COLLEGIATE BOARD RESOLUTION – RDC No. 945 OF 29 NOVEMBER 2024

Provides for the guidelines and procedures to conduct clinical trials in Brazil with a view to subsequently granting marketing authorization to 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, items III and IV of Law no. 9,782 of 26 January 1999, and item VI, paragraph 1 of Article 187 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Resolution, as decided upon in a meeting held on 27 November 2024, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 1. This Resolution aims to define the guidelines and procedures to conduct clinical trials with medicinal products, including the submission of the Clinical Medicinal Product Development Dossier (DDCM, in Portuguese).

Section II

Scope

Article 2. This Resolution applies to clinical trials with medicinal products that will have all or part of their clinical development in Brazil for marketing authorization purposes.

Paragraph 1. Clinical trials with medicinal products granted marketing authorization in Brazil must follow all the provisions of this Resolution when providing support for: new therapeutic indication, new administration route, new concentration, new pharmaceutical form, expansion of use, new dosage regimen, new combinations or any post-marketing authorization change that requires clinical data, and renewal of marketing authorization;

Paragraph 2. The description in the caption of this article applies to synthetic and semi-synthetic, herbal, specific, and dynamized medicinal products, medicinal gases, radiopharmaceuticals, and biological medicinal products, including biosimilars.

Article 3. Post-marketing (phase IV) clinical trials and non-interventional clinical research are not covered by this regulation and should only be initiated after obtaining the pertinent ethical approvals in accordance with Brazilian specific federal regulations on ethics in research.

Article 4. This Resolution does not apply to equivalence and relative bioavailability studies, scientific or technological research, and clinical trials with cosmetics, medical devices, food, and advanced therapy medicinal products (ATMPs), which must follow specific standards.

Article 5. Anvisa may issue specific standards and guidelines for cases not covered by this Resolution, such as new clinical trial designs or new categories of medicinal products and establish new regulatory procedures in cases of public health emergencies or other exceptional situations recognized by Anvisa.

Section III

Definitions

Article 6. For the purposes of this Resolution, the following definitions are adopted:

I – Audit: a systematic and independent examination of the activities and documents associated with the trial to determine whether the activities evaluated and associated with the trial were performed, and the data were recorded, analyzed, and rigorously reported in accordance with the protocol, with the standard operating procedures defined by the sponsor, with Good Clinical Practices (GCP) and the applicable regulatory requirements;

II – Equivalent Foreign Regulatory Authority (EFRA): foreign regulatory authority or international entity that has regulatory practices aligned with those of Anvisa, and that may be considered by Anvisa in a practice of regulatory reliance;

III – Good Clinical Practices (GCP): a standard for the design, conduct, execution, monitoring, auditing, record, analysis, and reporting of clinical trials that ensures the credibility and accuracy of the data and results reported, and the protection of the rights, integrity, and confidentiality of the trial participants, in accordance with the GCP guidelines set out in the International Council for Harmonisation (ICH) guide, ICH E6 (R2) and its updates;

IV – Good Manufacturing Practices (GMP): part of Quality Assurance that ensures that products are consistently produced and controlled, with quality standards appropriate for their intended use;

V – Good Laboratory Practices (GLP): quality system that encompasses the organizational process and conditions under which non-clinical studies related to health and environmental safety are planned, developed, monitored, recorded, archived, and reported;

VI – Investigator's Brochure (IB): compilation of clinical and non-clinical data related to experimental medicinal products, relevant to the study of such medicinal products in humans;

VII – Clinical Trial Risk Category: stratification of clinical trials with similar potential risks, based on the experience of use and level of safety information available for the experimental medicinal product, allowing clinical trials to be differentiated as being of low, moderate and high risk;

VIII – Low Risk Clinical Trial Category: clinical trials (phase 3) with medicinal products or therapies with a known safety profile, which represent a minimal additional risk to the safety of clinical trial participants, compared to usual medical practice;

IX – Moderate Risk Clinical Trial Category: clinical trials involving medicinal products or therapies with a known safety profile, or that have approved DDCM with substantial modifications, representing an average additional risk to the safety of clinical trial participants compared to usual medical practice;

