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Organ: Ministry of Health/Brazilian National Health Surveillance Agency/Collegiate Board

NORMATIVE INSTRUCTION IN No. 136, OF MARCH 30, 2022

Provides for Good Manufacturing Practices complementary to Investigational Drugs.

The Collegiate Board of the Brazilian National Health Surveillance Agency, in the use of the powers conferred on it by arts. 7, item III, and 15, items III and IV of Law No. 9,782, of January 26, 1999, and considering the provisions of art. 187, item VII and Paragraphs 1 and 3, of the Internal Regulations, approved by the Collegiate Board Resolution - RDC No. 585, of December 10, 2021, resolves to adopt the following Normative Instruction, as resolved in an Extraordinary Meeting - RExtra No. 6, held on March 30, 2022, and I, Chief Executive Officer, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Art. 1. This Normative Instruction has the objective of adopting the guidelines of Good Manufacturing Practices for Investigational Drugs of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), as complementary requirements to be followed in the manufacturing of investigational drugs in addition to the General Guidelines for Good Manufacturing Practices for Drugs.

Section II

Scope

Art. 2. This Normative Instruction applies to companies that perform manufacturing operations of investigational drugs.

Section III

Definitions

Art. 3. For the purposes of this Normative Instruction, the following definitions are adopted:

I - reference sample: samples of a batch of raw materials, packaging material or medicinal product in its primary packaging which are stored for the purpose of analysis, if necessary, during the shelf life of the product;

II - retention sample: samples of a fully packaged batch of a medicinal product with all its components required for sale to the consumer, such as secondary packaging of the presentation, labeling, package leaflets, variable data recordings, which are stored for identification purposes;

III - product specification file: reference file containing, or referring to files that contain, all the information necessary to write detailed written instructions on processing, packaging, quality control tests, batch release and shipment of an investigational drug;

IV - blinding: procedure in which the treatment condition is kept unknown for one or more parts of the study, considering, in the case of an investigational drug, intentional masking of the product's identity according to the sponsor's instructions;

V - randomization code: list in which the treatment assigned to each clinical trial participant is identified from the randomization process;

VI - Drug Clinical Development Dossier (DDCM): compilation of documents to be submitted to Anvisa with the purpose of evaluating the steps inherent to the development of an investigational drug aiming to gather information to support the registration or post-registration changes of the mentioned product;

VII - double-blind: procedure in which clinical trial participant(s), investigator(s), monitor(s) and, in some cases, data analyst(s) are unaware of the treatment condition(s);

VIII - clinical trial – research conducted in human beings with the purpose of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamics effect of the investigational drug and/or identifying any adverse reaction to the investigational drug and/or studying the absorption, distribution, metabolism and excretion of the investigational drug to verify its safety and/or efficacy;

IX - manufacturer or importer of investigational drugs: any holder of authorization to manufacture or import;

X - investigator: person responsible for conducting a clinical trial in the place where the trial is conducted or the leader of the group, called the principal investigator, in case the study is conducted by a group of people;

XI - investigational drug: pharmaceutical product under test, object of the Drug Clinical Development Dossier (DDCM), to be used in the clinical trial, in order to obtain information for its registration or post-registration; or dosage form of an active substance or placebo tested or used as a reference in a clinical trial, including a registered product when used or assembled (formulated or packaged) in a manner other than registered, or when used for an unregistered indication, or when used for more information on the registered form;

XII - order: instruction to process, pack or ship a certain number of units of investigational drugs;

XIII - sponsor: person, company, institution or organization responsible for initiating, administering, controlling and/or funding a clinical trial;

XIV - comparator product: experimental or commercialized drug - active control -, or placebo, used as a reference in a clinical trial;

XV - unblinding: opening of the blinding;

XVI - randomization: process of assigning clinical trial participants to the treatment group or to the control group, through random selection, in order to reduce bias;

XVII - reconstitution: process of dissolving or dispersing the finished investigational drug for administration to a clinical trial participant; or process of diluting or mixing the investigational drug(s) with other substance(s) used as a vehicle for the purposes of its administration. Reconstitution does not cover the mixing of several ingredients, including the active substance, to produce the investigational drug;

XVIII - shipment: packaging operation for shipment and dispatch of drugs to be used in clinical trials; and

XIX - single-blind: procedure in which the clinical trial participants are unaware of the treatment conditions.

