMP which may affect its quality or safety operate indeed according to what is intended and specified, as well as lead to the expected results;

XXIX - Quarantine: period when the cells or the ATMP remain waiting for:

a) results of the donor laboratorial screening tests;

b) results of the quality control tests;

c) end of processing, packaging, preservation, labelling and final signature for release; or d) definition about its destination, in the case of products involved in recall or that do not meet the quality specifications defined by the Cell Processing Center;

XXX - Technical Complaint: any notification of suspected abnormality or irregularity of a product or company related to the technical or legal aspects, regardless of the occurrence of damage to the individual or collective health;

XXXI - Traceability: the ability to recover the history from donor/patient selection, through the recovery or retrieval of the biological material to the release for use of the product that is being considered, by means of identification and records;

XXXII - Adverse Reaction: type of Adverse Event characterized by an unintentional response in the donor or in the recipient, associated to the procedures that involve the collection of the biological material or the therapeutic use of cells and ATMP, that result in the transmission of infections, death or risk to life, deficiency or incapacitating conditions, need for medical or surgical intervention, hospitalization or extension of the hospitalization, morbidity, among others;

XXXIII - Recipient: individual who received the transplant, infusion of implant of cells or ATMP;

XXXIV - Legal Responsible Person: individual who legally takes over the Cell Processing Center administration;

XXXV - Technical Responsible Person: legally qualified professional, with higher education degree and enrolled with the respective Professional Class Council, who takes over the technical responsibility of the Cell Processing Center, as well as the final responsibility for the quality and safety of the cells and ATMP provided for therapeutic use and for clinical research;

XXXVI - Room: environment delimited by walls in its whole perimeter, with one or more doors, which may have windows or devices for external view from its interior;

XXXVII - Dedicated Room: room intended to produce a single type of product;



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XXXVIII - Open System: in the case of exposure of the biological material to the environment. Insertion of needle or equivalent in sample sites of plastic bags, for collecting aliquots, should not be considered as system opening, provided it is performed within an ISO 5 Clean Environment;

XXXIX - CEP/CONEP System: is composed of the Brazilian Research Ethics Committee (CONEP, in Portuguese) of the National Council of Health (CNS, in Portuguese) of the Ministry of Health and the Research Ethics Committees (CEP, in Portuguese), forming a system that uses its own interrelation mechanisms, tools and instruments, in a cooperative work that aims, specially, to protect the research participants in Brazil, in a coordinated and decentralized manner;

XL - Closed System: in the case of no exposure of the biological material or product to the environment. Are considered as processing in closed system, for example, the transference of component(s) of the biological material between plastic bags and satellite plastic bags or transference plastic bags, attached through equipment for sterile connection of tubes;

XLI - Quality Management System: management system that runs and controls the activities of an organization, regarding quality;

XLII - Informed Consent Form (TCLE, in Portuguese): document in which the informed consent of the individual or his/her legal responsible person is expressed, in writing, and it must contain the necessary information, in clear and objective, easy to understand language, for full clarification about a certain procedure;

XLIII - Conventional Transplant of Hematopoietic Progenitor Cells (HPC): a type of cell therapy for the purpose of treatment or rescue after chemotherapy for the treatment of oncological, hematological or immunological diseases;

XLIV - Therapeutic Use: transfer of cells or ATMP in a same individual (autologous use) or between individuals (allogeneic use), with the purpose of obtaining recognized therapeutic property through transplant, infusion or implant for the purposes of this Resolution, excluding from this definition the use in clinical research;

XLV - Validation: set of actions to prove that processes or systems lead to the expected result; and

XLVI - Change Room: place that must have area for handwashing and for gowning, and serve as a barrier to the processing room, in order to ensure the access of professionals wearing exclusive use clothes.

CHAPTER II
GENERAL ASPECTS

Art.8 It is the Cell Processing Center's responsibility to ensure the quality and safety of available cells and ATMP for therapeutic use and clinical research.

Sole Paragraph. Only human cells and ATMP that comply with the Good Practices on Human Cells described herein must be provided.

Art.9 Human cells that do not fall under the definition of ATMP herein can only be provided



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for clinical research after approval of the respective project by the CEP/CONEP System.

Sole Paragraph. The human cells under the main clause of this article can only be provided for therapeutic use if proven that the respective therapeutic procedure is authorized by the Professional Class Council.

Art.10 ATMP can only be provided for clinical research after approval of the clinical research project by the CEP/CONEP System and by Anvisa; and they can only be provided for therapy upon the regularization of the product with Anvisa.

Art.11 The Cell Processing Center must have valid Health Permit, issued by the competent State, City or Federal District Health Authority, except establishments part of the Public Administration or instituted by it, to which the sole paragraph of art. 10 of Law 6,437, dated August 20, 1977, and legal State, City or Federal District complementary provisions apply.

§1 The establishment with a Cell Processing Center in its dependencies may request the inclusion of the description of this activity in its Health Permit, by complying with the provisions herein, and it is the competent State, City or Federal District Health Authority responsibility to deliberate on this request.

§2 The Health Permit renewal should be requested to the competent State, City or Federal District Health Authority.

Art. 12 If the Cell Processing Center closes its activities, it must inform this fact to the competent State, City or Federal District Health Authority and to Anvisa, and be responsible for the destination of the stored cells and ATMP and for the maintenance of the respective process records, for the period of time foreseen herein.

Sole Paragraph. The Cell Processing Center can share this responsibility with the health establishment to which it is linked, where applicable.

Art.13 In the event of robbery, theft or loss of cells or ATMP occurred in a health establishment or during transportation, the fact must be notified to the competent State, City or Federal District Health Authority and to Anvisa, within a maximum period of 1 (one) business day after the event.

§1 The notifications to the competent Health Authority and to Anvisa must contain the following data:

I - details of the robbed, stolen or lost material, including type and purpose, quantity and identification code;

II - date and place of the robbery, theft or loss; and

III - name of the transportation company, courier body or person responsible for the transportation, where applicable.

§2 The copy of the police report must be sent to the competent Health Authorities, provided



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in the main clause of this article, as soon as available.

CHAPTER III
TECHNICAL PROVISIONS

Section I
Competencies

Art.14 The competencies of Cell Processing Center are:

I - search for potential donors and interview a family member, when the donor is deceased, or interview the living donor him/herself or his/her legal responsible person, when underage or incapacitated;

II - check whether the donor selection has been performed or do it so, i.e., perform the clinical, social, physical, laboratorial screening and other pertinent assessments necessary to identify possible contraindication to the donation, recovery or use of the cells and ATMP;

III - recover the cells or receive cells obtained by personal from other establishments, transplant centers, hemotherapy services or hospital centers;

IV - pack and transport cells and samples from the collection site to the Cell Processing Center;

V - evaluate, process and pack cells, ATMP and aliquots for future tests;

VI - store cells, ATMP and aliquots for future tests;

VII - release and provide cells and ATMP for therapeutic use and/or clinical research;

VIII - provide to the professional requesting the product, all necessary information about the cells and ATMP;

IX - implement a Quality Management System as defined in this Resolution;

X - dispose cells and ATMP; and

XI - do all the records so as to preserve the traceability of the donors, cells and ATMP provided for therapeutic use, research, teaching, training, quality control, validation of processes or disposed and of the recipients, as well as keep the safety and confidentiality of the documents and registrations so that they are easily recoverable, according to Subsection III of Section II of this Chapter.

Art.15 The Cell Processing Center can outsource or delegate the activities under its responsibility, except the activities described in subparagraph V, VII, VIII and IX of art. 14, respected the normative notes and applicable legal provisions.

§1 It is allowed to outsource or delegate the storage of cells and ATMP after end of the



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quarantine, and it does not apply to aliquots for future tests that are not stored together with the cells and with the ATMP.

§2 The execution of the outsourced or delegated activities must be established through a contract, agreement or liability note with the service provider, according to Subsection VIII of Section II of Chapter III of this Resolution.

§3 If the activities described in §2 of this article are established by other institutions other than the Cell Processing Center, by a body part of the National Transplant System (SNT, in Portuguese) or by a SNT General Coordination delegated body, the Cell Processing Center must have a copy of the respective contract, agreement or liability note.

Section II
Quality Management System and Quality Assurance

Art.16 The Cell Processing Center must implement a Quality Management System, which will determine the implementation of the Quality Policy.

§1 The Quality Policy must be expressed in a document formally constituted and authorized by the Cell Processing Center, containing the intentions and global guidelines regarding the quality.

§2 The Quality Management System must have the following basic elements:

I - appropriate facilities, procedures, processes and organizational resources; and

II - Quality Assurance actions.

Art. 17 Quality Assurance must be described in the Quality Manual to be acknowledged by all employees of the establishment.

Art. 18 The Quality Manual must comprise or refer, at least:

I - the expected Quality Assurance actions;

II - the identification of which processes will be part of the Quality Assurance and how the quality requirements will be achieved;

III - the expected adequate infrastructure and resources, including the staff defined to perform the Quality Assurance activities; and

IV - the code of ethics and conduct of the establishment.

Art. 19 The Quality Assurance actions must ensure:

I - planning and development of all activities related to the Cell Processing Center, according to the technical and legal requirements, as well as to the Good Practices on Human Cells;

II - elaboration of the Internal Statute;



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III - adequacy of the qualification and capacitation of the professionals to the functions they perform;

IV - performance of all necessary controls regarding the critical processes, equipment, instruments, materials, reagents, *in vitro* diagnostics products, computerized system and suppliers, and other in process controls, validations, qualifications and calibrations;

V - validation of the Cell Processing Center critical processes and monitoring of the critical parameters established and approved by the respective validation process;

VI - implementation of a Documents Management system;

VII - processing, release and provision of cells and ATMP in compliance with the specifications established by the Cell Processing Center, except the condition of Exceptional Release of products foreseen in art. 54 herein;

VIII - non-release and non-provision of cells and ATMP prior to the review and final approval by the responsible parties;

IX - conduction of periodic internal audits to check compliance with applicable regulations;

X - compliance with biosafety and hygiene rules;

XI - identification, registration, investigation and execution of corrective and preventive actions related to technical complaints and adverse events including errors, accidents and occurrence of adverse reactions incurred from the retrieval process to the product provision and use;

XII - notification of information, technical complaints and adverse events, as defined in arts. 12 and 13 of this Resolution and Section XVI of this Chapter;

XIII - implantation of a recall system for cells and ATMP;

XIV - implantation of change control system; and

XV - performance of regular assessment of the validated critical processes, as well as of the quality of the available cells and ATMP, to check the consistency of the processes and to ensure continuous improvement.

Subsection I
Good Practices on Human Cells

Art.20 Compliance with the Good Practices on Human Cells must be ensured, under the Quality Assurance scope, so that the cells and the ATMP are obtained, transported, processed, stored, released and provided according to the quality and safety standards necessary for therapeutic use or clinical research.

Art.21 The Good Practices on Human Cells determine that:



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I - all activities developed in the Cell Processing Center are clearly defined and systematically reviewed;

II - all resources necessary for performing the activities developed in the Cell Processing Center are provided, including:

- a) qualified and trained staff;
- b) physical infrastructure;
- c) equipment, instruments, computerized systems, suppliers, support services and, where applicable, outsourced services;
- d) materials, reagents and *in vitro* diagnostics products; and
- e) approved and current SOPs.

