NORMATIVE INSTRUCTION (IN) NO. 127 OF 30 MARCH 2022

Provides for the Good Manufacturing Practices complementary to Biological Inputs and Medicinal Products.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, item III of Law no. 9,782 of 26 January 1999, and item VII, paragraphs 1 and 3 of Article 187 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Normative Instruction, as decided upon in the Extraordinary Meeting – RExtra 6, held on 30 March 2022, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 1. This Normative Instruction has the objective of adopting the guidelines on Good Manufacturing Practices for Biological Inputs and Medicinal Products of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), as complementary requirements to be followed in the manufacture of biological inputs and medicinal products in addition to the General Guidelines on Good Manufacturing Practices for Medicinal Products and the Specific Guidelines on Good Manufacturing Practices for Active Pharmaceutical Ingredients.

Section II

Scope

Article 2. This Normative Instruction applies to companies that carry out operations involved in the manufacture of biological inputs and medicinal products, including experimental medicinal products.

Sole paragraph. The Good Manufacturing Practices (GMP) for advanced therapy medicinal products (ATMP) are not within the scope of this regulation.

Article 3. For sterile biological medicinal products, the manufacture of the active pharmaceutical ingredient must comply with the provisions described in the Specific Guidelines on Good Manufacturing Practices for Active Pharmaceutical Ingredients up to the point immediately before they become sterile, and the provisions described in the General Guidelines on Good Manufacturing Practices for Medicinal Products in the subsequent manufacturing stages.

Article 4. The attachment to this Normative Instruction presents the scope of the Good Manufacturing Practices in the production of biological medicinal products.

Paragraph 1. The table in the attachment to this Normative Instruction is illustrative only and does not intend to describe the exact scope of the Good Manufacturing Practices in the production of biological medicinal products.

Paragraph 2. The GMP level increases in detail from the initial to the final stages in the manufacture of biological substances, and the GMP principles must always be complied with.

Paragraph 3. The inclusion of some initial manufacturing stages within the scope of the GMP does not necessarily imply that such stages are routinely subject to inspection by the health authorities.

Section III

Definitions

Article 5. For the purposes of this Normative Instruction, the following definitions are adopted:

I – adjuvant: a chemical or biological substance that enhances the immune response against an antigen;

II – allergoids: allergens chemically modified to reduce IgE reactivity;

III – anchorage: a delivery vehicle, support, or matrix that can provide the structure or facilitate the migration, binding, or transportation of cells and/ or bioactive molecules;

IV – antibodies: proteins produced by B lymphocytes that bind to specific antigens, and can be divided into 2 main types based on the main differences in their manufacturing method;

V – monoclonal antibodies (MAb): a homogeneous population of antibodies obtained from a single clone of lymphocytes or by recombinant technology, and which bind to a single epitope;

VI – polyclonal antibodies: derived from a series of lymphocyte clones, produced in humans and animals, produced in response to epitopes on most “non-self” molecules;

VII – antigens: substances capable of inducing specific immune responses, such as toxins, foreign proteins, bacteria, tissue cells;

VIII – area: a specific set of rooms within a building associated with the manufacture of any product or several products that have a common air treatment unit;

IX – Master Cell Bank (MCB): an aliquot of a homogeneous pool of cells, usually prepared from the cell clone selected under defined conditions, dispensed into multiple containers and stored under defined conditions. It is used to derive all working cell banks;

X – Working Cell Banks (WCB): homogeneous pool of microorganisms or cells that are evenly distributed in a number of containers derived from an MCB and that are stored in such a way as to ensure stability and readiness for use in production;

XI – Transgenic Working Bank: Working Cell Banks (WCBs) applied to transgenic plants or animals;

XII – Master Transgenic Bank: Master Cell Bank (MCB) applied to transgenic plants or animals;

XIII – bioburden: count and types of microorganisms present in raw materials, media, biological substances, intermediate products or products, being considered contamination when its level and/ or type exceeds specifications;

XIV – feeder cells: cells used in co-culture to maintain pluripotent stem cells;

XV – somatic cells: cells, other than reproductive cells (germ line), that constitute the body of a human or animal, and may be autologous (from the patient), allogeneic (from another human being), or xenogeneic (from animals), somatic living cells, which have been manipulated or altered *ex vivo*, to be administered to humans for therapeutic, diagnostic, or preventive purposes;

XVI – containment: the action of confining a biological agent or other substance within a defined space;

XVII – primary containment: a containment system that prevents the escape of a biological agent into the immediate work environment, involving the use of closed containers or biological safety booths, along with safe operating procedures;

XVIII – secondary containment: containment system that prevents the escape of a biological agent to the external environment or to other work areas, involving the use of rooms with specially designed air treatment, the existence of air chambers and/ or sterilizations for the exit of materials and safe operating procedures, and, in many cases, it may increase the effectiveness of primary containment;

XIX – *ex vivo*: procedures performed on tissues or cells outside the body to return to it;

XX – campaign manufacture: the manufacture of a series of batches of the same product, in sequence and within a certain period, followed by the complete execution of defined control measures before the manufacture of another product;

XXI – gene: DNA sequence that codes one or more proteins;

XXII – hapten: a low molecular weight molecule that is not antigenic unless attached to a “carrier” molecule;

XXIII – hybridoma: an immortalized cell line that secretes desired (monoclonal) antibodies and is typically derived from the fusion of B lymphocytes with tumor cells;

XXIV – *in vivo*: procedures performed on living organisms;

XXV – multi-product facility: a facility that manufactures, either simultaneously or in campaign mode, a range of different biological substances and medicinal products, and within which the equipment sequence(s) may or may not be dedicated to specific substances or products;

XXVI – deliberate release: deliberate release of genetically modified organisms into the environment;

XXVII – specific pathogen-free (SPF) material: materials of animal origin (for example, chickens, embryos, or cell cultures), used for the production or quality control of biological medicinal products derived from groups (for example, flocks or herds) of specific pathogen-free (SPF) animals;