X – High Risk Clinical Trial Category: clinical trials involving new medicinal products or therapies, representing a high risk to the safety of clinical trial participants;

XI – Clinical Trial Center: a legitimately constituted public or private organization, duly registered in the Brazilian Registry of Health Establishments (CNES, in Portuguese), in which clinical trials are carried out;

XII – Brazilian Technical Commission on Biosafety (CTNBio, in Portuguese): part of the Ministry of Science, Technology and Innovation (MCTI, in Portuguese), it is a multidisciplinary collegiate body of a consultative and deliberative nature, to provide technical and advisory support to the Brazilian Federal Government in the formulation, updating, and implementation of the Brazilian Biosafety Policy (PNB, in Portuguese) for GMOs and their derivatives, as well as in the establishment of technical safety standards and technical opinions regarding the authorization for activities involving research and commercial use of GMOs and their derivatives, based on the assessment of their animal and plant risk, to human health and to the environment;

XIII – Research Ethics Committee (CEP, in Portuguese): a collegiate body linked to the institution conducting the research, whether public or private, with an interdisciplinary composition, consisting of members from the medical, scientific and non-scientific areas, with an advisory and deliberative nature, which acts independently and autonomously to ensure the protection of the rights, safety, and well-being of research participants, before and during the research, through analysis, review, and ethical approval of research protocols and their amendments, as well as the methods and materials to be used to obtain and document the free and informed consent of research participants;

XIV – Independent Data Monitoring Committee (IDMC or Data and Safety Monitoring Board, DSMB): an independent committee, established by the sponsor, to evaluate, at defined intervals or as an emergency need, the progress of the clinical trial, the safety data and the critical efficacy endpoints, and recommend to the sponsor whether to continue, modify, interrupt, or suspend a trial;

XV – Clinical Trial Start Date: the first act of recruitment of a potential participant for a specific clinical trial, unless otherwise defined in the protocol;

XVI – Clinical Trial Start Date in Brazil: the first act of recruitment in Brazil of a potential participant for a specific clinical trial, unless otherwise defined in the protocol;

XVII – Clinical Trial End Date: corresponds to the date of the last visit of the last clinical trial participant in the world or another definition of the sponsor, expressly determined in the specific clinical trial protocol;

XVIII – Clinical Trial End Date in Brazil: corresponds to the date of the last visit of the last clinical trial participant in Brazil or another definition of the sponsor, expressly determined in the specific clinical trial protocol;

XIX – Derivative from Genetically Modified Organisms (GMO): product obtained from GMO and that does not have autonomous replication capacity or that does not contain a viable form of GMO;

XX – Import Document (ID): document issued by Anvisa, used in requests for import or export of investigational products, when necessary;

XXI – Clinical Medicinal Product Development Dossier (DDCM, in Portuguese): compilation of documents to be submitted to Anvisa for the purpose of evaluating the stages inherent to the development of an experimental medicinal product in order to obtain information to support the marketing authorization or post-marketing authorization changes of such product;

XXII – Specific Clinical Trial Dossier (DEEC, in Portuguese): compilation of documents to be submitted to Anvisa for the purpose of obtaining information regarding clinical trials to be conducted in Brazil, which are part of the Experimental Medicinal Product Development Plan;

XXIII – Amendment to the clinical trial protocol: any proposal for modification to an original clinical trial protocol, always presented with the justification that motivated it, and such amendment may or may not be substantial;

XXIV – Public health emergency: situation that demands the urgent use of measures to prevent, control, and restrain risks, damages and harms to public health declared in situations that may be epidemiological (outbreaks and epidemics), disasters, or lack of assistance to the population;

XXV – Clinical trial: any interventional clinical research with humans with the objective of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental medicinal product and/or identifying any adverse reaction to the experimental medicinal product and/or studying the absorption, distribution, metabolism, and excretion of the experimental medicinal product to verify its safety and/or efficacy;