III - SOPs written in clear and unequivocal language;

IV - necessary validations, qualifications and calibrations are performed;

V - records are done during the activities performed to show that all steps in the SOPs were followed and that the quantity and quality of the obtained product are compliant with the expected;

VI - the records allowing the traceability of the cells and ATMP are filed in a safe, organized way and with easily access;

VII - there is an implemented recall system capable of collecting any non-compliant cell or ATMP whose non-compliance has been detected after its distribution, and that makes the product disqualified for therapeutic use or clinical research; and

VIII - appropriate measures are taken and recorded regarding non-compliant cells and ATMP and, when applicable, measures are taken to prevent recurrences.

Subsection II
Internal Statute

Art.22 The Cell Processing Center must have an updated Internal Statute, as part of the Quality Manual, where the following items are present:

I - purpose of the establishment;

II - developed activities;

III - organizational chart, describing the staff structure; and

IV - nominal list, accompanied by the corresponding signature of all staff, according to Section III hereof, indicating the qualification, functions and responsibilities of each professional.

Sole Paragraph. The nominal list mentioned in subparagraph IV of this article may be present in the form of an attachment of the Internal Statute, to facilitate its updates.

Subsection III
Documents Management



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Art.23 The Cell Processing Center must implement a Document Management system that covers and describes the rules for standardization, control, preparation, change, approval, disclosure, maintenance, filing and periodic review of documents.

Art.24 The Documents Management must ensure that:

I - the generation of documents follows the steps recommended for its development;

II - only updated and approved documents are in use, and unwarranted use of obsolete documents is avoided;

III - the current versions of the documents are available everywhere they are used and to the employees who will perform the referred activities or need to consult them;

IV - all reviewed documents and the changes performed are duly approved;

V - there is control of the implemented changes as well as the maintenance of the history of all versions of the documents; and

VI - all the Cell Processing Center activities are described and documented in SOPs.

§1 Documents must be confidential and the access to them must be limited to the personnel authorized by the Technical Responsible person and to the Health Authority, for inspection and control measures purposes.

§2 The documents must be written with clarity, precision and logical order, so as to avoid ambiguity and imprecision.

§3 The documents must be reviewed according to the period established by the Cell Processing Center and whenever necessary.

Art.25 The documents may be printed, electronic, microfilmed or other qualified means, so that they are easily retrievable, and their traceability is guaranteed.

Sole Paragraph. If electronic means are used, the following requirements must be met:

I - data must be stored in back-ups and the Cell Processing Center must prove that the system is protected against frauds and allows the identification of data changes; and

II - the system must be validated, have access management, and the Cell Processing Center must provide urgency plans and replacement measures that allow the system to work or alternatives that maintain access to the necessary information in case of failures.

Art.26 The documents must be protected by physical or electronic means against accidental or voluntary damage, compliant with the current regulation regarding the protection against fire, as well as be kept in environmental conditions compatible with the maintenance of its integrity.

Art.27 The Cell Processing Center must keep filed, for at least 20 (twenty) years, as from the



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distribution or disposal of the cells or ATMP, the following documents or information about:

- I - the donor, including his/her clinical, social, physical and laboratorial screening;
- II - recovery of cells;
- III - packing and transportation of cells from the collection site to the Cell Processing Center;
- IV - processing, packing and storage of cells and ATMP;
- V - results of the quality control tests;
- VI - release of the cells and ATMP;
- VII - reason for disposal of the cells and ATMP;
- VIII - request and provision of cells and ATMP for therapeutic use;
- IX - request and provision of cells and ATMP for research, teaching, training, quality control and/or validation of processes;
- X - notifications of performed and non-performed transplants, infusions or implants;
- XI - document favorable to the conduction of the clinical research issued by the CEP/CONEP System and, where applicable, by Anvisa and other competent bodies;
- XII - TCLE for donation and for the other procedures performed by the Cell Processing Center;
- XIII - adverse events related to all developed activities;
- XIV - adverse reactions related to the obtaining the cells, in the case of living donor, and its use and of the ATMP;
- XV - Technical complaints of equipment, instruments, materials, reagents and *in vitro* diagnostics products used; and
- XVI - reports of non-compliances and the adopted measures.

§1 In addition to the documents described above, the Cell Processing Center can define other critical documents to be filed for at least 20 (twenty) years, as from the distribution or disposal of the cells and ATMP.

§2 The documents considered as non-critical by the Cell Processing Center must be filed for at least 5 (five) years, as from the distribution or disposal of the cells and ATMP.

Art.28 The Cell Processing Center may contract services specialized in filing and keeping documents, provided the requirements of this Resolution are met.



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Art.29 The forms and details on the maintenance of the documents must be defined in SOP describing, at least:

- I - the filing location regarding each document or group of documents;
- II - the duration, frequency of backups and support, where applicable;
- III - the method used; and
- IV - the people authorized to consult the files.

**Subsection IV
Qualification and Validation**

Art.30 The Cell Processing Center must implement qualification and validation actions necessary to prove that all processes defined as critical are under control, so as not to make the cells and the ATMP clinically ineffective or harmful to the recipient.

Art.31 The Cell Processing Center must define and document the essential elements of its qualification and validation in a Master Validation Plan containing, where applicable, the following steps:

- I - Design Qualification (DQ);
- II - Installation Qualification (IQ);
- III - Operational Qualification (OQ); and
- IV - Performance Qualification (PQ).

§1 The critical processes must only be implemented in the Cell Processing Center based on the results of the performed validations.

§2 Reference values defined before starting the validation may be based on studies performed by the Cell Processing Center itself or on published study data.

§3 The results and conclusions of qualifications and validations must be recorded.

Art.32 Any change in the physical infrastructure, equipment, instruments, computer systems or processes that may, directly or indirectly, affect the quality of the product, must be qualified or validated.

Art.33 All steps of the processes considered as critical must be subject to periodic assessment or review to ensure that they continue producing the expected results.

**Subsection V
Biosafety and Hygiene**

Art.34 Every biological material, for being potentially infectious, must be handled according



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to the applicable biosafety standards.

Art.35 The Cell Processing Center must keep biosafety and hygiene SOPs updated and provide them to all employees, comprising at least the following items:

I - standards and conducts of biological, chemical, physical, occupational and environmental safety and hygiene;

II - general behavior of the professionals in the Cell Processing Center and, particularly, behavior in the clean environments or of risk;

III - hygiene and clothing of professionals working in clean environments;

IV - instructions for use for personal (PPE) and collective (CPE) protective equipment;

V - procedures in case of accidental exposure to a biological or dangerous product;

VI - cleaning of materials, equipment and instruments;

VII - waste management; and

VIII - handling during transportation of biological material.

Art.36 Explicit warnings regarding the classification of the biosafety level of the environments, as well as the hygiene rules and necessary PPE and CPE must be posted at the entrance to each sector of the Cell Processing Center.

Sole Paragraph. Access to the different environments must be reserved for the authorized professionals.

Art.37 All professionals working at the Cell Processing Center must have their mandatory vaccination updated, according to the Ministry of Labor regulations.

Art.38 All personnel, including cleaning personnel, who perform their work in cryopreservation rooms, where cryogenic containers with liquid or gaseous nitrogen or any other low temperature fluid or gas are present, must be trained in the behavior in that environment and be warned of the risk of anoxia and burns associated with the presence and handling of these fluids or liquefied gases.

Art.39 The physical infrastructure, materials, equipment and instruments used in the Cell Processing Center must be kept clean and in hygiene conditions, and the periodicity of the cleaning and disinfection procedures must be described in SOPs, keeping the record of the performed cleanings.

Sole Paragraph. The used sanitizers must be categorized as products of professional/hospital use and be regularized with Anvisa, according to the RDC No. 59, dated December 17, 2010, and by the specific Resolutions, by category of product, or its changes, and must be used according to the manufacturer's instructions for use.



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Art.40 Environments for processing or for other activities of possible cross contamination of the cells or of ATMP, or exposure to blood pathogens must undergo cleaning before starting the activities of the day, between each batch of cells or ATMP and at the end of the daily activities, in a routine, programmed and documented manner.

Subsection VI
Quality Control general aspects

Art.41 The Cell Processing Center must implement quality control actions, with the objective of:

I - contributing for the cells and the ATMP to be released and provided only after all the parameters related to safety and quality of the product, along all the performed processes, have been met and deemed as satisfactory; and

II - contributing to the variability maintenance of the several processes under control and within the tolerance limits.

Art.42 Quality control must, at least:

I - define the analysis parameters and analytical methods for materials, reagents, *in vitro* diagnostics products, cells and ATMP, and in process controls

II - define the sampling procedures;

III - define the procedures for environmental monitoring;

IV - perform necessary qualifications and validations related to quality control;

V - monitor the outsourced services performance;

VI - monitor the environments and the critical equipment, in specific time intervals;

VII - establish the requirements for accepting batch of materials, reagents and *in vitro* diagnostics products before they start being used;

VIII - check the compliance with minimum requirements for safety and quality of the cells and of ATMP before releasing the product, as provided hereof, by reviewing the critical steps and quality controls records;

IX - ensure that the results or measurements out of tolerance limits are investigated;

X - implement and record the corrective and preventive actions, when results or measurements are out of tolerance limits and determine the impact of this deviation in the product quality and safety;

XI - approve changes that affect the quality of the cells and ATMP;



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XII - assess the need for recalling distributed cells and ATMP; and

XIII - ensure that complaints and returns of cells and ATMP related to the quality are recorded, investigated and, where necessary, that the corrective and preventive actions are implemented.

Art.43 The SOPs of the performed quality controls, including of the in process controls, must cover:

I - list of parameters and processes to be analyzed;

II - form of control and frequency of the tests;

III - sampling specifications, where applicable;

IV - tolerance limits and acceptability criteria for the analyzes results; and

V - assessments and record of analysis results.

Art.44 The Cell Processing Center must perform microbiological control of its environments and of the equipment that need this control, including the CO₂ incubator intended for the cultivation of cells and ATMP for therapeutic use or clinical research purposes, at time intervals defined by the Cell Processing Center, according to its work flow.

§1 Microbiological control of the clean environments is mandatory and must be performed, at least, during the "in operation" condition.

§2 The environments must not be contaminated by the sampling methods used.

Art.45 The Cell Processing Center that stores HPC for conventional transplant must perform annual assessment of the cell viability and, for the bone marrow Hematopoietic Progenitor Cells (HPC-BM), also, the total or granulocytic and monocytic colony forming units (CFU or CFU-GM), of percentage of cryopreserved units of each storage device, as defined by the establishment.

Sole Paragraph. In order to comply with the main clause of this article, viability analysis is acceptable and, where applicable, the CFU or CFU-GM test in HPC units intended for quality control and in units provided for therapeutic use.

Art.46 The quality control results must be analyzed and, when they are out of the pre-defined criteria, preventive and corrective actions must be adopted, keeping the records of results, non-compliances and adopted measures.

Subsection VII
Quality Control of the cells and ATMP

Art.47 The method used to perform the quality control must not jeopardize the integrity of the cells or ATMP, unless these biological materials are disposed after performing the respective tests.



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Sole Paragraph. Sampling must be representative, traceable and properly adapted to the control method used and, when applicable, upon validation for purposes of proving the sensitivity of the method.

Art. 48 The cells and ATMP can only be released for therapeutic use and clinical research after observing the criteria defined on Section V of this Chapter, and the following tests are performed:

I - for HPC-BM, for conventional transplant purposes, in product sample obtained postprocessing and before adding cryoprotectants:

- a) cell counts: total number of nucleated cells;
- b) cell viability test;
- c) microbiological tests, in this case the provisions of art. 49 hereof must be followed; and
- d) residual volume of red blood cells or hematocrit in the product, where there is a major or bi-directional ABO incompatibility.