XXVIII – look-back method: a documented procedure for tracking biological medicinal substances or products that may be adversely affected by the use or incorporation of animal- or human-

derived materials when they fail release testing due to the presence of contaminating agent(s), or when undesirable conditions become apparent in the source animal or human;

XXIX – axenic: culture of a single organism that is not contaminated with any other;

XXX – biosafety level (BSL): containment conditions necessary to safely handle organisms of different hazard levels, from BSL-1 (lowest risk, least likely to cause human disease) to BSL-4 (highest risk, causing severe disease and with the likelihood of dissemination and lack of effective prophylaxis or treatment);

XXXI – genetically modified organism (GMO): an organism, except humans, in which the genetic material has been altered in a way that does not occur naturally by mating and/ or natural recombination;

XXXII – plasmid: fragment of DNA normally present in a bacterial cell as a circular entity, separate from the cellular chromosome, which can be modified by molecular biology techniques, purified from the bacterial cell and used to transfer its DNA to another cell;

XXXIII – technical responsible officer: a professional recognized by the national regulatory authority as having the responsibility to ensure that each batch of finished product has been manufactured, tested, and approved for release in accordance with the legislation and regulations in force in the country;

XXXIV – working virus seeds (WVS): Working Cell Banks (WCB) applied to viruses;

XXXV – master virus seeds (MVS): Master Cell Bank (MCB) applied to viruses;

XXXVI – closed system: when a pharmaceutical or product is not exposed to the room's immediate environment during manufacturing;

XXXVII – transgenic: organism that contains a foreign gene in its normal genetic composition for the expression of biological pharmaceutical materials;

XXXVIII – contained use: operation in which genetically modified organisms are grown, stored, used, transported, destroyed, or disposed of and for which (physical/ chemical/ biological) barriers are used to limit their contact with the general population and the environment; and

XXXIX – zoonosis: diseases of animal origin that can be transmitted to humans.

Paragraph 1. Regarding item XIV of the caption of this article, for the culture of human embryonic stem cells, typical feeder layers include mouse embryonic fibroblasts (MEFs) or human embryonic fibroblasts that have been treated to prevent them from dividing.

Paragraph 2. Regarding campaign manufacture, provided for in item XX of the caption of this article, the products are not manufactured at the same time, but may be manufactured on the same equipment.

Paragraph 3. The groups of animals referred to in item XXVII of the caption of this article, such as flocks or herds, are defined as animals sharing a common environment and having their own caretakers, which have no contact with non-SPF groups.

CHAPTER II

GENERAL PROVISIONS

Article 6. The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes.

Sole paragraph. Regarding the caption of this article, the ways in which biological medicinal products are manufactured, controlled, and administered make some special precautions necessary.

Article 7. In certain cases, other legislation or regulations may apply to raw materials for biological products.

Paragraph 1. Determinations established by the national legislation must be followed for the control of tissues and cells used as starting material for pharmaceutical products, donation, collection, testing, processing, preservation, storage, and distribution.

Paragraph 2. When human blood or its components are used as inputs for biological products, the national legislation that establishes the technical requirements for donor selection, collection, testing, processing, storage, and distribution must be complied with.

Paragraph 3. The manufacture and control of genetically modified microorganisms must comply with local and national requirements:

I – appropriate containment must be established and maintained in facilities where any genetically modified microorganisms are handled;

II – recommendations must be obtained, in accordance with national legislation to establish and maintain the appropriate biological safety level, including measures to avoid cross-contamination; and

III – there must be no conflicts with GMP requirements.

Paragraph 4. Adequate containment must be established and maintained in facilities where genetically modified microorganisms are handled, in order to establish and maintain the appropriate level of biosafety, including measures to prevent cross-contamination.

Article 8. The manufacture of biological substances and medicinal products involves biological processes and materials, such as growing cells or extracting material from living organisms, unlike conventional medicinal products, which are manufactured using highly consistent chemical and physical techniques.

Paragraph 1. Biological processes have inherent variability, so the extent and nature of byproducts can fluctuate.

Paragraph 2. The principles of Quality Risk Management (QRM) are particularly important for this class of medicinal products and must be used to develop the control strategy at all manufacturing stages, minimizing variability and reducing the possibility of contamination and cross-contamination.

Article 9. Since the materials and conditions used in cultivation processes are designed to favor the growth of specific cells and microorganisms, there is a risk of foreign microbial contaminants growing in the manufacture of biological substances and medicinal products.

Paragraph 1. Some products do not have the ability to withstand purification techniques, particularly those designed to inactivate or remove adventitious viral contaminants.

Paragraph 2. Processes, equipment, facilities, utilities, conditions for preparing and adding buffers and reagents, sampling, and operator training should minimize the possibility of contamination.

Article 10. Manufacturing must be consistent with the specifications defined in the product marketing authorization or clinical trial authorization, including the number of generations (doublings, passages) between the seed lot or cell bank.

Article 11. Product-related specifications define whether, and at what stage, substances and materials can have a defined level of bioburden or need to be sterile.

Paragraph 1. For biological materials that cannot be sterilized (for example, by filtration), manufacturing must be conducted aseptically in order to minimize the introduction of contaminants.

Paragraph 2. The application of appropriate controls and environmental monitoring, and, whenever possible, *in situ* cleaning and sterilization systems, together with the use of closed systems, can significantly reduce the risk of accidental contamination and cross-contamination.

Article 12. Quality control of biological medicinal products normally involves biological analytical techniques, which usually present a greater variability than physical-chemical determinations.

Sole paragraph. A robust manufacturing process is essential, and in-process controls are particularly important in the manufacture of active pharmaceutical ingredients and biological medicinal products.

Article 13. Biological medicinal products that incorporate human tissues or cells must comply with specific national regulations regarding coding, processing, preservation, storage, and distribution.