CHAPTER II

GENERAL PROVISIONS

Art. 4 The total and partial manufacture of investigational drugs, as well as the various processes of division, packaging or presentation, are subject to manufacturing authorization.

Sole paragraph. The authorization mentioned in the caput of this article is not necessary when the establishment is responsible only for the reconstitution stage.

Art. 5. The elaborated and finalized investigational drug precedes the reconstitution process.

Art. 6 The reconstitution process must be performed as soon as possible before administration.

Sole paragraph. The process referred to in the caput of this article must be defined in the Drug Clinical Development Dossier (DDCM) and in the clinical study protocol, or related document, available at the administration site.

CHAPTER III

SPECIFIC PROVISIONS

Section I

Quality management

Art. 7 The Quality System designed, assembled and verified by the manufacturer or importer must be described in procedures, available to the sponsor, taking into account the principles of Good Manufacturing Practices (GMP) and the guides applicable to investigational drugs.

Art. 8 Product specifications and manufacturing instructions can be changed during development, but full control and traceability of changes must be maintained.

Section II

Personnel

Art. 9. All personnel involved with investigational drugs must be adequately trained in the specific requirements for these types of products.

Sole paragraph. Even in cases where the number of employees involved is small, there must be, for each batch, a separate person for production and quality control activities.

Art. 10. The Technical Manager must ensure that there are systems that meet the requirements of good manufacturing practices and that they have extensive knowledge of the pharmaceutical development process and clinical trials.

Section III

Facilities and equipment

Art. 11. Care regarding the risk of cross-contamination should be reinforced in the manufacture of investigational drugs, since toxicity, potency and sensitization potential may not be fully known during the development stage.

Sole paragraph. The design of equipment and facilities, inspection/testing methods and acceptance limits to be used after cleaning must reflect the nature of the risks addressed in the caput of this article.

Art. 12. Good Manufacturing Practices for investigational drugs should take into account the use of field production, when appropriate.

Art. 13. The choice of cleaning solvent should be based on the solubility of the investigational drug.

Section IV

Documentation

Subsection I

Specifications and instructions

Art. 14. Specifications for raw materials, primary packaging materials, intermediate products, bulk products and finished products; master formula and processing and packaging instructions must be as complete as possible according to the information available at the development stage.

Paragraph 1 The information mentioned in the captut of this article shall be periodically reassessed during development and updated as necessary.

Paragraph 2 Each new version must take into account the most recent data, the current technology used, regulatory and pharmacopeial requirements and must allow traceability to the previous document.

Paragraph 3 Any changes must be performed in accordance with a written procedure, which must address any implications for product quality, such as stability and bioequivalence.

Paragraph 4 The rationale for changes must be recorded and the consequences of a change in product quality and in any ongoing clinical trials must be investigated and documented.

Subsection II

Orders

Art. 15. The order must request the production and/or packaging of a certain number of units and/or their shipment and be issued by, or on behalf of, the sponsor.

Art. 16. The order must be in written form, although it may be transmitted electronically, being precise enough to avoid any ambiguity.

Art. 17. The order must be formally authorized.

Art. 18. The order must refer to the product specification file and the investigational drug dossier.

Subsection III

Product specification files

Art. 19. The product specification file must be continually updated as product development proceeds, ensuring proper traceability to previous versions.

Art. 20. The product specification file must include, at a minimum, the following documents, or refer to them:

I - specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished products;

II - manufacturing methods;

III - in-process control and methods;

IV - copy of the approved label;

V - clinical trials protocols and relevant randomization codes, as appropriate;

VI - relevant technical quality agreements with contractors, when applicable;

VII - stability data; and

VIII - storage and transport conditions.

Sole paragraph. The listing addressed in the items of the caput of this article is not intended to be exclusive or exhaustive, and the contents of the product specification file may vary depending on the product and stage of development.

Art. 21. The information in the product specification file must form the basis for evaluating the suitability of an investigational drug with a view to its certification and release and, therefore, must be accessible to the Person Delegated by the Pharmaceutical Quality Management System.