II - for peripheral blood Hematopoietic Progenitor Cells (HPC-PB), for conventional transplant purposes, in product sample obtained postprocessing and before adding cryoprotectants:

- a) cell counts: total number of nucleated cells;
- b) cell viability test;
- c) cell phenotyping: CD34+ viable cells count;
- d) microbiological tests, in this case the provisions of art. 49 hereof must be followed; and
- e) residual volume of red blood cells or hematocrit in the product, where there is a major or bi-directional ABO incompatibility.

III - for umbilical cord and placental blood Hematopoietic Progenitor Cells of (HPC-UCB), for conventional transplant purposes, in product sample:

- a) full blood count, through automated count, in product sample obtained before processing;
- b) ABO and RhD typing, before processing or it can be performed in sample collected at any moment before adding cryoprotectants;
- c) test for detecting abnormal hemoglobin, with distinction of hemoglobin A, A2, S and C, and if they are in heterozygosis or homozygosis, in sample collected at any moment before adding cryoprotectants;
- d) determination of HLA antigens, in the case of allogeneic use;
- e) cell counts: total number of nucleated cells and erythroblasts, in product sample obtained postprocessing and before adding cryoprotectants;
- f) cell viability test, in product sample obtained postprocessing and before adding cryoprotectants;
- g) cell phenotyping: CD34+ viable cells count, in product sample obtained postprocessing and before adding cryoprotectants; and
- h) microbiological tests, in this case the provisions of art. 49 hereof must be followed.

IV - for cells (other than HPC-BM, HPC-PB or HPC-UCB, for conventional transplant purposes) and ATMP, in a final product sample:

- a) total count of relevant cells;
- b) identity or phenotyping test adequate for the product and quantification of the present cell populations;
- c) cell viability;



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d) purity test: it includes, where applicable, verification of substances or cells that may be harmful to the recipient and, in the case of substantial manipulation, verification of endotoxins presence is mandatory;

e) microbiological tests: the provisions of art. 49 hereof must be followed and, when applicable, repeat the respective tests in the final product and, in the case of substantial manipulation, the test for detecting contamination by mycoplasma must also be included;

f) detection of nucleic acid of the viruses CMV, HIV-1 and HIV-2, HTLV-I and HTLV-II, EBV, HBV, HCV and B19, and, where applicable, of other viral agents clinically relevant in humans, only in the case of substantial manipulation for allogeneic use;

g) cytogenetics, only in the case of substantial manipulation; and

h) potency test, where applicable: the cells relevant biological activity, if known, or of the other products synthesized by the cells must be defined and quantified.

§1 Tests on items "a" and "b" of subsection I and "a", "b" and "c" of subsection II of this article can be performed exclusively in product samples obtained before processing, when the product is not submitted to red blood cell volume reduction or to other process that may significantly affect the count and viability parameters of the total nucleated cells and CD34+ cells.

§2 In the hypothesis of §1 of this article, the establishment must prove, through process validation, that the deplasmation itself, does not significantly affects the relevant parameters of count and viability of the total nucleated cells and CD34+ cells.

§3 If certain product release tests in items "d", "e", "f", "g" and "h" of subsection IV of this article cannot be performed in the final product, but only in intermediate product and/or as in process controls, or they are not considered applicable for the product in question and, thus, dispensed from performing, such fact must be duly justified.

Art.49 The microbiological tests for detecting bacterial (aerobic and anaerobic) and fungal contamination, and where applicable, contamination by mycoplasma, must be performed, at least, in product samples obtained postprocessing and before cryopreservation, before or after adding cryoprotectants.

Art.50 In case of therapeutic use of the cells is needed before obtaining the results of the product microbiological analyses, provision of the biological material may occur upon registration of the formal justification by the professional responsible for its provision.

§1 As soon as available, the results referred in the main clause of this article must be recorded and communicated to the professional responsible for the recipient patient.

§2 The determinations of the main clause of this article do not apply to the ATMP that are susceptible to registration with Anvisa, once these products can only be released after obtaining negative results in the tests provided in item "e" subparagraph IV of art.48 hereof, also considering the provision contained in §3 of the same art. 48.

Art.51 In case of positive microbiological result, the microorganism must be identified, the causes of contamination investigated and, where applicable, preventive and corrective actions taken.

Sole Paragraph. For products with positive microbiological test, the Cell Processing Center



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must have SOP for the management of the relative risk to the other cells and ATMP from this donor, which are still stored or have already been distributed.

Art.52 In addition to the tests defined hereof, the Cell Processing Center may establish other requirements to release the therapeutic use products.

Art.53 The Cell Processing Center must establish in SOPs the test methods used in each analysis and the tolerance values or values ranges for critical characteristics defined for each product, such as minimum quantity and recovery of cells specific populations, cell viability, cell identification, sterility and functional assays.

Art.54 The Cell Processing Center must keep SOPs foreseeing the possibility of occurring exceptional release of products, due to emergency situations or under recipient's special clinical circumstances.

§1 The exceptional release of product requires assessment considering the risk-benefit relation of using this product, in a joint decision involving the Cell Processing Center, the team of professionals responsible for the patient and the recipient or his/her legal responsible person, and the contact among those involved must be documented, keeping the respective records.

§2 In case of an exceptional release of the product, noncompliant quality and safety parameters, with their respective results and reference or tolerance ranges, must be properly informed to the professional who will use it.

§3 Allogeneic donors with HIV-positive nucleic acid testing (NAT) or confirmed HIV serological test must never be used.

§4 The exceptional release does not apply to ATMP that are susceptible to registration with Anvisa.

Art.55 If the Cell Processing Center provides or intends to provide in the future HPC-UCB for conventional transplant, the stored final product must have:

I - negative microbiological test; and

II - minimum cellularity of 5×10^8 (five hundred million) total viable nucleated cells and 1.25×10^6 (one million, two hundred and fifty thousand) CD34+ viable cells.

§1 The Cell Processing Center may decide to increase the minimum value accepted for storing the HPC-UCB unit in its facilities, according to the quality policy.

§2 Storage of HPC-UCB, for allogeneic related or autologous use, with positive microbiological test or with cellularity below 5×10^8 (five hundred million) of total viable nucleated cells and/or below 1.25×10^6 (one million and two hundred and fifty thousand) CD34+ viable cells, can be performed in the case of clinical indication for use existing at the moment of collection or diagnosed in the neonate.

Art.56 The release of each batch of cells or of ATMP must be accompanied by the identification and signature of the person responsible for this release.



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Sole Paragraph. When the release of batches is performed using computerized system, the system should ensure that only designated people can do so.

Subsection VIII
Outsourcing activities

Art.57 Outsourcing activities of the Cell Processing Center must be carried out under contract, agreement or liability note with the service provider.

Sole Paragraph. The contract, agreement or liability note must describe the relations established between the parties and define the responsibilities and the minimum criteria regarding the contracted services.

Art.58 The service provider must have physical infrastructure, equipment, knowledge, experience and competent staff to satisfactorily perform the service requested by the Cell Processing Center and comply with the technical and legal requirements.

§1 The Cell Processing Center must ensure that all outsourced activities are performed according to the current regulation and the minimum criteria established by it.

§2 The Cell Processing Center must establish criteria for periodic evaluation of the outsourced party and keep records of these evaluations.

Art.59 Outsourcing activities does not exempt the Cell Processing Center from the compliance with the technical and legal requirements established by the current legislation, being liable jointly with the service provider, towards the health authorities, regarding the technical, operational and legal aspects inherent to the outsourced activity.

Art.60 The service provider must have a Health Permit as well as other types of health authorizations/certifications, as applicable, issued by the competent Health Authorities and that cover the action regarding the outsourced activity, all those updated and current during the services provision, except establishments part of the Public Administration or instituted by it, to which the sole paragraph of art. 10 of Law 6,437, dated August 20, 1977, and legal state, city or Federal District complementary provisions apply.

Sole Paragraph. Service providers that are not subject to health legislation are exempt from the obligation determined in the main clause.

Subsection IX
Materials and *in-vitro* diagnostics products

Art.61 The used materials and *in vitro* diagnostics products must be regularized with Anvisa, respectively, according to Collegiate Board Resolution - RDC No. 185, dated October 22, 2001, RDC No. 36, dated August 26, 2015, and RDC No. 40 dated August 26, 2015, and their amendments.

Art.62 The Cell Processing Center must keep records of the origin, validity and batch number of all used materials, reagents and *in vitro* diagnostics products.



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Art.63 The materials used to collect and process the cells and ATMP, that get in contact with them, must be sterile, apyrogenic and, where applicable, non-cytotoxic, of pharmaceutical grade and of single use.

§1 There must be process for cleaning, disinfection or sterilization of the medical devices that can be processed, according to the Collegiate Board Resolution - RDC No. 15, dated March 15, 2012, and its amendments.

§2 Materials that state in a label, package insert or package the prohibition or inadequacy for use in humans must not be used during the recovery, processing or cryopreservation activities of cells and ATMP for therapeutic use or in clinical research.

Art.64 In the case of Gene Therapy Products, the records of the tests of identity, integrity, purity and potency related to the line of mother cells and vector must be kept. (amended by RDC No. 260, dated December 21, 2018)

Art.65 The reagent or solution prepared or aliquoted by the Cell Processing Center itself must be identified with a label identifying the name, concentration, batch number and expiry date, in addition to the information regarding potential risks.

§1 Other information, such as the reagent preparation date, identification of who prepared or aliquoted it and the storage conditions, when not included in the label, must be recorded in a document apart, so that they are traceable.

§2 Records of the preparation and quality control of the prepared and/or aliquoted reagents must be kept.

Art.66 The use of materials, reagents and *in vitro* diagnostics products must comply with the recommendations of the manufacturer, including preservation, storage conditions and shelf lives, and their revalidation is not allowed after expiry date.

Art.67 The Cell Processing Center that performs in-house methodologies or technologies must proceed with the description and record of their development process steps, as well as their validation protocol and report.

Sole Paragraph. The use of in-house methodologies for conducting donor laboratory screening tests is forbidden, according to art. 112 hereof.

Art.68 The use of animal origin products must be avoided and, when unavoidable, justified.

§1 In case the use of animal origin products is unavoidable, these must have certification of absence of infectious agents and contaminants and comply with RDC No. 305, dated November 14, 2002, and its amendments.

§2 For growth factors, identity, purity and potency measures must be established, to ensure reproducibility of the cell culture characteristics.

Art.69 The Cell Processing Center must perform the qualification of suppliers of materials,



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reagents and *in vitro* diagnostics products , based on their ability to meet pre-established requirements, in compliance with RDC No. 185, dated October 22, 2001, RDC No. 36 and RDC No. 40, both dated August 26, 2015, and RDC No. 67, dated October 8, 2007, and their amendments, as well as in compliance with the Brazilian Pharmacopeia and the Brazilian Pharmacopeia National Formulary, in its latest editions, being allowed to adopt an official monograph of foreign pharmaceutical codes, in the absence of the national reference, where applicable.

Art.70 The acquired materials, reagents and *in vitro* diagnostics products must be assessed regarding the analysis and acceptance parameters defined by the Cell Processing Center, before they start being used.