Paragraph 1. Collection and testing of human tissues or cells must be conducted according to an appropriate quality system and in accordance with the applicable national regulations.

Paragraph 2. National traceability requirements apply from the donor, maintaining donor confidentiality, in the stages applicable to the tissue establishment, to the institution where the product is used.

Article 14. Active pharmaceutical ingredients and biological medicinal products must comply with the applicable national regulations on minimizing the risk of transmission of Transmissible Spongiform Encephalopathy (TSE) agents.

CHAPTER III

SPECIFIC PROVISIONS

Section I

Personnel

Article 15. All personnel, including cleaning, maintenance, or quality control personnel, performing activities in areas where biological medicinal products are manufactured and tested, must receive initial and regular training, specific to the products manufactured and related to their work, including any specific product, personal, and environmental protection measures.

Article 16. The health status of the employees must be taken into consideration for product safety.

Sole paragraph. When necessary, the personnel involved in the production, maintenance, testing, and care of the animals should receive specific and appropriate vaccinations and undergo regular health assessments.

Article 17. Employees who present alterations in their health status, which may adversely affect product quality, must be prevented from working in the production area and appropriate records must be maintained.

Article 18. The production of BCG vaccine and tuberculin products must be restricted to employees carefully monitored by regular examinations of their immune status or chest X-ray.

Article 19. Employee health monitoring must be commensurate with the risk, and medical advice must be sought in the case of employees involved with hazardous organisms.

Article 20. Where it is necessary to minimize the possibility of cross-contamination, the movement of personnel, including quality control, maintenance, and cleaning personnel, must be controlled based on QRM principles.

Paragraph 1. In general, employees must not move from areas where there is exposure to live microorganisms, genetically modified organisms, toxins, or animals, to facilities where other products, inactivated products, or different organisms are handled.

Paragraph 2. If the passage referred to in Paragraph 1 of this Article is unavoidable, contamination control measures must be based on QRM principles.

Section II

Facilities and equipment

Article 21. The degree of environmental control of particulate and microbial contamination in production facilities must be adapted to the product and the production stage, and the level of contamination of the raw materials and the risks to production must be considered.

Sole paragraph. The environmental monitoring program must include methods to detect the presence of specific microorganisms (for example, host organism, anaerobes, etc.) whenever indicated by the QRM process.

Article 22. Manufacturing and storage facilities, processes, and environmental classifications must be designed to prevent external contamination of products.

Paragraph 1. Preventing contamination must be prioritized, as it is more appropriate than detecting and removing contamination, even though contamination is likely to become evident during processes such as fermentation and cell culture.

Paragraph 2. Environmental monitoring programs and material bioburden testing are intended to verify a state of control.

Paragraph 3. When processes are not closed and product is exposed to the immediate environment of the room (for example, during additions of supplements, media, buffers, gases),

control measures must be implemented, including engineering and environmental controls based on QRM principles.

Article 23. Dedicated production areas must be used for handling live cells capable of persisting in the manufacturing environment until inactivation, or pathogens capable of causing serious human disease (biosafety level 3 or 4).

Article 24. Manufacture in a multi-product facility may be acceptable when the following considerations and measures, or equivalent actions (as appropriate to the type of product involved), are part of an effective control strategy to prevent cross-contamination using QRM principles:

I – knowledge of the main characteristics of all cells, organisms, and any adventitious agents handled in the same facility (for example, pathogenicity, detectability, persistence, susceptibility to inactivation);

II – when production is characterized by multiple small batches of different starting materials, factors such as the health status of the donors and the risk of total loss of the medicinal product must be taken into consideration for the acceptance of concurrent work during the development of the control strategy;

III – living organisms and spores (where relevant) must be prevented from circulating in unrelated areas or equipment;

IV – control measures must be taken to remove organisms and spores before subsequent manufacture of other products, including measures related to the heating, ventilation, and air conditioning (HVAC) system;

V – cleaning and decontamination to remove organisms and spores must be validated;

VI – environmental monitoring, specific to the microorganism used in manufacturing, must be conducted in adjacent areas during manufacturing and after completion of cleaning and decontamination, and attention must be paid to the risks arising from the use of certain monitoring equipment (for example, airborne particulate monitoring) in areas working with live and/ or spore-forming organisms;

VII – products, equipment, auxiliary equipment (for example, for calibration and validation), and disposable items must be moved and removed from these areas in such a way as to avoid contamination of other areas, other products, and different stages of the product (for example, avoiding contamination of inactivated products or toxoid-derived products with non-inactivated products); and

VIII – campaign production followed by validated cleaning and decontamination procedures.

Article 25. For the final manufacturing stages (formulation, filling, and packaging), the need for dedicated facilities depends on the considerations described in Article 24, along with additional considerations, such as the specific needs of the biological medicinal product and the characteristics of other products, including any non-biological products, in the same facility.

Sole paragraph. Other control measures for the final manufacturing stages may include the need for specific addition sequences, mixing speeds, time and temperature controls, light exposure limits, and containment and cleanup procedures in case of spills.

Article 26. The measures and procedures required for containment – for the safety of the environment and the operator – must not conflict with those for product quality.

Article 27. Air treatment units must be designed, built, and maintained in such a way as to minimize the risk of cross-contamination between different manufacturing areas.

Sole paragraph. The units referred to in the caption of this article may require specific segregation for certain areas, according to an evaluation based on QRM principles, which must take into consideration the possibility of using single-pass airflow systems.

Article 28. Positive pressure areas must be used to process sterile products, and negative pressure is acceptable for containment reasons in specific areas at the point of pathogen exposure.

Paragraph 1. Whenever negative pressure areas or safety booths are used for aseptic processing of materials with particular hazards (for example, pathogens), these must be surrounded by a clean, positive pressure zone of an appropriate grade.

Paragraph 2. Pressure cascades must be clearly defined and continuously monitored with appropriate alarm systems.

Article 29. The equipment used during the handling of living organisms and cells, including those for sampling, must be designed to prevent any contamination during the process.