XXVI – Clinical Research: set of scientific procedures developed systematically with humans with a view to:

a) evaluating the action, safety, and efficacy of medicines, products, techniques, procedures, medical devices or health care, for therapeutic, preventive or diagnostic purposes;

b) verifying the distribution of risk factors, diseases, or conditions in the population;

c) evaluating the effects of factors or conditions on health;

XXVII – Complex clinical trial: unconventional clinical trial in the sense that it has elements, characteristics, methods, or a combination of them, including new approaches, which add complexity to its design, conduct, analyses or reports;

XXVIII – Post-marketing (phase IV) clinical trial: a type of clinical trial that aims to evaluate potential adverse events, toxicities or side effects that may occur over time, related to the new treatment and that are not always observed in previous clinical trials. Likewise, the post-marketing (phase IV) clinical trial may be carried out to evaluate the efficacy/effectiveness of the

new treatment over time during its use by the population, after its approval and availability on the market;

XXIX – Adverse Event (AE): any adverse medical occurrence in a clinical trial participant to whom an investigational product was administered, and which does not necessarily have a causal relationship with the treatment. An AE, therefore, is any unfavorable and unintentional sign, for example, an abnormal laboratory finding, symptom or disease temporarily associated with the use of a medicinal product, whether or not considered related to its use;

XXX – Serious Adverse Event (SAE): any adverse medical occurrence with a investigational product, occurring at any dose and resulting in death, risk of death, persistent or significant disability or incapacity, congenital anomaly/birth defect and situations requiring hospitalization or prolonged hospitalization;

XXXI – Reference Safety Information (RSI): the RSI is a list of expected serious adverse reactions, which are classified using preferred terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA). It is used to assess the expected outcome of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials;

XXXII – Inspection: the act by a regulatory authority of conducting an official review of the documents, facilities, records, and any other resources considered by the authority to be related to the clinical trial and which may be located where the trial is conducted, at the sponsor's facilities, the Clinical Research Representative Organization (CRRO) or at other locations that the regulatory authority considers appropriate;

XXXIII – Brazilian Research Ethics Body: an interdisciplinary and independent collegiate body, part of the Ministry of Health, under the coordination of the technical area responsible for the field of science and technology, with a normative, consultative, deliberative, and educational nature, competent to regulate, monitor and ethically control research, with a view to protecting the integrity and dignity of research participants, and to contributing to the development of research within ethical standards;

XXXIV – Active Pharmaceutical Ingredient (API): any substance introduced into the formulation of a pharmaceutical form that, when administered to a participant, acts as an active ingredient, and may exert pharmacological activity or another direct effect in the diagnosis, cure, treatment, or prevention of a disease, and may also affect the structure and functioning of the human body;

XXXV – Investigator: person responsible for conducting a clinical trial at the site where the trial is conducted. If the study is conducted by a group of people, the investigator is the leader of the group and will be called the main investigator;

XXXVI – Investigator-Sponsor: an individual responsible for conducting and coordinating clinical trials, either individually or in a group, carried out under his/her immediate direction in an independent manner, developed with the investigator's own financial and material resources, from national or international research funding entities, private entities, and other non-profit entities;

XXXVII – Experimental medicinal product: pharmaceutical product under test, object of the DDCM, to be used in the clinical trial, with the purpose of obtaining information for its marketing authorization or post-marketing authorization or renewal of marketing authorization;

XXXVIII – Comparator medicinal product: medicinal product granted marketing authorization or placebo used in the control group of a clinical trial to allow comparison of its results with those of the group that received the medicinal investigational product;

XXXIX – Modified comparator medicinal product: comparator medicinal product granted marketing authorization that has undergone any modification, except repackaging with compatible material, to be used in the clinical trial;

XL – Monitoring: act of continually reviewing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practices (GCP), and applicable regulatory requirements;

XLI – Genetically Modified Organism (GMO): organism whose genetic material – DNA/RNA (deoxyribonucleic acid/ribonucleic acid) has been modified through any genetic engineering technique;

XLII – Clinical Research Representative Organization (CRRO): any company regularly established in the Brazilian territory contracted by the sponsor or by the investigator-sponsor, which partially or fully assumes, with Anvisa, the sponsor's duties;