Subsection X
Equipment and instruments

Art. 71 The Cell Processing Center must:

I - have equipment and instruments according to its complexity, and in the quantity necessary to meet its demand;

II - keep SOPs containing the specifications, behaviors in case of accidents, qualification, maintenance and location of equipment and instruments, and provide them to the sector employees;

III - implement a preventive and corrective maintenance program of equipment;

IV - observe the necessary conditions to install equipment, according to the instructions of the manufacturer;

V - check and calibrate the instruments and equipment in regular intervals, in compliance with the use and the instructions of the manufacturer; and

VI - keep records of origin (manufacturer) and series of the used equipment and instruments.

§1 All the processes associated to a certain equipment and instrument, such as the operations of verification, qualification and requalification and preventive and corrective maintenances must be planned before being performed and recorded, informing day, person responsible for the intervention and description of the intervention, among other information.

§2 The defective equipment or instrument must not be used, and it must be removed from the working area or identified as out of use, until its corrective maintenance.

Art.72 The used equipment and instruments, national and imported, must be regularized with Anvisa, according to RDC No. 185, dated October 22, 2001, or RDC No. 40, dated August 26, 2015, and its amendments, and other applicable standards.

Art.73 Worksheets for control of routine use, maintenance, calibration and cleaning of equipment and instruments must be available for consultation.



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Art.74 There must be devices for continuous monitoring of the internal temperature and, where applicable, the liquid nitrogen level and the CO₂ level of the equipment supplied by these substances, so as to identify possible failures of the storage equipment/incubator or in the liquid nitrogen or CO₂ supply.

§1 In the case of storage equipment in which the products are immersed in liquid nitrogen, the control can be performed only by determining the level of liquid nitrogen in the equipment and monitoring of the internal temperature is exempted.

§2 When the products are kept in the nitrogen vapor phase, it is necessary to have continuous temperature monitoring devices.

§3 Monitoring records must be performed periodically, as defined by the Cell Processing Center in SOP.

Art.75 Refrigerators, cold storages, freezers, and ultra-freezers must have an alarm to signal temperature conditions out of the specified limits.

Art.76 Every equipment must be properly identified and arranged in areas that are benefited by ventilation or acclimatization system.

Art.77 The Cell Processing Center must establish emergency procedures in case of mechanical failure or deficiency in the power feed of critical equipment, so as to avoid or minimize temperature variations of stored cells or ATMP.

Section III
Personnel

Art.78 The Cell Processing Center must have qualified, enabled and trained personnel in agreement with the activities performed.

Art.79 The Cell Processing Center must promote initial basic training and establish periodic training program of its professionals, as needed, and every time procedures are changed.

§1 The Cell Processing Center must keep records of the performed trainings.

§ 2 The training program must ensure that every professional:

I - knows and understands the Cell Processing Center organizational chart, the Quality Assurance system and the biosafety and hygiene standards related to performing his/her functions;

II - is properly informed on the ethical, legal and administrative background of his/her job;

III - knows the general aspects regarding the cells and ATMP processed in the Cell Processing Center;

IV - knows and understands the relevant scientific and technical principles for the tasks assigned to him/her; and



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V - shows competence in performing the tasks under his/her responsibility.

§3 For qualification and training proof purposes can be presented diplomas, certificates, declarations, recommendation letters, attestations, official letters, among others.

Art. 80 The Cell Processing Center must have:

I - Legal Responsible person, that can be the same of the institution where the Cell Processing Center is installed;

II - Technical Responsible person;

III - person responsible for the Quality Assurance actions;

IV - responsible physician who coordinates the medical activities of the establishment, especially the donor selection;

V - person responsible for processing the cells and ATMP; and

VI - person responsible for quality control actions.

§1 The Technical Responsible person may also take over the legal responsibility for the Cell Processing Center.

§2 The responsible persons mentioned in subparagraphs I to VI of this article may also perform activities at the Cell Processing Center, sharing functions and responsibilities.

§3 The functions of the Technical Responsible person and of the person responsible for Quality Assurance must be performed by distinct individuals, and it is their responsibility to appoint the other professionals to perform each activity of the Cell Processing Center, observing the necessary professional qualifications and trainings.

Art.81 The Technical Responsible person must be a professional of higher education degree in Health, who has practical experience of at least two (2) years in a Cell Processing Center.

Sole Paragraph. The Cell Processing Center must designate a Technical Responsible substitute who meets the same requirements as the titular.

Art. 82 The Technical Responsible person is liable for:

I - coordinating the activities performed in the Cell Processing Center according to the established in the Quality Management System;

II - ensuring compliance with the requirements established herein;

III - providing the Health Authorities with all necessary information; and

IV - being ultimately responsible for the quality and safety of the cells and ATMP.



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Section IV
Premises

Art.83 It is the Cell Processing Center responsibility to plan, prepare and implement the respective physical infrastructure after assessment and approval by the competent State, City or Federal District Health Authority, according to the determinations of Law 6,360 dated September 23, 1976, as well as to meet the specific requirements herein.

§1 Power supply, lighting, temperature, humidity and ventilation of the facilities must be appropriate, so as not to affect directly or indirectly the quality of the products during the manipulation processes or proper working of the equipment.

§2 The Cell Processing Center must have an emergency plan in case of power supply failure, and it must also observe the instructions of the equipment manufacturers, as well as assess and map the critical equipment regarding the requirement or need for uninterruptible power supply – UPS use.

Art.84 The project, configuration and design of the water purification equipment and of the water storage and distribution systems, if any, must be adequate to maintain the intended water quality grade.

Sole Paragraph. Microbiological control and sanitizing mechanisms must be adopted for water purification systems kept at room temperature, especially when the equipment remain static during periods of low or no water demand.

Art.85 The physical infrastructure of the Cell Processing Center must consist of environments arranged to accommodate the circulation of professionals, materials, reagents, *in vitro* diagnostics products, biological material and wastes, allowing their cleaning and maintenance, in a manner to avoid cross-flows that may result in increased risk of occurrence of non-compliances.

Art.86 In case the Cell Processing Center is installed inside the facilities of or linked to another Health Service, it may use the general infrastructure of that service, such as cafeteria, laundry, linen room, materials sanitation and sterilization, warehouse, waste collection, utilities room, power generator and other supporting services, observing the rules inherent to the shared infrastructures.

Art.87 The physical infrastructure of the Cell Processing Center must have, at least, environments for performing the following activities:

I - administrative;

II - receipt of biological material;

III - cells and ATMP processing; and the production of gene therapy vectors or manipulation of Gene Therapy Products demands dedicated rooms or isolated environments (by using isolators technology), as determined in art. 157 hereof; (amended by RDC No. 260, dated December 21, 2018)

IV - storage of cells and ATMP; and



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V - quality control.

§1 The administrative activities must not be performed inside the laboratorial environment.

§2 The laboratorial environments, including clean environment, that need special temperature and humidity conditions, must have such parameters controlled, monitored and recorded.

§3 The area for storage of cells and ATMP must exist in the Cell Processing Center even when the storage activity of these biological materials is outsourced.

§4 In case the Cell Processing Center performs non-clinical research with cells of human origin, they can be manipulated in the same room or area where the cells and ATMP for therapeutic use or clinical research are manipulated, provided the staff is properly trained and the Good Practices conditions are observed, so as there is no cross-flows between the products and materials used for therapeutic use or for clinical research and the products and materials for non-clinical research.

Subsection I

Conditions of the cryopreservation room and/or liquid nitrogen storage room.

Art.88 If the Cell Processing Center has a system to store cells and ATMP in liquid nitrogen tanks, or if there is a nitrogen supply safety system for mechanical freezer storage, the cryopreservation and/or the storage room must have:

I - a floor coated with easy maintenance material and resistant to low temperatures and heavy loads;

II - an external view from its interior;

III - an access door(s) opening from inside to outside, equipped with anti-panic device;

IV - a mechanical exhaust system for dilution of nitrogen residual traces, that promotes the forced exhaustion of all air of the cryopreservation and storage room, with discharge to the external environment of the building;

V - a sensor for leveling the environmental oxygen with sound and visual alarms, inside and outside the cryopreservation and storage room; and

VI - a thermometer to monitor the environmental temperature, indicating the minimum and maximum values.

§1 The replacement air must come from the neighbor environments or supplied by insufflation of external air, with minimum filtering with G1 class filter.

§2 The capture grids of the mechanical exhaust system must be placed near to the floor.

§3 The Cell Processing Center must assess the need of one or more sensors for leveling



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environmental oxygen, according to the configuration and to the room area.

§4 Long cuff protective gloves against very low temperatures and in non-combustible material, as well as goggles or visor must be available for the employees.

Art.89 There must be SOPs defining measures to adopt in case of accidents or alarms triggering.

Subsection II
Clean Environment

Art. 90 The air classification for the ISO conditions is given in Table 1 of the Annex of this Resolution and it must be met according to the specifications of standard ISO 14644 "Cleanrooms and associated controlled environments".

§1 Determination of the grade of air quality and cleanliness for suspended particles must be performed, at least, in the "in operation" condition.

§2 Particles count must be determined measuring, at least, the 0.5 µm size particles and, where applicable, 5.0 µm, according to Table 1 of the Annex of this Resolution.

Art.91 "In operation" ISO 5 condition must be kept in the immediate surroundings of the cells and the ATMP, as well as of materials and reagents that will get in direct contact with them, every time they are exposed to the environment or when aliquots or samples are withdrawn for quality control or diagnosis.

§1 The environment with air quality of particle count equivalent to the "in operation" ISO 5 environment must be surrounded by an "in operation" ISO 8 environment.

§2 The "in operation" condition must be reached with the environment functioning according to a defined process and with a specified number of people in local.

§3 If unidirectional flow modules with no barrier are used, the determination of the clean area extension must be documented and clearly visually demarcated, and the exposure of the products to the environment must be limited to this area.

§4 Isolators must be installed inside an "in operation" ISO 8 environment, according to § 1 of this article, unless the equipment manufacturer indicates that this condition is not necessary to maintain the air classification required for the process.

Art.92 The systems and the equipment operating in a clean environment must be qualified and requalified, according to the dispositions of Subsections IV and X, of Section II, of Chapter II of this Resolution.

§1 The qualification and the requalification of clean rooms and of equipment or unidirectional flow modules must consider/be conducted according to the ISO 14644 specifications "clean rooms and associated controlled environments".



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§2 The qualification and the requalification of biological safety cabinets must consider/be conducted according to the specifications of standard NSF 49 "Biosafety Cabinetry: Design, Construction, Performance, and Field Certification".

Art.93 The Cell Processing Center, that performs minimal manipulation in open system or substantial manipulation, must have a change room and an air lock contiguous to the room where the cells and or the ATMP are processed.

§1 The air lock must be designed to meet the ISO 8 classification (at rest).

§2 The change room could be considered an air lock, provided it is designed for such purpose, meeting the provisions in § 1 of this article and on art. 104 hereof.

Art.94 The Cell Processing Center that only performs minimal manipulation in closed system must obtain the samples for quality control or the aliquots within environments with air quality of particles count equivalent to ISO 5 classification (in operation). In such case, the ISO 8 surrounding environment, the change room and the air lock are not mandatory.

Art.95 The recovery time of the air classification for the clean environment must be known, in case of system shutdown and after finishing the cleaning between the processing of different batches of cells or of ATMP.

Art.96 Alert and action limits must be established for detection of microbial contamination and for monitoring the air quality trend in the clean environments.

§1 The limits expressed in colony forming units (CFU) for the microbiological monitoring of the clean environments "in operation" are described in Table 2 of the Annex hereof.

§2 The clean environments must be regularly monitored for detecting the onset of resistant microorganisms.