Article 30. The primary containment system must be designed and tested periodically to ensure the prevention of biological agent escapes into the immediate work environment.

Article 31. On-site cleaning and sterilization systems must be used wherever possible.

Article 32. The valves on fermentation vessels must be able to be completely steam sterilized.

Article 33. Ventilation filters must be hydrophobic and validated for their scheduled service life, with integrity testing at appropriate intervals, based on QRM principles.

Article 34. Drainage systems must be designed so that effluents can be effectively neutralized or decontaminated to minimize the risk of cross-contamination.

Sole paragraph. Compliance with specific local regulations must be maintained to minimize the risk of contamination of the external environment, according to the biological hazard of waste materials.

Article 35. Due to the variability of biological products or manufacturing processes, some raw materials, such as culture medium components and buffers, may need to be measured or weighed during the production process.

Paragraph 1. In the cases referred to in the caption of this article, the stocks of the substances may be kept in the production area for a determined period, based on defined criteria, such as the manufacturing duration of the batch or campaign.

Paragraph 2. The materials referred to in the caption and in Paragraph 1 of this article must be stored appropriately.

Section III

Animals

Article 36. In addition to compliance with TSE regulations, other adventitious agents of concern (zoonoses, source animal diseases) must be monitored and recorded by a follow-up health program.

Paragraph 1. A specialist must be consulted when establishing the health programs referred to in the caption of this article.

Paragraph 2. Health problems in the animals must be investigated regarding their suitability for use in manufacturing or as sources of raw materials, in quality control and in safety testing.

Paragraph 3. The suitability of using other animals that have been in contact with those with health problems must be assessed.

Paragraph 4. Decisions related to Paragraphs 2 and 3 of this article must be documented.

Paragraph 5. A fully traceable procedure must be in place that informs the decision-making process on the continued suitability of biological medicinal products and active pharmaceutical ingredients in which materials of animal origin have been used or incorporated.

Paragraph 6. The decision-making process referred to in Paragraph 5 of this article may include retesting of retained samples from previous collections from the same donor animal (when applicable) to establish the last negative donation;

Paragraph 7. The withdrawal period for therapeutic agents used to treat the animals must be documented and used to determine the removal of these animals from the program for defined periods.

Article 37. Special care must be taken to prevent and monitor infections in the source animals/ donors.

Paragraph 1. The care referred to in the caption of this article must include the supply, facilities, handling, biosafety procedures, testing regimes, bed control, and feeding materials, especially for animals free of specific pathogens, which must follow pharmacopeial requirements.

Paragraph 2. The monitoring of animal health and housing must be defined for other categories of animals (for example, healthy chickens, flocks, or herds).

Article 38. For products manufactured from transgenic animals, traceability of their breeding from the source animals must be maintained.

Article 39. National requirements for the protection of animals used for scientific purposes must be observed.

Article 40. The housing of animals used in the production and control of biological medicinal products and active pharmaceutical ingredients must be separate from the production and control areas.

Article 41. For different animal species, the main criteria, such as weight and health status of the animals, must be defined, monitored, and recorded.

Article 42. Animals, biological agents, and tests performed must be properly identified to avoid any risk of exchange and to control all identified hazards.

Section IV

Documentation

Article 43. Specifications for biological raw materials may need additional documentation on the source, origin, distribution chain, manufacturing method, and controls applied to ensure an appropriate level of control, including their microbiological quality.

Article 44. Some types of products may require a specific definition of which materials constitute a batch, particularly cells.

Sole paragraph. For autologous and donor situations, the manufactured product must be viewed as a batch.

Article 45. When donors of human cells or tissues are used, there must be complete traceability, starting from the raw materials, including all substances coming into contact with the cells or tissues, to the confirmation of receipt of the products at the point of use, all while maintaining the privacy of individuals and confidentiality of health-related information.

Paragraph 1. Traceability records must be retained for 30 (thirty) years after the product's expiration period.

Paragraph 2. Special care must be taken to maintain the traceability of products for special use cases, such as matching donor cells.

Paragraph 3. National requirements apply to blood components when used as supporting material or raw material in the medicinal product manufacturing process.

Section V

Production

Article 46. Given the variability inherent to many biological medicinal products and active pharmaceutical ingredients, the stages that enhance process robustness by reducing variability and increasing reproducibility at different stages of the product life cycle, such as process design, must be reassessed during product quality reviews.

Article 47. Since culture conditions, media, and reagents are designed to promote the growth of microbial organisms or cells, typically in an axenic state, a control strategy must be established to ensure that robust stages prevent or minimize the unwanted occurrence of bioburden, endotoxin, and associated metabolites.

Sole paragraph. For cell- and tissue-derived medicinal products, where production batches are often small, the risk of cross-contamination between cell preparations from different donors with various health status must be controlled in accordance with defined procedures and requirements.

Section VI

Raw materials and starting materials

Article 48. The source, origin, and suitability of starting materials and biological raw materials (for example, cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) must be clearly defined.

Paragraph 1. When the time to perform the required tests is long, it may be permissible to use raw materials before the test results are available.

Paragraph 2. The risk of using potentially non-compliant material and its potential impact on other batches must be clearly known and assessed, in accordance with QRM principles, and in such cases the release of the final product is conditioned to the satisfactory results of these tests.

Article 49. The identification of all raw materials must conform to the requirements appropriate to their manufacturing stage, as defined in the General Guidelines on the Good Manufacturing Practices for Medicinal Products, Specific Guidelines on the Good Manufacturing Practices for Active Pharmaceutical Ingredients, and Supplementary Guidelines on the Good Manufacturing Practices for Medicinal Products.

Article 50. The risk of contamination of raw materials along the supply chain must be assessed, with particular emphasis on TSE.

Sole paragraph. Materials that come into direct contact with the manufacturing equipment or product (such as the media used in aseptic technique experiments and lubricants that may come into contact with the product) must be taken into consideration.