XLIII – Research participant: an individual who, freely and with informed consent, or with the clarification and authorization of his/her legal guardian, voluntarily participates in the research;

XLIV – Sponsor: an individual or legal entity, under public or private law, that supports research through financing, infrastructure, human resources, or institutional support;

XLV – Scientific or technological research involving humans: research that, individually or collectively, has direct interaction with the human being, without the purpose of granting marketing authorization for the investigational product;

XLVI – Placebo: a formulation that does not contain an active ingredient, administered to the clinical trial participant as a comparator or for the purpose of masking the treatment;

XLVII – Investigational product: a product used as an experimental medicinal product, active comparator or placebo or any other product to be used in a clinical trial;

XLVIII – Complex investigational product: formulations and/or pharmaceutical inputs or active substances with physical-chemical or biological characteristics or properties that confer complexity;

XLIX – Optimized analysis procedure: a technical evaluation mechanism facilitated or simplified by regulatory reliance practices or by risk or complexity criteria of the clinical trial or experimental medicinal product;

L – Clinical Trial Protocol: a document that describes the objectives, design, methodology, statistical considerations, and organization of the trial. It also provides the context and rationale for the clinical trial;

LI – Adverse Drug Reaction (ADR): a harmful and unintentional response attributed to a medicinal product, at doses normally used for prophylaxis, diagnosis, or treatment of diseases or for the modification of a physiological function. In the context of clinical development, there are often no well-established doses and adverse drug reactions do not have a well-established causal relationship with the product and, therefore, are considered suspicious;

LII – Annual clinical trial monitoring report: an annual document containing specific information on the conduct of a given clinical trial in all centers participating in the study in Brazil, in accordance with the clinical protocol and GCP;

LIII – Development Safety Update Report (DSUR): harmonized periodic report containing information on the safety and development of an experimental medicinal product;

LIV – Final clinical trial report: document containing specific information on the conduct of a given clinical trial in all centers participating in the study in Brazil, in accordance with the clinical protocol and GCP;

LV – Reliance: the act by which Anvisa can consider and give significant weight to the assessments carried out by a reliable Equivalent Foreign Regulatory Authority (EFRA), as a sole or complementary reference, for its decisions;

LVI – Continuous submission: procedure for presenting partial data as they are generated, prior to the final submission of the Clinical Medicinal Product Development Dossier (DDCM, in Portuguese);

LVII – Active substance: is the substance with pharmacological effect for the intended therapeutic activity, used in the production of a given biological product;

LVIII – Suspected Serious, Unexpected Adverse Reaction (SUSAR) – this is an adverse reaction that simultaneously meets the conditions of serious, unexpected and with a reasonable possibility of a causal relationship, that is, suspected with the experimental medicinal product and active comparator, as defined below:

a) serious: see Serious Adverse Event;

b) unexpected: a suspected adverse medicinal product reaction (SRAM, in Portuguese) whose nature or severity is not consistent with the information available for the investigational product, in the investigator's brochure (IB), Safety Information Summary (SIR) or package insert. The reaction may not be listed in the IB, SIR or package insert or not be listed in the specificity or seriousness that was observed. The classification of unexpected is based on the perspective of previous observations, not on what can be anticipated from the pharmacological properties of a medicinal product;

c) suspected: reasonable possibility that the investigational medicinal product and active comparator have caused the adverse reaction.

CHAPTER II

RESPONSIBILITIES

Article 7. The responsibilities for Good Clinical Practices (GCP) defined by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) through ICH E6 (R2), and its updates, are hereby adopted, without prejudice to other responsibilities provided for in a complementary manner in accordance with this Resolution.

Section I

Review Body of Ethics in Research

Article 8. Research involving humans must be submitted to prior ethical analysis, to be carried out by the Research Ethics Committees (CEPs, in Portuguese) in accordance with specific legislation and regulations of the Brazilian Research Ethics Body, in order to guarantee the dignity, safety, and well-being of the research participant.

Paragraph 1. The Brazilian Research Ethics Body and the CEPs are not linked to Anvisa; therefore, clinical trial protocols may be submitted in parallel to the ethical and regulatory bodies.