§3 If the limits are exceeded, corrective actions must be taken, as described in SOPs.

Art.97 Tests or assays reports on equipment qualification and environments certification must contain, at least:

I - standards and procedures applied;

II - measuring instruments used and copy of the calibration certificate;

III - measurement conditions with occupational status and relevant factors;

IV - map of the area, with the location of the measurement points;

V - test results;

VI - conclusion; and

VII - date, legible name, registration in the Professional Class Council and signature of the



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professional who performed the test or assay.

Sole Paragraph. The calibration standards must be traceable to the International System of Units or to the Brazilian Calibration Network.

Art.98 The disinfectants and detergents used must be monitored with the purpose of detecting possible microbial contamination.

§1 The dilutions must be kept in previously cleaned containers and must not be kept for long periods of time, unless they are sterilized.

§2 Partially empty containers must not be completed.

§3 The disinfectants and detergents used in the ISO 5 environments must have their sterility proven before using.

Art.99 In the clean environments, all exposed surfaces must be flat and impermeable, so as to minimize the accumulation or release of particles or microorganisms, allowing the repeated application of cleaning agents and disinfectants, where applicable.

Art.100 In the clean environments there must not be surfaces that cannot be cleaned.

§1 The facilities must have the minimum of saliences, shelves, cabinets and equipment.

§2 Sliding doors must not be used.

Art.101 The linings must be sealed, so that contamination from the space above them is avoided.

Art.102 Pipes, ducts and other utilities must be installed so that they do not create difficult-to-clean spaces.

Art.103 Facilities intended for hand hygiene must never be in environments where the cells and ATMP are processed.

Art.104 Sinks and drains must not exist in ISO 5 environments and, if possible, they must be avoided in the other clean environments.

§1 When necessary to install them, sinks and drains must be designed, located and maintained in a way as to minimize the risk of microbial contamination, and must have efficient, easy to clean siphons which are adequate to prevent air and liquids backflow.

§2 The soil channels, if present, must be open, easy to clean and be connected to external drains, so that the introduction of microbial contamination is avoided.

Art.105 Both air lock doors cannot be simultaneously opened, and there must be a system that prevents such fact from occurring.



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Art.106 It must be ensured that the air system does not allow dissemination of particles originated from people, equipment, materials or operations, for the areas of cells and ATMP manipulation.

§1 Alarm system must be installed to indicate the occurrence of failures in the ventilation system.

§2 Pressure differential indicator must be installed between the environments where such difference is important, and the observed pressure differences must be regularly recorded.

Art.107 The presence of materials that generate particles in the clean environments must be reduced to the minimum, and completely avoided when processing cells and ATMP.

Section V
Donor selection and exclusion criteria

Art. 108 The autologous or allogeneic donor selection must follow criteria previously defined in SOPs, including clinical and social screening, physical assessment, laboratorial screening and other pertinent assessment related to the potential donor, according to this Resolution and other standards addressed by Ministry of Health.

§1 The selection criteria must ensure protection to the donor and recipient's safety.

§2 In case the donor selection is not performed by the Cell Processing Center, the latter must check if the professionals responsible for the selection, did it according to the minimum criteria defined in this Resolution and other regulations addressed by Ministry of Health.

§3 The establishments can define additional or complementary selection and exclusion criteria to those defined in this Resolution.

Art.109 The establishment responsible for obtaining the TCLE must provide all information related to the donation process, risks involved, laboratory tests, among others necessary for the understanding and signing the TCLE, which must be written in a clear and comprehensible language for the lay person, and it must contain the following items, when applicable:

I - information about the risks to the donor;

II - information on the purpose or use of the collected cells;

III - information on the laboratory tests that will be performed for the donor qualification;

IV - authorization for access to clinical data and medical history of the donor, to obtain information with potential importance for the therapeutic use procedure or clinical research;

V - authorization to store the necessary aliquots, such as cells, plasma, serum or donor DNA, for future tests;

VI - authorization to dispose units that do not meet the criteria for storage, therapeutic use or clinical research; and



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VII - information on the possibility of denying or withdrawing the donation at the several phases of the process, as well as, when it is the donation of hematopoietic progenitor cells (for use in conventional transplant), information on the consequences to the recipient, if the withdrawal occurs after the beginning of the conditioning regimen.

Sole Paragraph. In the case of donor with age below 18 or incapacitated, the TCLE must be signed by the parents or legal responsible person.

Art. 110 Clinical and social screenings and physical evaluation of allogeneic donor must include, at least:

I - general physical evaluation and health history, including ongoing pregnancy;

II - questions related to anesthesia risk identification, for bone marrow donors, or to venous, central or peripheral access, for donors by apheresis;

III - vaccination history;

IV - history of travel and exposure to infectious agents, as well as the prevalence of local infectious diseases;

V - history of blood transfusion and use of blood products;

VI - history of tissues, cells or organs transplant and xenotransplantation;

VII - questions related to the identification of increased risk of blood-transmissible infectious diseases;

VIII - questions related to the identification of the disease transmission risk or inherited conditions;

IX - questions related to the identification of risk of hematological or immunological diseases transmission;

X - history of malignant diseases; and

XI - presence of signs in the body of the donor that suggest risk or symptom of malignant or sexually transmissible diseases, such as:

- a) skin or mucosal lesions;
- b) scars or surgical incisions;
- c) jaundice;
- d) hepatomegaly; and
- e) diffuse lymphadenopathy.

§1 If autologous donor, clinical and social ability assessment must be done, according to subsections I and II of this article, and clinical, social and physical assessment is not mandatory for donor's eligibility foreseen in subsections III to XI.



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§2 The interview referred to in this article must be done with the donor him/herself, and in the case of donor with age below 18 or mentally incapacitated, this may be accompanied and assisted by the parents or legal responsible person.

Subsection I
Laboratory screening for allogeneic and autologous cell donors

Art. 111 Cell donors must mandatorily be submitted to laboratory test for detection of makers for communicable diseases, according to criteria determined in this Resolution and further current legislation.

§1 The laboratory tests referred to in the main clause of this article must be repeated, if necessary, with the purpose of meeting the deadlines provided in subparagraphs I to V of art. 139 herein.

§2 In the case of HPC-UCB donation, the laboratory tests referred to in the main clause must be performed in maternal samples.

§3 Donation of islets of Langerhans must follow the criteria for cells donation described in this Resolution.

§4 In the case of the pooled NAT tests, the group of samples that presents a positive result must be dismembered and their samples individually tested for identification of the concerned infectious agents.

Art.112 The laboratory tests for detecting communicable diseases must be performed with *in vitro* diagnostics products registered with Anvisa for blood donors screening.

Art. 113 Tests for detecting HCV, HBV and HIV markers performed on the cells donors samples, allogeneic and autologous, live or deceased are:

I - for HCV:

- a) detection of anti-HCV antibody or HCV antigen-antibody combined assay; and
- b) detection of HCV nucleic acid (NAT).

II - for HBV:

- a) detection of hepatitis B virus surface antigen (HBsAg);
- b) detection of antibody against HBV capsid – anti-HBc including IgG or IgG + IgM search; and
- c) detection of HBV nucleic acid (NAT).

III - for HIV:

- a) detection of anti-HIV antibody or HIV combined p24 antigen and antibody assays; and
- b) detection of HIV nucleic acid (NAT).

§1 The tests referred to in item 'a' of subparagraph III of this article must include the search for antibodies against HIV subtype 1, including group O, and HIV subtype 2.

§2 In the case of obtaining cells for autologous purposes, the tests described in



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subparagraphs a and b of subparagraphs I and III and a, b and c, of subparagraph II of this article must be performed, when the cells are cryopreserved and stored in devices that do not guarantee absence of cross-contamination risk.

§3 When the product intended for autologous use is fresh or the storage is in a device that ensures the absence of cross-contamination, the provision of art. 125 of this Resolution is valid.

Art.114 The tests to detect other markers of blood-transmissible infections performed in cells donors samples, allogeneic or autologous, live or deceased are:

I - Infection by HTLV I and II: 1 (one) test for detection of anti-HTLV I/II antibody;

II - Chagas disease: 1 (one) test for detection of anti-*T cruzi* antibody;

III - syphilis: 1 (one) test for the detection of antitreponemal or non-treponemal antibody;

IV - toxoplasmosis, in the case of HCP-UCB for conventional transplantation: anti-Toxoplasma antibody detection ('total and IgM' or 'IgG and IgM'); and

V - malaria, for donors living in endemic regions, with active transmission, or coming from these regions less than 12 months ago: test for detection of plasmodium or plasmodial antigens.

Sole Paragraph. Additional tests must be performed, as necessary, to assess the possibility of transmission of other infectious and non-infectious diseases.

Art.115 According to provisions defined by Anvisa or by the Ministry of Health, other laboratory tests or methodologies can be included in the screening of cells donors.

Art.116 The performance of serological tests and NAT for communicable diseases must follow the algorithms provided on Anvisa website.

§1 In case of reagent or inconclusive serological result, the test must be repeated in duplicate with the same sample.

§2 When the HIV, HCV and/or HBV NAT test is positive, it is not necessary to perform NAT tests in duplicate, to release the test result.

§3 The procedures for solving discrepant or inconclusive results in the laboratory screening must be recorded.

§4 It is not mandatory that the establishment responsible for the donor selection performs the confirmatory tests, in second sample collected from the donor.

§5 If the confirmatory tests referred to in §4 of this article are not performed, the establishment responsible for the laboratory screening must convene the donor for orientation and referral to another laboratory responsible for performing communicable diseases confirmatory tests.

Art.117 When the screening tests are reagent/positive or inconclusive in a donor who, in



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previous donations, presented with non-reagent/negative tests (characterizing the seroconversion and/or laboratory turning), look-back procedures must be adopted.

§1 When the seroconversion is detected only by a serological test, before starting the look-back procedures it is necessary to perform tests with the same sample, to confirm the initial serum result, using a serological test with methodological principle distinct from the initial test performed or from another manufacturer.

§2 When the HIV, HCV and/or HBV nucleic acid testing (NAT) is positive, alone or associated to seroconversion detected by the serological test, the look-back procedures must begin immediately, not being necessary to perform a confirmatory test of the initial reagent serological result.

§3 The Cell Processing Center must have SOP for management of the risk related to look-back actions established due to results obtained during the laboratory screening of donors or during the quality control stage, containing the expected contact with the establishments/professionals to which the cells and the ATMP were distributed, or with the respective distributors.

Art.118 ABO and RhD typing and irregular antibody screening (IAS) must be performed in a sample of the donor for autologous and allogeneic use, in the following situations:

I - HPC, for conventional transplant, except HPC-UCB, which immunohematological tests must be performed on a product sample and according to subparagraph III of art. 48 of this Resolution;

II - when final products contain red cells; and

III - whenever this information is necessary for the donor selection or therapeutic use of other cells or of ATMP.

§1 If there is ABO incompatibility between the donor and the recipient, titration of anti-A and/or anti-B isohemagglutinins of the recipient (major or bi-directional ABO incompatibility) or of the donor (minor or bi-directional ABO incompatibility) must be carried out.

§2 The IAS and the titration of anti-A and anti-B isohemagglutinins of the recipient must be repeated up to 72 (seventy-two) hours before the therapeutic use, if the recipient received blood transfusion since the last tests performed.

§3 For HPC-UCB, abnormal hemoglobin detection test must be performed on a mother sample, collected at the moment of the delivery or up to 48 (forty-eight) hours later.