Article 51. A control strategy must be established to protect the product and the preparation of solutions, buffers, and other additions, based on the principles and guidance contained in the appropriate sections of the Supplementary Guidelines on the Good Manufacturing Practices for Sterile Medicinal Products.

Paragraph 1. For products where final sterilization is not possible and the ability to remove microbial byproducts is limited, the controls required for the quality of the raw materials and the aseptic manufacturing process become very important.

Paragraph 2. Where the product marketing authorization or experimental use authorization determines an admissible type and level of bioburden, for example, at the active pharmaceutical ingredient stage, the control strategy must address the means by which this is kept within specified limits.

Article 52. When sterilization of raw materials is required, it must be carried out using heat whenever possible.

Sole paragraph. When heat sterilization is not possible, other appropriate methods may be used for the inactivation of biological materials (for example, irradiation and filtration).

Article 53. The use of antibiotics in the early stages of manufacturing to reduce bioburden should be avoided.

Sole paragraph. When necessary, the use of antibiotics must be justified and carefully controlled, and they must be removed from the manufacturing process at the stage specified in the product marketing authorization or experimental use authorization.

Article 54. For human tissues and cells used as raw materials in biological medicinal products, it must be ensured that:

I – their procurement, donation, and testing are regulated in some countries, and supply sites must have the appropriate approvals from the competent national authority(ies), which must be verified as part of the raw material supplier management;

II – if such human cells or tissues are imported, they must meet equivalent national quality and safety standards;

III – the tissues and cells are released by the person in charge at the tissue establishment before shipment to the manufacturer of the medicinal product, after the normal controls on the medicinal product's raw materials have been applied;

IV – the transportation of human tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties, so that the manufacturing sites have documented evidence of adherence to specified storage and transportation conditions;

V – the continuation of the traceability requirements initiated in tissue establishments through the recipient(s) and vice versa, including materials in contact with the cells or tissues, must be maintained; and

VI – there must be a technical agreement between the responsible parties (for example, manufacturers, tissue centers, sponsors, marketing authorization holders) that defines their respective responsibilities.

Paragraph 1. In certain cases of human tissues and cells, used as raw materials in biological medicinal products, the processing of these materials is conducted in tissue establishments, for example, by deriving early cell lines or banks before establishing an MCB.

Paragraph 2. In addition to the provisions of item III of the caption of this article, the test results of all tissues and cells supplied by the tissue service must be available to the medicinal product manufacturer, and this information must be used to make appropriate decisions about segregation and storage of materials.

Paragraph 3. Regarding item III of the caption and Paragraph 2 of this article, in cases where manufacturing must be started before the results of the tissue test are received, tissues and cells may be sent to the medicinal product manufacturer, as long as controls are in place to avoid cross-contamination with the tissue and cells that have been released by the person in charge to the tissue establishment.

Article 55. When human or animal cells are used in the manufacturing process as feeder cells, appropriate controls over their supply, testing, transportation, and storage must be established, including compliance with national requirements for human cells.

Section VII

Seed lots and cell bank systems

Article 56. The production of biological medicinal products and active pharmaceutical ingredients, obtained through microbial culture, cell culture, or propagation in embryos and animals, must be based on a viral seed lot and/ or Master and Working Cell Bank system, in order to avoid unwanted loss of properties due to repeated subcultures or multiple generations.

Article 57. The number of generations (doublings, passages) between the seed lot or cell bank, the active pharmaceutical ingredient, and the finished product must be consistent with the specifications defined in the medicinal product marketing authorization or experimental use authorization.

Article 58. As part of product life cycle management, the establishment of seed lots and cell banks, including the generation of the Master and Working Cell Banks, must be carried out under circumstances that are proven to be appropriate.

Paragraph 1. There must be an appropriately controlled environment to protect the seed lot and the cell bank, as well as the personnel handling them.

Paragraph 2. During the establishment of the seed lot and cell bank, no other living or infectious material (for example, viruses, cell lines, or cell strains) shall be handled simultaneously in the same area or by the same people.

Paragraph 3. For stages prior to generation of the master seed lot or cell bank, where only GMP principles may be applied, documentation must be available to demonstrate traceability from initial supply and genetic development, including issues related to the components used during development that have potential impact on product safety (for example, reagents of biological origin).

Paragraph 4. The requirements of pharmacopeial monographs must be applied when establishing seed lots and cell banks.

Article 59. After establishing Master and Working Cell Banks and master and working seed lots, quarantine and release procedures must be followed, which must include appropriate characterization and testing for contaminants.

Paragraph 1. Fitness for use must be demonstrated by monitoring the consistency of characteristics and quality of successive product batches.

Paragraph 2. Evidence of the stability and recovery of seed lots and banks must be documented, and records must be kept in a manner that allows for trend assessment.

Article 60. Seed lots and cell banks must be stored and used in a way that minimizes the risk of contamination or alteration (for example, stored in the vapor phase of liquid nitrogen in sealed containers).

Sole paragraph. Control measures for the storage of different cells and/ or seed lots in the same area or equipment must avoid mixing or interchanging and consider the infectious nature of the materials in order to avoid cross-contamination.

Article 61. Storage containers must be sealed, clearly labeled, and kept at an appropriate temperature.

Article 62. An inventory of seed lot and cell bank stock must be maintained.

Article 63. The storage temperature of seed lots and cell banks must be recorded continuously and, when used, the liquid nitrogen level must be monitored.

Sole paragraph. Deviations from the limits established for the storage temperature referred to in the caption of this article and corrective and preventive actions taken must be recorded.

Article 64. Stock splitting and storage in different locations must be carried out in order to minimize the risk of total loss.

Sole paragraph. Controls at the different storage sites must provide the safeguards described in this Section to minimize the risks of contamination or alteration.

Article 65. Storage conditions and stock handling must be managed in accordance with the same procedures and parameters.