Sole paragraph. When different manufacturing steps are performed at different locations under the responsibility of different Technical Officers, it is acceptable to keep separate files with information limited to that of relevance to the activities of the respective locations.

Subsection IV

Master formulas and manufacturing instructions

Art. 22. For every manufacturing or supply operation, there must be clear and adequate written instructions and records.

Sole paragraph. When an operation is not repetitive, it may not be necessary to develop master formulas and manufacturing instructions.

Art. 23. The collection of records from this phase must be used as a reference in the preparation of the final version of the documents to be used in the manufacturing routine once the sanitary registration has been granted.

Subsection V

Packaging instructions

Art. 24. Investigational drugs are typically packaged individually for each clinical trial participant included in the study.

Art. 25. The number of units to be packaged must be specified prior to commencement of packaging operations, including the units required to perform quality control and retention samples to be held.

Art. 26. Reconciliations must be performed to ensure that the correct amount of each required product has been accounted for at each stage of processing.

Subsection VI

Manufacturing, packaging and testing records

Art. 27. Batch records must be sufficiently detailed to allow the sequence of operations performed to be accurately determined.

Sole paragraph. The records referred to in the caput of this article must contain any relevant observations that justify the procedures used and any changes made, as well as the improvement of product knowledge and the development of manufacturing operations.

Art. 28. Batch production records must be kept for the period required by current good drug manufacturing practices.

Section V

Manufacturing

Subsection I

Packaging materials

Art. 29. The specifications and quality controls applied must include measures to protect against unintentional breaking of the blinded study model due to changes in appearance between different batches of packaging material.

Sole paragraph. Measures to protect against unintentional unblinding must be included in the product specification file.

Subsection II

Manufacturing operations

Art. 30. During development, critical parameters must be identified and in-process controls must primarily be used to regulate the process.

Paragraph 1 In-process controls and provisional parameters can be deduced from previous experiences, including those acquired during earlier stages of development.

Paragraph 2 The information must be continuously worked on by the responsible team as experience with manufacturing is gained.

Paragraph 3 The parameters and in-process controls identified must be justified according to the knowledge available at each time.

Art. 31. The manufacturing processes of investigational drugs must not be validated to the extent required for other drugs, however, facilities and equipment used must be qualified.

Paragraph 1 In the case of sterile drugs, the sterilization process must be validated in accordance with the standard required for other drugs.

Paragraph 2 The processes intended for viral removal or inactivation or removal of other impurities of biological origin must be validated in accordance with the standard required for other drugs.

Art. 32. Simulation tests of the aseptic process must consider the maximum batch size of investigational drug as the number of units to be filled in the simulation.

Paragraph 1 When possible, a greater number of units should be filled to increase the confidence level of the process.

Paragraph 2 The manual steps of aseptic processing must be addressed in the aseptic process simulation studies.

Subsection III

Principles applicable to the comparator product

Art. 33. If the comparator product is modified, data such as stability, comparative dissolution profile and bioavailability shall be made available to demonstrate that the changes did not significantly alter the original product quality characteristics.

Art. 34. The shelf life stated for the comparator product in its original packaging may not apply to the product that has been repackaged in a different container, which may not offer equivalent protection, or be compatible with the product.

Paragraph 1 An appropriate use-by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which they may be subject, must be determined by the sponsor or on its behalf.

Paragraph 2 The use-by date must be justified and must not be later than the expiry date of the original packaging.

Paragraph 3 There must be compatibility between the use-by date and the duration of the clinical trial.

Subsection IV

Masking of the products under study

Art. 35. When studies are blinded, systems should be in place to ensure that masking is achieved and maintained, while allowing for the identification of masked products when necessary, including their original batch numbers.

Sole paragraph. Rapid identification of the product should also be possible in an emergency.

Subsection V

Randomization codes

Art. 36. Procedures should describe the generation, security, distribution, handling and retention of any randomization code used to package investigational drugs and the mechanisms for breaking this code.

Art. 37. Appropriate records must be kept.

Subsection VI

Packaging

Art. 38. When necessary, handling different products on the same packaging line at the same time during the packaging of investigational drugs is allowed.

Sole paragraph. The risk of product mixing must be minimized by using trained personnel, proper procedures and/or specialized equipment.