Art.119 Laboratory results or other abnormal findings in the donor selection tests must be reported to the respective donor or, when the latter is deceased, to the closest relative in the parental or family line, with the proper referral to the specialized assistance service, for the applicable measures to be taken.

Sole Paragraph. The contact with the donor or deceased donor relative, as well as his/her proper referral, must be documented, keeping the respective records.



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Art.120 The establishment responsible for performing the laboratory tests must perform quality control of the reagents and of the respective tests, keeping the respective records.

Subsection II
Laboratory screening for related and not related allogeneic donor

Art.121 Laboratory screening for allogeneic donor must follow the criteria described in Subsection I of this Section, in addition to the provisions in this Subsection II.

Art.122 The selection of allogeneic donor, regarding the histocompatibility, must be performed where applicable according to the criteria defined in this Resolution and other current specific regulations.

§1 Determination of HLA antigens of hematopoietic progenitor cells donors, for conventional transplant purposes, must be performed on a sample obtained from the donor or from the product, in a laboratory licensed by the competent Health Authority and authorized by the Ministry of Health, according to the current specific legislation.

§2 The need to determine HLA antigens of hematopoietic progenitor cells, for other purposes other than conventional transplant, and of other cells, must be assessed on a case by case basis.

Art.123 Allogeneic donor must also be submitted to anti-CMV antibody ('total and IgM' or 'IgG and IgM') in addition to the tests for communicable diseases listed in Subsection I of this Section.

Subsection III
Laboratory screening for autologous donor

Art.124 The laboratory screening for autologous donor must follow the criteria described in Subsection I of this Section, in addition to the provisions in this Subsection III.

Art.125 If the product for autologous purpose is released for fresh use or if storage occurs in a device that ensures the absence of cross-contamination, it is not mandatory to perform NAT tests according to subparagraphs I, II and III of art. 113 of this Resolution, and in this case the following tests may be performed: combined antibody + HCV antigen detection; detection of HBV surface antigen (HBsAg) and detection of antibody against HBV capsid (anti-HBc) with IgG or IgG + IgM search; and combined detection of antibodies against HIV subtype 1, including group O, and subtype 2 of HIV + p24 antigen.

Subsection IV
Allogeneic donor exclusion criteria

Art.126 The exclusion criteria of the candidate for cells donation for allogeneic use, including cells used as starting material to produce ATMP are:

I - reagent/positive test for HIV-1 or HIV-2 virus;

II - reagent/positive test for HTLV-I or HTLV-II virus;



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III - non-reagent HBsAg test with reagent anti-HBc except when the donor is anti-HBs reagent;

IV - reagent HBsAg test and/or NAT positive for the HBV virus; in the case of HPC for non-related conventional transplant purposes, this condition is applicable, except when the recipient also presents a reagent HBsAg test and/or NAT positive test;

V - reagent anti-HCV test and/or NAT positive for the HCV virus; in the case of HPC for non-related conventional transplant purposes, this condition is applicable, except when the recipient also presents a reagent anti-HCV test and/or NAT positive test;

VI - reagent test for *Trypanosoma cruzi*;

VII - indications that the results of the donor's blood samples analysis will not be valid due to the occurrence of hemodilution above 50% (fifty percent), when previous non-hemodiluted sample is not available or when there are no validated laboratory tests to be used in this type of sample;

VIII - malignant neoplastic disease, except basal cell carcinoma of the skin and cervical carcinoma *in situ*;

IX - clinical condition that puts the health of the donor at risk;

X - condition observed in the clinical, social and laboratory screenings that may result in a serious risk to the health of the recipient; and

XI - temporary incapacity conditions for blood donation, according to specific current legislation.

§1 In the case of HPC-BM and HPC-PB, in addition to the criteria described in subparagraphs I to XI of this article, are also exclusion criteria of the candidate for non-related allogeneic donation:

I - individuals under 18 years or above 59 years, 11 months and 29 days at the donation date;

II - ongoing pregnancy; and

III - sickle cell trait or sickle cell disease, only for HPC-PB.

§2 For HPC-UCB, in addition to the criteria described in subparagraphs I to XI of this article, are also exclusion criteria of the candidate for non-related allogeneic donation:

I - maternal age below 18 (eighteen) years or pregnant woman who has not undergone at least two documented pre-natal visits;

II - gestational age below 35 (thirty-five) weeks;

III - rupture of membranes for more than 18 (eighteen) hours;

IV - labor with an abnormality report;



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V - presence of clinical evidence, during pregnancy or labor, of an infectious process or disease that may interfere with placental vitality;

VI - serious fetal distress;

VII - fetus with congenital abnormality;

VIII - maternal temperature equal to or above 38°C (thirty-eight degrees Celsius) during labor;

IX - pregnant woman in a situation of increased risk for blood-transmissible infections;

X - pregnant woman taking hormones or drugs therapies that may be deposited in tissues;

XI - pregnant woman with a personal history of autoimmune systemic disease or neoplasm;

XII - pregnant woman and her relatives, biological parents and their relatives or biological siblings of the newborn with a history of hereditary diseases of the hematopoietic system, such as thalassemia, enzymatic deficiencies, spherocytosis, elliptocytosis, Fanconi's anemia, porphyria, platelet diseases, chronic neutropenia or other neutrophil diseases, as well as a history of chronic granulomatous disease, immunodeficiency, metabolic diseases, or other genetic diseases that can be transmitted by the umbilical cord blood;

XIII - pregnant woman included in the other exclusion criteria intended for the protection of the recipient, described in the current technical resolutions for blood donation; and

XIV - positive test for cytomegalovirus (CMV) or toxoplasmosis (IgM class antibodies).

§3 The provisions of the main clause of this article do not apply in the case of donation for allogeneic related use of HPC, for conventional transplant purposes, which donor exclusion criteria are established in articles 127 to 129 of this Resolution.

Art.127 The exclusion criteria of the candidate for HPC-BM and HPC-BP donation for related allogeneic use, for conventional transplant purposes are:

I - reagent/positive test for HIV-1 or HIV-2 virus;

II - reagent/positive test for HTLV-I or HTLV-II virus;

III - non-reagent HBsAg test with reagent anti-HBc, except when the donor is anti-HBs reagent;

IV - reagent HBsAg test and/or NAT positive for the HBV virus, except when the recipient also presents a reagent HBsAg test and/or NAT positive test;

V - reagent anti-HCV test and/or NAT positive for the HCV virus, except when the recipient also presents a reagent anti-HCV test and/or NAT positive test;



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VI - reagent test for *Trypanosoma cruzi*;

VII - clinical condition that puts the health of the donor at risk;

VIII - indications that the results of the donor blood samples analysis will not be valid due to:

- a) occurrence of hemodilution above 50% (fifty percent), when previous non-hemodiluted sample is not available or when there are no validated laboratory tests to be used in this type of sample; or
- b) treatment with immunosuppressant agent.

IX - ongoing pregnancy; and

X - sickle cell trait or sickle cell disease, only for HPC-PB.

Art.128 The exclusion criteria of the candidate for HPC-UCB donation for related allogeneic use, for conventional transplant purposes are:

I - reagent/positive test for HIV-1 or HIV-2 virus;

II - non-reagent HBsAg test with reagent anti-HBc, except when the maternal sample presents an anti-HBs reagent result;

III - reagent HBsAg test and/or NAT positive for the HBV virus, except when the recipient also presents a reagent HBsAg test and/or NAT positive test;

IV - reagent anti-HCV test and/or NAT positive for the HCV virus, except when the recipient also presents a reagent anti-HCV test and/or NAT positive test; and

V - HPC-UCB with homozygosis for the HbS mutation (sickle cell anemia) or thalassemia, with double heterozygosis for the HbS mutation and for thalassemia (HbS/Beta-thalassemia), or with double heterozygosity for the HbS mutation and for another variant hemoglobin, resulting in serious phenotype (examples: HbS/D Punjab, HbS/OArab, HbS/C).

Sole Paragraph. HPC-UCB in heterozygosis for the HbS mutation or for thalassemia (trait), and donors with presence of two traits, each one in different genes (thalassemia trait, for example, alpha and beta), can be accepted, upon evaluation described in §1 of art. 54.

Art.129 The inconclusive test for HIV-1 and/or HIV-2, as well as the reagent/positive or inconclusive tests for HTLV, HBV, HCV, T. cruzi, syphilis, CMV and toxoplasmosis, where applicable, must be investigated and analyzed towards the results of the other donor screening steps, and informed to the professional responsible for the patient who will decide about the use of the product due to emergency situations or in special clinical circumstances of the recipient, in compliance with provisions of art. 54 of this Resolution and its paragraphs.

Subsection V
Autologous donor exclusion criteria



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Art.130 The presence of reagent/positive laboratory test results for communicable diseases is not an exclusion criterion for the recovery, processing, storage and release of cells and ATMP for autologous use, and this condition must be known by the professional responsible for the patient.

Art.131 Confirmation of ongoing pregnancy implies temporary exclusion of the candidate for donation of HPC-BM and HPC-PB for autologous use.

Art.132 The exclusion criteria of the candidate for HPC-UCB for autologous use are:

I - gestational age below 32 (thirty-two) weeks;

II - presence of clinical evidence, during pregnancy or labor, of an infectious process or diseases that may interfere with placental vitality;

III - labor with an abnormality report;

IV - serious fetal distress.

Section VI
Retrieval

Art. 133 Retrieval of biological material for further processing and obtaining cells and ATMP must follow the criteria established by this Resolution and by other current specific regulations.

Sole Paragraph. The retrieval process must ensure the donor protection.

Art.134 The collection of biological material must be performed by a professional with higher education degree in Health. This professional must be registered in the Professional Class Council and be trained for such activity and/or be oriented by the Cell Processing Center.

§1 The bone marrow collection must be performed by a physician and, when for conventional transplant purposes, it must occur in a surgical center.

§2 The peripheral blood collection by apheresis is responsibility of the Technical Responsible person for the establishment that performed the apheresis.

§3 The umbilical cord and placental blood collection is responsibility of the Technical Responsible person for the Cell Processing Center to which the collected unit will be sent for processing.

§4 The retrieval of biological material must respect the definitions of the competent body from Ministry of Health and/or the Professional Class Councils.

Art.135 The collection of biological material must be performed with aseptic technique so as to prevent or minimize microbial contamination and to preserve the conditions of cells and of ATMP.

Sole Paragraph. Umbilical cord blood must be recovered in a system suitable for this procedure and it must take place in a hospital or maternity-hospital regularized with the competent



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Health Authority.

Art.136 The Cell Processing Center must have SOPs regarding the retrieval of biological materials, when this step is under its responsibility, and such SOPs must cover the packing procedures.

Art.137 The Cell Processing Center must obtain and keep documents containing the following information regarding the retrieval of biological material:

I - identification of donor code, name (if possible), date of birth, age and sex;

II - date, time of start and end, and place of retrieval;

III - identification of the retrieved materials;

IV - description, if any, of the occurrence of any change regarding the retrieval SOP, with its justification;

V - occurrence of adverse events, with their descriptions;

VI - results of the clinical, social, physical and laboratorial screening of the donor/patient;

VII - result of the macroscopic assessment of the biological material, where applicable;

VIII - time interval between the cardiorespiratory arrest and the retrieval of the organ (islets of Langerhans) or of the cells in the case of deceased donor;

IX - conditions of the donor's body maintenance, if refrigerated or not, in the case of deceased donor;

X - hemodilution calculation, where applicable; and

XI - identification of the professional responsible for the retrieval.