Sole paragraph. Once containers are removed from the seed lot/ cell bank management system, they must not be returned to stock.

Section VIII

Operating principles

Article 66. The management of alterations must periodically consider the effects of alterations on the quality of the finished product, including their cumulative effects.

Article 67. Critical process operating parameters or other parameters affecting product quality must be identified, validated, documented, and maintained within the requirements established.

Article 68. A control strategy for the entry of items and materials into production areas must be based on QRM principles to minimize the risk of contamination.

Paragraph 1. For aseptic processes, thermally stable items and materials entering a cleanroom or contained area should preferably do so through an autoclave or double-door oven.

Paragraph 2. Thermolabile items and materials must enter the production areas through an antechamber with interlocked doors, where they will be subject to effective surface sanitization procedures.

Paragraph 3. Sterilization of items and materials in other locations is acceptable, as long as multiple packages are provided, in accordance with the number of stages of entry into the cleanroom, and as long as they enter through antechambers with adequate surface sanitization precautions.

Article 69. The growth-promoting properties of the culture medium must be demonstrated to be suitable for the intended use.

Paragraph 1. Whenever possible, the culture medium referred to in the caption of this article should be sterilized on site.

Paragraph 2. Inline sterilization filters for routine addition of substances (such as gases, media, acids or alkalis, defoamers, etc.) to fermenters should be used whenever possible.

Article 70. The addition of materials or cultures to fermenters and other containers and sampling must be carried out under carefully controlled conditions to avoid contamination.

Sole paragraph. When the addition or sampling referred to in the caption of this article occurs, it must be ensured that the containers are correctly connected.

Article 71. The continuous monitoring of some production processes (for example, fermentation) may be necessary.

Paragraph 1. The monitoring data must be part of the batch record.

Paragraph 2. If continuous culture is used, special attention must be paid to the quality control requirements arising from this type of production method.

Article 72. The centrifugation and mixing of products can lead to the formation of aerosols, and containment of such activities is necessary to minimize cross-contamination.

Article 73. Accidental spills, especially from living organisms, must be handled quickly and safely.

Article 74. Validated decontamination measures must be available for each organism or groups of related organisms.

Sole paragraph. Whenever different lineages of very similar unique species of bacteria or viruses are involved, the decontamination process may be validated with a representative strain, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

Article 75. If obviously contaminated, such as through spills or aerosols, or if a potentially hazardous organism is involved, production and control materials, including documentation, must be appropriately disinfected, or information transferred through other means.

Article 76. The methods used for sterilization, disinfection, removal, or viral inactivation must be validated.

Article 77. In cases where a viral inactivation or removal process is carried out during manufacturing, measures must be taken to avoid the risk of a new contamination of treated products with untreated items.

Article 78. For products that are inactivated through the addition of a reagent (for example, microorganisms during vaccine manufacturing), the process must ensure complete inactivation of the living organism.

Sole paragraph. In addition to thoroughly mixing the culture with the inactivating agent, consideration must be given to contact of all product contact surfaces exposed to the live culture and, when necessary, transfer to a second container.

Article 79. A control strategy must be developed for equipment and other chromatography-related items, since a wide variety of equipment is used for chromatography.

Paragraph 1. QRM principles must be used to develop a strategy to control associated matrices, supports, and equipment when used in campaign manufacturing and multi-product environments.

Paragraph 2. The reuse of the same matrix at different processing stages is not considered appropriate and is discouraged.

Paragraph 3. Acceptance criteria, operating conditions, service life, regeneration methods, sanitization, and sterilization of columns must be defined.

Article 80. If ionizing radiation is used in the manufacture of biological medicinal products, including the sterilization of materials and equipment, the complementary guidelines on good practices related to this technology must be consulted.

Article 81. There must be a system in place to ensure the integrity and closure of containers after filling, as well as special procedures for handling leaks, whenever finished or intermediate products pose a risk.

Article 82. Procedures must be available for keeping the product within any specified limits, such as time and temperature, during filling and packaging operations.

Article 83. Containers containing live biological agents must be handled in such a way as to avoid contamination of other products or the escape of live agents into the work environment or the external environment.

Sole paragraph. Risk management must consider the viability of such organisms and their biological classification.

Article 84. Care must be taken in the preparation, printing, storage, and labeling, including any specific text to specific patient products or signifying the use of genetic engineering of the contents in the primary container and secondary packaging.

Article 85. Labels must be checked for compatibility with ultra-low storage temperatures whenever these are used.

Article 86. When intermediate products can be stored for long periods (days, weeks, or longer), consideration must be given to including batches of finished products manufactured from materials stored for their maximum periods in the follow-up stability program.

Section IX

Quality Control

Article 87. In-process controls are of greater importance to ensure the consistent quality of biological medicinal products and active pharmaceutical ingredients than for conventional products.

Sole paragraph. In-process control testing must be performed at appropriate stages of production to control conditions that are important for the quality of the finished product.

Article 88. Certain cell types (for example, autologous cells) can be made available in limited quantities and, when allowed in the marketing authorization, a modified strategy of sample testing and retention can be developed and documented.

Article 89. For cell-based products, sterility testing must be conducted in antibiotic-free cell cultures or cell banks, in order to provide evidence of the absence of bacterial and fungal contamination and to enable the detection of fastidious organisms, when appropriate.

Article 90. For biological medicinal products with short shelf life that require batch certification prior to completion of all finished product quality control testing (for example, sterility testing), an appropriate control strategy must be in place.

Paragraph 1. Controls need to be built based on an improved understanding of the product and process performance, considering the controls and attributes of the raw materials.

Paragraph 2. An accurate and detailed description of the entire release procedure, including the responsibilities of the personnel involved in the evaluation of analytical and production data, is essential.

Paragraph 3. A continuous assessment of the effectiveness of the quality assurance system must be adopted, including the maintenance of records in a way that allows for trend assessment.