Art. 39. Precautions against labeling errors, such as label reconciliation, line release, in-process control checks should be performed by properly trained personnel and should be intensified, considering that the packaging and labeling procedures for investigational drugs, in general, are more complex and more prone to errors.

Art. 40. Packaging must ensure that the investigational drug remains in good condition during transport and storage at intermediate destinations.

Art. 41. Mechanisms for identifying attempts to open or tamper with the outer packaging during transport must be available and included in the product specification file.

Subsection VII

Labeling

Art. 42. The following information should be included on labels unless its absence can be justified - for example, the use of a centralized electronic randomization system:

I - name, address and telephone number of the sponsor, hired Contract Research Organization or investigator (the main contact for information about the product, clinical trial and emergencies);

II - presentation, route of administration, number of units and, in the case of open trials, the name/identifier and concentration/potency;

III - batch and/or code number to identify the content and packaging operation;

IV - test reference code that allows identification of the trial, the location, the investigator and the sponsor, if not provided elsewhere;

V - identification number of the clinical trial participant in the study/treatment number and, whenever relevant, the visit number;

VI - name of the investigator, if not included in the information in items I or IV of the caput of this article;

VII - instructions for use, which may refer to a package leaflet or other explanatory document intended for the trial participant or the person who administers the product;

VIII - "Only for use in clinical trials" or similar text;

IX - storage conditions;

X - period of use (use-by date, expiration date or retest date, as applicable), considering, at least, in the month/year format, and in a way that avoids any ambiguity; and

XI – “Keep out of the reach of children”, except when the product is for use in trials in which the product is not taken home by clinical trial participants.

Paragraph 1 The information listed in the items of the caput of this article must appear on the primary and secondary packaging, except in the cases provided for in articles 43 and 44 of this Normative Instruction.

Paragraph 2 The information must be in the language of the country where the clinical trial takes place, however other languages may be included.

Paragraph 3 The address and telephone number of the main contact for information about the product, clinical trial and for emergency unblinding need not appear on the label when the clinical trial participant has received a package insert or card providing these details, and has been instructed to keep this contact in their possession at all times.

Art. 43. When the drug is supplied to the clinical trial participant or the person administering it in a primary package, together with the secondary package, with the proposal that they remain together, and the secondary package contains the data listed in art. 42 of this Normative Instruction, the following information must be included in the identification of the primary packaging:

I - name of sponsor, contracted research organization or investigator;

II - presentation, route of administration, dosage and, in the case of open trials, name/identifier and concentration/potency;

III - batch and/or code number for content identification and packaging operation;

IV - trial reference code that allows identification of the study, location, investigator and sponsor, if not provided elsewhere; and

V - identification number of the person under study/treatment number and, when applicable, the visit number.

Sole paragraph. The description of the route of administration mentioned in item II of the caput of this article can be excluded for oral solid dosage forms.

Art. 44. If the primary packaging is a blister or small units, such as ampoules, in which the information required in art. 42 of this Normative Instruction cannot be exposed, an outer packaging that presents a label with this information must be provided, however, the primary container must contain the following items:

I - name of sponsor, contracted research organization or investigator;

II - route of administration, quantity of dosage units and, in the case of open trials, name/identifier and concentration/potency;

III - batch and/or code number for content identification and packaging operation;

IV - trial reference code that allows identification of the study, location, investigator and sponsor, if not provided elsewhere; and

V - identification number of the person under study/treatment number and, when applicable, the visit number.

Sole paragraph. The description of the route of administration mentioned in item II of the caput of this article can be excluded for oral solid dosage forms.

Art. 45. Symbols or pictograms may be used to clarify certain labeling information.

Art. 46. Additional information, warnings or handling instructions may be displayed.

Art. 47. If it is necessary to change the expiration date, an additional label shall be affixed to the experimental medicinal product.

Paragraph 1. The additional label must indicate the new expiration date and repeat the batch number.

Paragraph 2. The additional label may be overwritten to the old expiration date, but may not be overwritten to the original batch number for quality control reasons.

Paragraph 3 The operation mentioned in the caput of this article must be performed in a duly authorized manufacturing site.

Paragraph 4. Exceptionally, provided that the operation is duly justified, it may be performed in a place authorized by the sponsor of the clinical trial, by a pharmacist or other authorized healthcare professional.