Sole Paragraph. The establishment where the biological material collection occurs must ensure the provision of the information discriminated in subsections I to XI to the Cell Processing Center, as provided in the main clause of this article.

Section VII
Blood collection for laboratorial screening

Art.138 The blood samples for laboratorial screening must be collected according to the criteria determined in this Resolution and to other specific current regulations, being performed so as to avoid risks of microbial contamination and samples exchange.

Art.139 The blood samples for donor's laboratorial screening, as well as aliquots referred by subsections I to III of art. 167 ~~166~~ of this Resolution, must be collected: (amended by RDC No. 260, dated December 21, 2018)



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I - up to 30 (thirty) days prior to the HPC-BM and HPC-PB recovery, for conventional transplant;

II - at the time of the delivery or up to 48 (forty-eight) hours after the collection of HPC-UCB, for conventional transplantation, considering the provisions of §2 of art. 111 of this Resolution;

III - up to 7 (seven) days before or 7 (seven) days after the HPC recovery, for purposes other than the conventional transplant, and other cells recovery;

IV - up to 7 (seven) days prior to retrieval, to perform pregnancy test, where applicable; and

V - before or up to 7 (seven) days after the retrieval to perform ABO and RhD and IAS typing, also considering the obligation to comply with the determinations of art. 118, main clause, §1 and §2 of this Resolution.

Art.140 In the case of deceased donors, the blood sample for laboratory screening must be collected prior to blood circulation cessation, if possible, and within the period informed in the manufacturer's instructions of the *in vitro* diagnostics product used for screening.

Sole Paragraph. In the absence of instructions issued by the manufacturer, the conditions and time for the collection of the deceased donor sample must comply with the validation performed by the Cell Processing Center or by the laboratory that will perform the test.

Art.141 The hemodilution calculation must be performed when the donor has received blood transfusion, components and/or infusion of colloids within 48 (forty-eight) hours prior to cardiorespiratory arrest or collection of blood sample, whichever occurred first; or infusion of crystalloids within the hour prior to the cardiorespiratory arrest or collection of the blood sample, whichever occurred first.

Section VIII
Post-retrieval packing and transportation

Art.142 The retrieved biological material, and the biological samples intended for assessment of the cells and the ATMP must be packed so as to preserve their integrity and the stability during all the transportation, as well as to ensure the safety of the staff involved in this process.

Sole Paragraph. The package must be suitable for each type of biological material and regularized with Anvisa.

Art.143 Packing and transportation of the biological material and samples must follow the provisions of the RDC No. 20, dated April 10, 2014, and its amendments, if applicable, and other applicable regulations.

§1 The primary or internal packaging of each biological material and each biological sample must contain, at least:

I - donor's identification code;

II - type of biological material or biological sample and its identification code; and



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III - in the case of autologous donation, the information "For autologous use only".

§2 The outer or tertiary packaging of the biological materials or biological samples must contain, at least:

I - information that the transported material is fragile and that, therefore, must be handled carefully;

II - the alert sentence: "BIOLOGICAL MATERIAL FOR HUMAN USE. DO NOT SUBMIT TO RADIATION (X-RAYS)";

III - identification of the origin establishment;

IV - identification and contact phone of the destination establishment;

V - specifications regarding the storage and transportation conditions that are important for the quality and safety of the cells, ATMP and biological samples; and

VI - other information as determined by the RDC No. 20, dated April 10, 2014, and its amendments.

Art.144 Irradiation of biological material is expressly prohibited during the transportation process, including in airports.

Art.145 The need to use intermediary or secondary packaging must be assessed by the Cell Processing Center.

Art.146 Packing of cells from more than one donor in a same primary packaging is not allowed.

Art.147 Packing of different types of biological material from the same donor in a same primary packaging is not allowed.

Art.148 The Cell Processing Center must define and validate the temperature conditions of the biological materials and biological samples during transportation, so as to preserve the integrity and stability of the transported material.

§1 The bone marrow units, peripheral blood and umbilical cord blood recovered must be transported to the Cell Processing Center at temperature between 2°C (two degrees Celsius) and 24°C (twenty-four degrees Celsius) positive, in a package with isothermal component.

§2 Given that the period between the end of the recovery and the start of the processing or fresh infusion of the unit of HPC, for conventional transplant, must not exceed 48 (forty-eight) hours, the time to transport these units must respect such time limit.

Art.149 There must be mechanisms to record the internal temperature of the transportation recipient at the moment of its shipment to the Cell Processing Center.

Sole Paragraph. Record of the departure temperature must be assessed and filed by the destination



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establishment, along with the record of the arrival temperature.

Section IX
Receipt of the biological material

Art.150 The Cell Processing Center must check if the packing and transportation conditions of the biological materials and biological samples to be received meet the provisions of this Resolution and the additional requirements defined by the establishment itself.

Art.151 When receiving the shipment/cargo, the destination establishment must check and record:

I - the package and label integrity;

II - the transportation duration;

III - the material arrival temperature after transportation.

Sole Paragraph. When receiving cryopreserved material packed in a dry-shipper, the receiver must also check and record the container weight and send such information to the sender.

Art.152 The Cell Processing Center must establish, in SOPs, the acceptance and rejection criteria of the biological material and biological samples received.

Art.153 Storage of biological samples and their shipment to the outsourced laboratory, where necessary, must follow the SOPs defined by the Cell Processing Center or by the service responsible for performing the laboratory screening or other tests.

Art.154 The biological material, after its arrival at the Cell Processing Center and before starting its processing, must be kept at temperature between 2°C (two degrees Celsius) and 8°C (eight degrees Celsius) positive or another validated temperature range.

Section X
Processing

Art.155 The biological materials must be processed according to SOPs defined by the Cell Processing Center.

Art.156 The time interval between biological material collection and the beginning of processing or fresh infusion of cells or ATMP must be monitored and recorded.

§1 The time interval between the completion of the bone marrow, peripheral blood and umbilical cord blood recovery and the beginning of processing or fresh infusion in conventional HPC transplantation must not exceed 48 (forty-eight) hours.

§2 The Cell Processing Center may establish a time interval between the end of bone marrow, peripheral blood or umbilical cord blood recovery and the beginning of processing or fresh infusion, in a conventional transplant, above 48 (forty-eight) hours, provided the new time interval is



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validated by the establishment, with technical-scientific proof of the quality and safety of the product.

§3 The Cell Processing Center must define and validate the maximum time interval between recovery and processing or fresh infusion of the other types of cells and ATMP.

Art.157 Manipulation and exposure of the cells and ATMP during the processing must occur in environment with air quality with particle count equivalent to ISO 5 (in operation) classification.

Art.158 SOPs regarding the process must be established so as to preclude cross-contamination or exchange.

§1 Simultaneous processing, within a same area, of cells or of ATMP of different batches or types, from a same donor or from different donors, is prohibited.

§2 Vectors and Gene Therapy Products must not be produced or manipulated in the same room as other types of cells or ATMP (advanced cellular therapy products or tissue engineering products), and (amended by RDC No. 260, dated December 21, 2018)

I - manipulation of Gene Therapy Product can be performed within the same room or area used to produce vector, provided there is an approved protocol for environment cleaning and disinfection ensuring the non-occurrence of cross-contamination; and (amended by RDC No. 260, dated December 21, 2018)

II - production of vectors for gene therapy, using the cultivation of bacteria or another procedure and/or supplies that may contaminate other production processes, must be performed in a room exclusive for this activity, and different vectors or derivative vectors must not be simultaneously produced in the same room.

Art.159 Cells and ATMP that need to be cryopreserved must be submitted to controlled and monitored cryopreservation process or to an equivalent process that keeps the product viability.

Sole Paragraph. In case of equipment of programmed temperature decay, all temperature curves generated must be analyzed and approved by the responsible person.

Section XI
Post-processing packing and labelling (final product)

Art.160 Packing must be done to preserve the sterility, integrity and stability conditions of the cells and the ATMP during the whole storage period.

Art.161 Labels of the released products must be inviolable and remain intact throughout the whole storage period, until the expiry date of the product, and must contain the following information:

I - type of cell or ATMP and its identification code;

II - identification of the Cell Processing Center;



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III - unique identification code of the product batch;

IV - full name of the recipient, when known at the moment of the post-processing labeling;

V - expiry date, or indication of undetermined validity, when the final product is kept at a temperature equal to or below 150°C (one hundred and fifty degrees Celsius);

VI - the information "For autologous use only", in the case of autologous donation;

VII - quantity (volume, cell count results by type of surface marker and cell concentration, where applicable);

VIII - presentation form (fresh, frozen, cryopreserved, lyophilized, etc.), where applicable;

IX - cryopreservation date, in the case of cryopreserved product;

X - test results for communicable diseases;

XI - ABO and RhD typing, in the case of HPC for conventional transplantation purposes;

XII - processing type (minimal or substantial manipulation), where applicable;

XIII - processing date, if pertinent, in the case of non-cryopreserved fresh infusion products;
and

XIV - presence of residues potentially harmful to the recipient.

§1 If it is not possible to include all the information referred to in the main clause on the label, the information in subparagraphs IX to XIV of this article may be provided in a separate document, which must accompany the product when it leaves the Cell Processing Center.

Art.162 In the case of HPC-UCB, bar-coded labels containing the unique identification numbering/code of the product must be placed in the following locations:

I - on the formulary containing pre-natal, delivery and newborn data;

II - on the Informed Consent Form;

III - on the formulary containing data about the recovery, packing, transportation, processing, cryopreservation and storage of the material and the results of the laboratory tests performed; and

IV - on each bag of cells.

Art.163 The package of the cells and ATMP must be suitable for each type of biological material and be regularized with Anvisa.

Sole Paragraph. HPC and other cryopreserved cells bags must be packed in metallic or other type of material protective cases, according to the specification and certification issued by the



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manufacturer.

Section XII
Storage

Art.164 Storage of cells and ATMP must occur under controlled conditions that ensure the maintenance of their quality and safety.

Art.165 The storage temperature conditions of the final products must be controlled, monitored and recorded.

Art.166 All cells and ATMP that undergo substantial manipulation and/or cryopreservation process before their use, must have a sample of the final product stored along and under the same conditions of the corresponding product.

Sole Paragraph. HPC-UCB must have at least two segments contiguous to the final product bag, under the conditions established in the main clause of this article.

Art.167 The following aliquots, at least, must be stored for future tests:

I - aliquots from the HPC-UCB unit:

- a) 2 (two) plasma aliquots;
- b) 1 (one) aliquot of genomic DNA preparation material; and
- c) 1 (one) aliquot of viable nucleated cells.

II - aliquots of the mother's sample, when donating HPC-UCB:

- a) 2 (two) aliquots of serum or plasma; and
- b) 1 (one) aliquot of genomic DNA preparation material or one aliquot of viable mononuclear cells.

III - for other cells and ATMP:

- a) 2 (two) aliquots of viable cells; and
- b) 1 (one) donor serum or plasma aliquot.

§1 Aliquots must be stored at each batch of cells or ATMP and, in the case of batches of cells which underwent thawing, expansion and administration in patients, 1 (one) new aliquot of the cells expanded and provided for use must be stored.

§2 The aliquots must be kept throughout the whole product storage period and, at least, for 12 (twelve) months after its therapeutic use when the Cell Processing Center has this information or for twelve (12) months after the expiry date of the product.

Art.168 Aliquots for performing laboratory tests must be packed and stored in specific controlled temperatures and so as to prevent any exchange of samples.