Paragraph 4. Alternative methods to obtain equivalent data to enable batch certification must be considered (for example, rapid microbiological methods).

Article 91. The procedure for batch certification and release may be conducted in two or more stages – before and after the results of the complete final analytical tests are available – and must include:

I – assessment by designated person(s) of batch processing records and environmental monitoring results that must comprehend production conditions, all deviations from habitual procedures, and analytical results available for review and conditional certification by the Person Delegated by the Pharmaceutical Quality Management System;

II – assessment of the final analytical tests and other available information before the finished product is sent for final certification by the Person Delegated by the Pharmaceutical Quality Management System; and

III – a procedure to describe the actions to be taken (including the relationship with the clinical staff), in cases where out-of-specification results are obtained after product release, and such events must be fully investigated and the relevant corrective and preventive actions to avoid recurrence must be taken and documented.

CHAPTER IV

PROVISIONS FOR SPECIFIC TYPES OF PRODUCTS

Section I

Products of animal origin

Article 92. The guidelines in this chapter apply to biological active pharmaceutical ingredients obtained from animal raw materials from establishments such as slaughterhouses.

Paragraph 1. Since supply chains can be extensive and complex, controls based on QRM principles must be applied to the inputs referred to in the caption of this article.

Paragraph 2. The requirements of appropriate pharmacopoeial monographs, including the need for specific testing at defined stages, must be consulted for the inputs referred to in the caption of this article.

Paragraph 3. Documentation demonstrating the traceability of the supply chain and the clear roles of the participants in the chain, including a process map that is sufficiently detailed and up to date, must be established for the inputs referred to in the caption of this article.

Article 93. Monitoring programs must be implemented for animal diseases that are of concern to human health.

Paragraph 1. Reports from reliable sources on national prevalence of disease must be considered in assessing risk and mitigation factors, which includes the World Organization for Animal Health (*Office International des Epizooties*– OIE).

Paragraph 2. The provisions in the caption of this article must be supplemented by information on health monitoring and control programs at the national and local levels, the latter to include the sources (for example, farm or feedlot) from which the animals are taken, and the control measures in place during transportation to slaughterhouses.

Article 94. When slaughterhouses are used to obtain animal tissue, they must operate strictly in accordance with the applicable regulations.

Sole paragraph. Reports from national regulatory organizations verifying compliance with food, safety, quality, and veterinary and phytosanitary legislation requirements must be considered.

Article 95. Control measures for pharmaceutical raw materials in establishments such as slaughterhouses must include appropriate elements of the Pharmaceutical Quality Management System to ensure a satisfactory level of operator training, traceability, control, and consistency of materials.

Article 96. Control measures must be implemented for raw materials to prevent interventions that could affect the quality of the materials, or at least provide evidence of such activities, during their progression through the production and supply chain.

Paragraph 1. The control measures referred to in the caption of this article include the movement of material between initial collection sites, partial and final purification, storage sites, distributors, consolidators, and intermediaries.

Paragraph 2. Details of such control measures must be recorded within the traceability system, and any failures must be recorded, investigated, and appropriate action taken.

Article 97. Periodic audits must be performed at the raw material supplier, verifying compliance with material controls at the different manufacturing stages.

Paragraph 1. Failures must be investigated at a depth appropriate to their importance and full documentation of the investigation must be available.

Paragraph 2. Systems must be in place to ensure that effective corrective and preventive actions are taken.

Section II

Allergen products

Article 98. The materials referred to in this Section may be manufactured by extraction from natural sources or by recombinant DNA technology.

Paragraph 1. Origin materials must be described in sufficient detail to ensure consistency with their supply, for example, mentioning the common and scientific name, origin, nature, contaminant limits, and method of collection.

Paragraph 2. Animal byproducts must be obtained from healthy sources.

Paragraph 3. Appropriate biosafety controls must be in place for colonies (for example, mites, animals) used for allergen extraction.

Article 99. The allergen product must be stored under defined conditions to minimize deterioration.

Article 100. The stages in the allergen production process, including the pretreatment, extraction, filtration, dialysis, concentration, or lyophilization stages, must be described in detail and validated.

Article 101. The modification processes for making modified allergen extracts (for example, allergoid and conjugates) must be described.

Sole paragraph. Intermediate products of the manufacturing process must be identified and controlled.

Article 102. Mixtures of allergen extracts must be prepared from individual extracts of single-source materials.

Sole paragraph. Each individual extract must be considered as an active substance.

Section III

Hyperimmune sera

Article 103. Special care must be taken in the control of antigens of biological origin to ensure their quality, consistency, and absence of adventitious agents.

Article 104. The preparation of materials used to immunize the animals (for example, antigens, hapten carriers, adjuvants, stabilizing agents), and the storage of such material immediately prior to immunization must be compliant with written procedures.

Article 105. Vaccination, test bleeding, and collection bleeding schedules must be in accordance with those approved in the marketing authorization.

Article 106. The manufacturing conditions for the preparation of antibody subfragments and any additional modifications must be in accordance with validated and approved parameters.

Sole paragraph. When such enzymes are made up of several components, their consistency must be ensured.

Section IV

Vaccines

Article 107. Whenever eggs are used, the health status of all source animals used for egg production must be assured (regardless of whether they are free of specific pathogens or healthy).

Article 108. The integrity of the containers used to store intermediate products and the wait periods must be validated.

Article 109. Containers containing inactivated products must not be opened or sampled in areas containing live biological agents.

Article 110. The sequence of addition of active ingredients, adjuvants, and excipients during the formulation of an intermediate or finished product must conform to the specifications.

Article 111. When organisms with a higher biosafety level (for example, pandemic vaccine strains) need to be used in manufacturing or testing, appropriate containment arrangements must be established.

Sole paragraph. Approval of the arrangements referred to in the caption of this article must be obtained from the competent national authority(ies) and the approval documents must be made available for verification.