Paragraph 5. Provided it is duly justified, the operation may be performed at the place of research under the supervision of the pharmacist of the clinical trial site or other healthcare professional, in accordance with national regulations or, where this is not possible, by clinical trial monitor(s), who must be adequately trained.

Paragraph 6. The operation shall be performed in accordance with GMP principles, standard and specific operating procedures and under contract, if applicable, and shall be verified by a second person.

Paragraph 7 Additional labeling must be properly documented in the test documentation and batch records.

Section VI

Quality control

Art. 48. In the case of investigational drugs, analytical controls are of major importance because the manufacturing processes are not fully standardized or validated.

Art. 49. Quality control must be performed in accordance with the product specification file in accordance with the required information.

Art. 50. Verification of the effectiveness of product de-characterization for use in blinded studies must be performed and recorded as part of quality control.

Art. 51. For fully packaged products, reference and retention samples are considered interchangeable.

Art. 52. Reference and retention samples of the investigational drug, including de-characterized products, must be kept for at least two years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is longer.

Art. 53. Consideration should be given to maintaining retention samples until the clinical report has been prepared to allow confirmation of product identity in the event of, and as part of, an investigation of inconsistent study results.

Sole paragraph. The possibility of storing the cited samples until the preparation of clinical trial reports should be considered, so that they can be accessed in case of investigation motivated by the report's conclusions.

Art. 54. The storage location of reference and retention samples must be defined in a technical quality agreement between the sponsor and the manufacturer(s) and must allow timely access by the health authorities.

Art. 55. The reference sample must be of sufficient size to allow the performance of at least two complete analytical controls of the batch, on different occasions, in compliance with the DDCM presented for authorization to perform the clinical trial.

Art. 56. In the case of retention samples, it is acceptable to store information related to the final packaging as written or electronic records, if such records provide sufficient information.

Sole paragraph. In the case of electronic registration, the system must be validated.

Section VII

Batches release

Art. 57. The release of investigational drugs must not take place until the Person Delegated by the Pharmaceutical Quality Management System has certified that the relevant requirements have been met.

Art. 58. The evaluation of each batch for the purpose of certifying its release may include, as appropriate:

I - batch records, including control reports, in-process control reports and release reports demonstrating compliance with the product specification file, order, protocol and randomization code, including all planned deviations or changes, as well as any additional checks or tests, and must be completed and endorsed by staff authorized to do so in accordance with the quality system;

II - production conditions;

III - validation status of facilities, processes and methods;

IV - verification of packaged units;

V - when relevant, the results of any analyzes or tests performed after importation;

VI - stability reports;

VII - source and verification of storage and transport conditions;

VIII - audit reports referring to the manufacturer's quality system;

IX - documents attesting that the manufacturer is authorized to manufacture investigational drugs or comparators for export by the competent authorities of the exporting country;

X - when relevant, regulatory requirements for registration, applicable GMP standards and any official verification of compliance with GMP; and

XI - all other factors of which the Person Delegated by the Pharmaceutical Quality Management System is aware, that are relevant to the quality of the batch.

Sole paragraph. The relevance of the above elements is affected by the country of origin of the product, the manufacturer and the marketing status of the product and its stage of development.

Art. 59. The sponsor must ensure that the elements taken into account by the Person Delegated by the Pharmaceutical Quality Management System when certifying the batch are consistent with the required information.

Art. 60. When investigational drugs are manufactured and packaged in different locations, under the supervision of different Technical Officers, the recommended parameters applicable to each one must be reviewed in the certification.

Art. 61. Where allowed, according to local regulations, packaging or labeling at the place where the clinical trial will be conducted, or under the supervision of a pharmacist or other healthcare professional authorized by local regulations, does not require certification by the Technical Officer.

Sole paragraph. In the case described in the caput of this article, the sponsor is responsible for ensuring that the activity is properly documented and performed in accordance with GMP principles and should seek guidance from the Technical Officer in this regard.

Section VIII

Expedition

Art. 62. Investigational drugs must remain under the sponsor's control until the following steps are completed:

I - certification by the Person Delegated by the Pharmaceutical Quality Management System; and

II - release after compliance with the relevant requirements.