§1 Cells, serum, plasma and purified DNA aliquots, referred by subsections I to III of art. 167 of this Resolution must be kept in temperature equal to or below 70°C (seventy degrees Celsius) negative.



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§2 Aliquots for DNA preparation can be stored as a purified DNA, cryopreserved cells or card suitable for DNA storage, in this case, to be stored according to the manufacturer's orientation.

Art.169 HPC-BM and HPC-PB units, for conventional transplant purposes, that need cryopreservation must be stored at temperature equal to or below 80°C (eighty degrees Celsius) negative, and variation of up to 4°C (four degrees Celsius) above this temperature is acceptable.

Art.170 HPC-UCB units must be kept at temperature equal to or below 150°C (one hundred and fifty degrees Celsius) negative.

Art.171 The Cell Processing Center must define and validate the temperature for the other types of cells and ATMP, that are not stored at temperature equal to or below 150°C (one hundred and fifty degrees Celsius) negative.

Art.172 After performing the quality control tests, the Cell Processing Center must classify the products in one of the categories: "released" or "disqualified" for therapeutic use.

§1 Cells and ATMP from different types and classifications, that demand the same temperature conditions, can be stored inside the same storage device, provided there are clear disposition and identification, able to distinguish them.

§2 When the products under quarantine, the products for non-therapeutic purposes and the products already released for therapeutic use are stored in a same storage device using liquid nitrogen, they must preferably be kept in the vapor phase and, if they are in the liquid phase, external protective package (overwrap) must be used which do not allow contamination of the liquid nitrogen by eventual microorganisms present in the biological materials or cross-contamination.

§3 In the case of storage devices containing only products under quarantine, stored in the nitrogen liquid phase and without an overwrap, the Cell Processing Center must establish SOP defining the risk management measures to be adopted, in case of damage or rupture of any package containing product with positive/reagent result for communicable diseases or microbiological tests.

Section XIII

Product request, transportation to the site of use and notification of transplant or therapeutic use

Art.173 Cells must only be delivered for therapeutic use or clinical research upon documented request by the competent body of the Ministry of Health or the professional who will use them, containing:

I - recipient identification code;

II - identification of the requesting professional and respective institution;

III - characteristics and quantity of the requested product;

IV - purpose for requesting the product, either therapeutic use or clinical research;



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V - date of request, place and expected date of use of the product; and

VI - in the case of clinical research, proof that the research project is approved by the responsible Research Ethics Committee.

Sole Paragraph. The provisions of the main clause of this article do not apply to ATMP that are susceptible to registration with Anvisa, which must follow current specific legislation.

Art.174 The cells and the ATMP must only be delivered for use in basic research, teaching, training, quality control or process validation upon documented request by the professional or institution that will use them, containing:

I - identification of the professional or institution;

II - characteristics and quantity of the cells or ATMP requested;

III - request date; and

IV - declaration of the requesting professional or institution acknowledging that the product will not be intended for therapeutic use or clinical research.

Art.175 To provide HPC-UCB, for conventional transplant purposes, the Cell Processing Center must:

I - have a sample of DNA or umbilical cord blood cells available and, upon request, send it to the Transplant Center for performing the sample identity confirmatory tests;

II - provide a confirmatory test for the determination of HLA antigens in the case of allogeneic use;

III - perform a new count and determination of cell viability; and

IV - perform a functional test to determine monocytic granulocytic colony forming units (CFU or CFU-GM) or another equivalent, and/or perform a CD34+ cell viability test.

§1 The tests described in subparagraphs II to IV of this article must be performed in an aliquot of the HPC-UCB unit from a segment contiguous to the cryopreservation bag, for autologous and allogeneic use.

§2 The results and values obtained in the tests described in subparagraphs II to IV of this article, as well as other necessary information, must be provided to the professional responsible for the patient, together with the information contained in art. 161 of this Resolution.

Art.176 The cells and ATMP delivered for therapeutic use or clinical research must be accompanied, where applicable, of the following documentation containing information complementary to those in the label:

I - use of the product a single time and in only 1 (one) recipient, or only in the research



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project for which it was requested;

II - storage conditions before use;

III - transport conditions;

IV - instructions for use of the product (thawing, washing, dilution, etc.);

V - mention of which quality and safety parameters are not available at the time of the product release;

VI - in the case of exceptional release of products, foreseen in art. 54 of this Resolution, the unmet quality and safety parameters, with the respective results obtained and the reference or acceptance ranges;

VII - information about possible biological risks present in the product, as well as reagent/positive or inconclusive results of laboratory tests for transmissible infections and microbiological ones;

VIII - information on the obligation of the professional or institution requesting the product to communicate the Cell Processing Center if the use of the product occurred according to subparagraph IV of this article or if there were changes or interurrences, with the report of which they were;

IX - information on the obligation of the professional or institution requesting the product to notify the Cell Processing Center about the occurrence of adverse reactions related to the use of the product and their description; and

X - information on the need for disposal or return, if the product is not used.

Art.177 The product delivery must be done to the requesting professional, to a member of the team responsible for the patient or to the person who has the authorization given by the requesting professional/team responsible for the patient, in writing and signed.

Sole Paragraph. For the ATMP that are registered with Anvisa, the product delivery mentioned in the main clause of this article must follow the specific current legislation.

Art.178 The transport of the product must follow the provisions of the RDC No. 20, dated April 10, 2014, where applicable, and other applicable regulations.

Art.179 The Cell Processing Center must define and validate the temperature conditions of cells and ATMP during transport to preserve their integrity and stability.

Art.180 The following conditions should be kept during transportation of HCP-BM, HCP-PB and HCP-UCB, between health establishments:

I - in the case of units for fresh infusion – temperature between 2°C (two degrees Celsius) and 24°C (twenty-four degrees Celsius) positive, packed with isothermal component;



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II - in the case of units cryopreserved at 80°C (eighty degrees Celsius) negative – temperature equal to or below 65°C (sixty-five degrees Celsius) negative;

III - in the case of units cryopreserved at 150°C (one hundred and fifty degrees Celsius) negative or below – temperature equal to or below 150°C (one hundred and fifty degrees Celsius) negative.

§1 When liquid nitrogen is the refrigerant material, a dry-shipper must be used, keeping the product in a specific protective packaging.

§2 In the case referred to in §1 of this article, the volume of liquid nitrogen must be enough to keep the internal temperature of the container for a minimum period of 48 (forty-eight) hours beyond the estimated time of its arrival at the destination establishment.

§3 For cryopreserved cells or ATMP, the internal temperature of the transport container must be continuously monitored by a device that allows the verification of temperature variations out of the established limit.

§4 Transport temperature ranges different from those specified in the subparagraphs of this article may be defined by validation by the establishment.

Art.181 After delivering the cells or ATMP to the requester, their temporary storage until use is a responsibility of the professional to whom the delivery has been done.

Art.182 The Cell Processing Center must establish SOP for the receipt and record of the notifications of transplant, infusion or implant performed.

Section XIV
Production data

Art.183 The Cell Processing Center must send biannually and whenever requested, its production data to the Office of Blood, Tissues, Cells and Organs/Anvisa, according to tools and orientations defined by this Agency and published in its website.

Sole Paragraph. The determinations of the main clause of this article do not apply for the ATMP that are susceptible to registration with Anvisa.

Section XV
Waste disposal and return of cells and ATMP

Art.184 The procedures regarding the waste management of the Cell Processing Center must be described in the Health Services Waste Management Plan (PGRSS, in Portuguese), according to the current health and environmental regulations.

Art.185 Waste disposal, when not performed by the Cell Processing Center, can be outsourced.

Art.186 In the case of disposing of distributed cells and ATMP, this must be arranged by the professional responsible for them or for the Cell Processing Center that received the distributed



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product.

§1 In the event of the disposal foreseen in the main clause of this article, a report communicating the fact must be sent to the Cell Processing Center of origin, accompanied by the justification.

§2 If distributed cells and ATMP return to the Cell Processing Center of origin, such products must be kept in quarantine until their reassessment, and it is decided about their disposal or reintegration to the inventory.

Section XVI
Technical complaints and adverse events

Art.187 The Cell Processing Center must have mechanisms to identify, investigate and execute corrective and preventive actions related to the technical complaints and adverse events observed in its facilities or under its responsibility, occurred from the retrieval to the provision and use of the product.

§1 Applicable corrective and preventive actions must be documented, keeping the respective records of the implemented actions.

§2 The Cell Processing Center must notify the Health Surveillance National System (SNVS, in Portuguese), through information system defined by the Health Surveillance Investigation and Notification System (VIGIPÓS, in Portuguese), the occurrence of technical complaints of the equipment, instruments, materials, reagents and *in vitro* diagnostics products used in their facilities.

§3 The notification of adverse events, when necessary, must be done according to the determinations of the VIGIPÓS or specific guidelines to be established by the National Hemovigilance System, by the National Biovigilance System, or by the National Pharmacovigilance System, according to the concrete case need.

Art.188 The Cell Processing Center must have SOP for risk management in cases of infection or disease transmission to the recipient.

Sole Paragraph. The SOP mentioned in the main clause of this article must provide:

I - donor traceability;

II - communication with the responsible body of the National Transplant System, where applicable; and

III - conducts to be adopted, including the convocation of other recipients of cells or ATMP from this same donor and/or analysis of the destination of products from this donor that were not used and are still stored in the Cell Processing Center.

Art.189 The Cell Processing Center must notify to the SNVS, the reagent/positive tests for communicable diseases, which are mandatorily notifiable, detected during donor selection and those detected in the recipients after the transplant, infusion or implant.



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CHAPTER IV
FINAL AND TRANSIENT PROVISIONS

Art.190 The new Cell Processing Centers and those that intend to restart their activities must meet, in full, the provisions of this Resolution, before starting to operate.

Art.191 The Cell Processing Centers in operation on the date this Resolution becomes in force will have 365 (three hundred and sixty-five) days to comply with the provisions of Sections II and III of Chapter III of this Resolution.

Sole Paragraph. The other provisions, not mentioned in the main clause of this article, are of immediate fulfillment for Cell Processing Centers in operation on the date this Resolution enters into force.

Art.192 Failure to comply with the provisions contained in this Resolution constitutes a health infraction, according to Law 6.437, dated August 20, 1977, without prejudice to the applicable civil, administrative and penal liabilities.

Art.193 The RDC No. 56, dated December 16, 2010, and RDC No. 9, dated March 14, 2011, are revoked.

Art.194 This Resolution enters into force 60 (sixty) days after the date of its publication.

JARBAS BARBOSA DA SILVA JR.



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ANNEX

Table 1: Maximum number of particles per m³ of air in environments classified as ISO Class 5 and ISO Class 8, in Cell Processing Centers.

Class – ISO 14644-1*	Maximum number of particles per m ³ of air	
	≥ 0.5 µm	≥ 5.0 µm
ISO Class 5	3 520	
ISO Class 8	3 520 000	29 300

* ISO 14644-1:2015 (second edition 2015-12-15)

Table 2: Microbial contamination limits, considering different techniques.

Class	Sedimentation plates (90 mm diameter; CFU/4 hours) ¹	Contact plates (55 mm diameter; CFU/plate)	Gloves contact test (5 fingers: CFU/glove)	Air sample (CFU/m ³)
ISO 5 in operation	< 1	< 1	< 1	< 1
ISO 8 in operation	50	25	-	100

¹The service must ensure the adequate environmental condition for exposure of individual plates; depending on the conditions, the plates must be exchanged so that they keep their microbial detection properties.