Section V

Recombinant products

Article 112. The process condition during cell growth, protein expression and purification must be maintained within validated parameters to ensure a consistent product, with a defined range of impurities within the capability of the process to reduce them to acceptable levels.

Paragraph 1. The type of cell used in production may require an increase in the measures established in the caption of this article to ensure the absence of viruses.

Paragraph 2. In the case of production involving multiple harvests, the continuous growing period must be within the specified limits.

Article 113. Purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses, and other impurities must be validated and ensure that such impurities are within the established limits.

Section VI

Monoclonal antibodies

Article 114. Monoclonal antibodies can be manufactured from murine hybridomas, human hybridomas, or by recombinant DNA technology.

Article 115. Appropriate control measures must be ensured for the different source cells (including feeder cells, if used) and the materials used to establish the hybridoma/ cell lineage in a way to ensure product safety and quality.

Paragraph 1. Verifications must be performed on whether the control measures are within the approved limits, and special emphasis must be placed on the absence of viruses.

Paragraph 2. Data from products generated by the same manufacturing technology platform may be acceptable to demonstrate the adequacy of the control measures referred to in the caption of this article.

Article 116. The criteria must be monitored at the end of a production cycle and for early termination of the production cycle to ensure that they are within the approved limits.

Article 117. The manufacturing conditions for the preparation of antibody subfragments (for example, Fab, F (ab')2, scFv) and any other modifications (for example, radioactive marking, conjugation, chemical binding) must be in accordance with validated parameters.

Section VII

Products derived from transgenic animals

Article 118. A higher requirement is required to demonstrate batch-to-batch consistency of products derived from transgenic animals, in all respects, since the consistency of raw materials from a transgenic source is likely to be more problematic than is normally in the case of non-transgenic biotechnological sources.

Article 119. A variety of species can be used to produce biological medicinal products, which can be expressed in body fluids (for example, milk) for collection and purification.

Sole paragraph. Animals must be clearly and uniquely identified, and backup measures must be implemented in case the primary marker is lost.

Article 120. The arrangements for housing and care of the animals must be defined in such a way as to minimize the animals' exposure to pathogens and zoonotic agents.

Paragraph 1. Appropriate measures must be defined to protect the external environment.

Paragraph 2. A health monitoring program must be defined with all results documented, any incidents must be investigated, and their impact on animal maintenance and on previous batches of product must be assessed.

Paragraph 3. Care must be taken to ensure that any therapeutic products used to treat the animals do not contaminate the product.

Article 121. The genealogy of the parental animals in relation to the production animals must be documented.

Sole paragraph. Considering a transgenic line will be derived from a single genetic founder animal, material from different transgenic lines should not be mixed.

Article 122. The conditions under which the product is collected must be in accordance with the conditions established in the marketing authorization.

Sole paragraph. The collection schedule and the conditions under which animals can be removed from production must be established according to approved procedures and defined acceptance limits.

Section VIII

Products derived from transgenic plants

Article 123. Further measures, in addition to those established in Chapter III of this Normative Instruction, may be necessary to prevent contamination of master and working transgenic banks by foreign plant materials and relevant adventitious agents.

Sole paragraph. The stability of the gene within the defined number of generations must be monitored.

Article 124. The plants must be clearly and individually identified, and the presence of key plant characteristics, including health status, throughout the culture, must be checked at defined intervals during the growing season, in order to ensure consistency of yield between cultures.

Article 125. Whenever possible, safety measures should be defined for culture protection, in order to minimize exposure to contamination by microbiological agents and cross-contamination with other plants.

Article 126. Measures must be taken to prevent materials such as pesticides and fertilizers from contaminating the product.

Article 127. A monitoring program must be established and all results must be documented, as well as any incidents must be investigated, assessing their impact on the continuity of the culture in the production program.

Article 128. The conditions under which plants can be removed from production must be defined in a procedure.

Paragraph 1. Acceptance limits must be defined for materials (for example, host proteins) that may interfere with the purification process.

Paragraph 2. Checks must be performed to verify whether the results are within the approved limits.

Article 129. Environmental conditions (such as temperature, rainfall) that may affect the quality attributes and yield of the recombinant protein, from the time of planting, through cultivation, until harvest and interim storage of harvested materials, must be documented.

Sole paragraph. Principles from documents such as Guidelines on Good Agricultural and Collection Practices for Herbal Raw Materials must be taken into consideration.

CHAPTER V

FINAL PROVISIONS

Article 130. Non-compliance with the provisions contained in this Normative Instruction constitutes a health infraction, pursuant to Law no. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 131. Normative Instruction – IN No. 36 of 21 August 2019 is hereby revoked.

Article 132. This Normative Instruction shall enter into force on 2 May 2022.

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ANNEX

Illustrative guidance on the manufacturing activities within the scope of this Normative Instruction:

Type and source of material	Example of product	GMP application to manufacturing stages presented in gray			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, immunologic sera	Collection of plants, organs, animal material, or fluid	Cut, mixture, and/ or initial processing	Isolation and purification	Formulation, filling
2. Virus or bacteria/ fermentation/ cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment and maintenance of MCB, WCB, LIVO, LIVT	Cell culture and/ or fermentation	Inactivation when applicable, isolation, and purification	Formulation, filling
3. Biotechnological fermentation/ cell culture	Recombinant products, monoclonal antibodies, allergens, vaccines	Establishment and maintenance of MCB, WCB, MSL, WSL	Cell culture and/ or fermentation	Isolation, purification, and modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins	Transgenic bank of master items and items in operation	Collection, cut, mixture, and/ or initial processing	Isolation, purification, and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergens	Transgenic bank of master items and items in operation	Cultivation, harvest	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Enzymes derived from urine, hormones	Collection of fluid	Mixture and/ or initial processing	Isolation and purification	Formulation, filling
7. Human and/ or animal sources	Products derived from cells and tissues	Donation, procurement, and testing of initial tissues/ cells	Initial processing, isolation, and purification	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, filling