Sole paragraph. Both steps must be recorded and maintained in the relevant files by or on behalf of the sponsor.

Art. 63. The sponsor must ensure that the details set out in the Drug Clinical Development Dossier and considered by the Person Delegated by the Pharmaceutical Quality Management System are consistent with what is accepted according to the progress of the study by the competent authorities.

Sole paragraph. Appropriate arrangements to meet this requirement must be established through a change control process to the Product Specification File and defined in a Technical Agreement between the Person Delegated by the Pharmaceutical Quality Management System and the sponsor.

Art. 64. Dispatch of investigational drugs must be conducted in accordance with instructions given by, or on behalf of, the sponsor in the dispatch order.

Art. 65. Decoding arrangements should be made available to responsible personnel before investigational drugs are transported to the location where the clinical trial will be conducted.

Art. 66. A detailed inventory of shipments made by the manufacturer or importer must be maintained.

Sole paragraph. The inventory referred to in the caput of this article must mention, in particular, the identification of the recipients.

Art. 67. Transfers of investigational drugs from one trial site to another should remain as an exception.

Paragraph 1 The transfers referred to in the caput of this article must be covered by standard operating procedures.

Paragraph 2 The history of the product outside the manufacturer's control, such as records of conservation and monitoring conditions, must be reviewed as part of the assessment of the product's suitability for transfer, and the opinion of the Person Delegated by the Pharmaceutical Quality Management System must be consulted.

Paragraph 3 When applicable, the product may have to be returned to the manufacturer, or to another authorized manufacturer for re-labeling and certification by the Person Delegated by the Pharmaceutical Quality Management System.

Paragraph 4 Records must be maintained, and full traceability must be ensured.

Section IX

Complaints

Article 68 The conclusions of any investigation performed in relation to a complaint that may arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor, if different.

Art. 69. The investigation must involve the Person Delegated by the Pharmaceutical Quality Management System and those responsible for the related clinical trial in order to assess any potential impact on the trial, product development and clinical trial participants.

Section X

Recall

Art. 70. The procedures for recalling investigational drugs and documenting the recall must be agreed by the sponsor, in collaboration with the manufacturer or importer, when different.

Sole paragraph. The investigator and monitor need to understand their respective obligations regarding the recall procedure.

Art. 71. The sponsor must ensure that the supplier of any comparator or other drug to be used in a clinical trial has a system in place to notify the sponsor in the event that any drug supplied needs to be recalled.

Section XI

Returns

Art. 72. Investigational drugs must be returned under the conditions agreed and defined by the sponsor, specified in approved written procedures.

Art. 73. Returned investigational drugs must be clearly identified and stored in a dedicated and properly controlled place.

Art. 74. Inventory records of returned drugs must be maintained.

Section XII

Destruction

Art. 75. The sponsor is responsible for the destruction of unused and/or returned investigational drugs.

Sole paragraph. Investigational drugs must not be destroyed without prior written authorization from the sponsor.

Art. 76. The quantities of investigational drugs delivered, used, and returned of the product must be recorded, reconciled and verified by the sponsor or its representative for each trial site and for each trial period.

Art. 77. Destruction of unused investigational drugs should be performed for a given trial site or trial period only after any discrepancies have been satisfactorily investigated and explained and reconciliation has been accepted.

Art. 78. Recording of destruction operations must be performed in such a way that all operations can be accounted for.

Sole paragraph. Records must be maintained by the sponsor.

Art. 79. When destruction of investigational drugs occurs, a dated certificate or receipt of destruction must be provided to the sponsor.

Sole paragraph. The documents referred to in the caput of this article must clearly identify, or allow traceability, of the batches and/or numbers of patients involved, and the actual quantities destroyed.

CHAPTER IV

FINAL PROVISIONS

Art. 80. Failure to comply with the provisions contained in this Normative Instruction constitutes a sanitary infraction, under the terms of Law No. 6437, of August 20, 1977, without prejudice to applicable civil, administrative and criminal liabilities.

Art. 81. Normative Instruction-IN No. 45 of August 21, 2019 is hereby revoked.

Art. 82. This Normative Instruction enters into force on May 2, 2022.

ANTONIO BARRA TORRES