Paragraph 2. The decisions of the ethical and regulatory bodies are parallel and independent, however, the trial for the purpose of medicinal product marketing authorization may only be initiated after approval by both.

Section II

The Sponsor

Article 9. The sponsor is responsible for all expenses related to procedures and examinations, especially those for diagnosis, treatment, monitoring, and hospitalization of the clinical trial participant, assistance and compensation for any damage suffered as a result of their participation in the research and other actions necessary to resolve adverse events related to the clinical trial.

Article 10. The sponsor must ensure that the data obtained on the safety and efficacy of the experimental medicinal product are sufficient to support human exposure by the proposed route of administration, by the chosen dosage, by the duration of the proposed treatment and in the population to be studied. +-

Article 11. The sponsor must be responsible for storing the clinical trial data for a period of 5 (five) years after the last approval of a marketing authorization request in Brazil, without prejudice to the provisions determined by specific legislation.

Sole paragraph. In the event of discontinuation of clinical development or its conclusion not followed by a marketing authorization request, the sponsor must maintain the clinical trial data for at least 2 (two) years after the discontinuation of clinical development or formal conclusion of such development, without prejudice to the provisions determined by specific legislation.

Article 12. The sponsor must ensure that the experimental medicinal product, modified active comparator medicinal product or placebo, when used, are manufactured in accordance with Good Manufacturing Practices (GMP) and are coded and labeled in a way that protects masking, if applicable, and characterizes them as products under clinical investigation.

Article 13. The sponsor is responsible for acquiring a sufficient quantity of the experimental medicinal product and other supplies to be used in the clinical trial and distributing them only to the institutions informed in the approved Clinical Trial Submission Form (FAEC, in Portuguese) and authorized by the ethics authority.

Sole paragraph. The sponsor is responsible for the final destination of the medicinal products and products that were not used in the clinical trial.

Article 14. The sponsor may transfer its functions to a CPO.

Paragraph 1. The transfer referred to in the caption of this article does not remove the sponsor's definitive responsibility for the quality and integrity of the clinical trial data.

Paragraph 2. Any functions related to the clinical trial that are transferred to a CPO and assumed by it must be specified in writing in a document signed by the sponsor and the CPO.

Section III

Investigator

Article 15. The investigator must conduct the clinical trial in accordance with the protocol agreed with the sponsor, with the GCP and with the pertinent regulatory and ethical requirements.

Article 16. The investigator must allow monitoring, audits, and inspections to be carried out.

Article 17. The investigator must ensure, without any cost to the participant, full health care for the clinical trial participant regarding any adverse events related to the clinical trial, including clinically significant laboratory results and findings.

Article 18. The clinical trial center must have facilities suitable for conducting the protocol, regarding physical structure, equipment, instruments, and human resources, and must also be compatible with the clinical trial population, such as the elderly, children, people with special needs, among others, and comply with specific regulations for health services.

Sole paragraph: The conditions described in the caption of this article are also valid in the case of external services/establishments contracted by the investigator.

Section IV

Investigator-Sponsor

Article 19. In the case of a clinical trial initiated by the investigator, the institution with which he/she has a link shall be the primary sponsor.

Paragraph 1. The primary sponsor may delegate responsibilities to the investigator, who shall be responsible for conducting the clinical trial at the institution and, in this case, the investigator-sponsor shall be the secondary sponsor.

Paragraph 2. In the case of delegation of responsibilities and activities, a written document must be signed between the parties.

Paragraph 3. The primary sponsor cannot delegate quality assurance, auditing, and monitoring activities of clinical trials to the sponsor-investigator but may delegate them to a CRO.

Paragraph 4. The primary sponsor must have its own or outsourced structure with, at least, the following units: management of adverse events; project management; data management; training; information technology; quality assurance and monitoring.

Paragraph 5. The institution referred to in the caption of this article must be the one in which the clinical trial will be conducted.

Paragraph 6. The responsibilities referred to in this article do not exclude the provisions of Sections II and III of this chapter on the responsibilities of the sponsor and investigator.

Article 20. In the case of donation of medicinal products already granted marketing authorization in Brazil for conducting a clinical trial, the donor will be the sponsor if there is an agreement for the transfer or ownership of the data obtained in the research to the donor.

Article 21. In the case of donation of medicinal products not granted marketing authorization in Brazil for clinical trials, the donor shares the responsibilities of the sponsor.

CHAPTER III

PROCEDURES AND REQUIREMENTS FOR AUTHORIZATION OF CLINICAL TRIALS

Section I

Submission of the Clinical Medicinal Product Development Dossier (DDCM)

Article 22. The documentation presented in the DDCM must guarantee the safety and rights of participants in all phases of clinical development, the quality of the experimental medicinal product and the data obtained in the clinical phases of development so that they allow an assessment of the efficacy and safety of the medicinal product.

Article 23. The DDCM may be submitted to Anvisa at any stage of the clinical development of the medicinal product for one or more phases of clinical trials.

Article 24. The sponsor must submit a DDCM to Anvisa only if it intends to conduct clinical trials with medicinal products in Brazilian territory.

Paragraph 1. The DDCM may be submitted by the sponsor, the sponsoring investigator, or the CRO.

Paragraph 2. The person responsible for the DDCM with Anvisa must be the same for all subsequent submissions of petitions related to it.

Paragraph 3. Submissions by CROs may only be made when the sponsor does not have a head office or branch in Brazil.

Paragraph 4. The submission of the DDCM of an investigator-sponsor must be made through the primary sponsor; and

Paragraph 5. In cases where an investigator-sponsor wishes to conduct a clinical trial with a medicinal product that already has a DDCM approved by Anvisa, the investigator-sponsor may use the information already sent by the holder of the initial DDCM, if the latter authorizes it, without the need to resubmit all the documentation. When no authorization is presented by the initial holder, the sponsoring investigator must submit to Anvisa all the information through updated and indexed literature that supports the proposed development rationale.

Article 25. The DDCM and all related processes and petitions must be filed electronically and the documentation submitted must allow for text searches, copies and contain bookmarks and hyperlinks that facilitate navigation.

Article 26. The DDCM will only be analyzed after the filing of at least one (DEEC), which must be done within 15 (fifteen) business days from the date of issuance of the DDCM file.

Sole paragraph. The absence of the DEEC, after the deadline described in the caption of this article, shall result in the rejection of the DDCM without technical analysis, except in cases of clinical trials involving more than one experimental medicinal product, whose DEEC has already been linked to one of the DDCMs of these medicinal products.

Article 27. At any time, the sponsor, CRO or sponsor-investigator may link new DEECs to the DDCM submitted.

Sole paragraph. The DEECs must be filed by the sponsor, CRO or investigator-sponsor, in the form of individual processes for each clinical trial and linked to the respective DDCM.

Section II

Specific DDCM Submission Requirements

Article 28. The primary DDCM petition to be submitted to Anvisa must contain the following documents:

I – DDCM petition form duly completed, according to the model available on Anvisa's website.

II – statement of commitment to distribute to the centers and use of products under investigation only after authorization of the DDCM and corresponding DEEC, when the import is authorized prior to the publication of the approval/rejection in the Federal Official Gazette.

III – investigational medicinal product development plan (PDME, in Portuguese), containing:

a) name of the API or active substance, category of investigational medicinal product (synthetic, biological, specific, dynamized, medicinal gas, herbal, or radiopharmaceutical), therapeutic class, pharmaceutical form, concentration, and administration route;

b) mechanism of action and indications to be studied;

c) general objectives and planned duration of clinical development;

d) a list, in tabular form, of the countries where the clinical development has been submitted, including details on the regulatory and ethical approval status, and respective clarifications or justifications in cases of approval with reservations, disapproval, interruption, or cancellation of clinical development in any of the countries where it was submitted;

e) scientific advisory opinion of any foreign regulatory authority, if any, on clinical development; and

f) in cases of linking new DEECs to the DDCM, and exclusion of protocols referred to in the PDME in which the corresponding DEECs were not submitted, the updated version of the PDME must be submitted, by means of a secondary petition to the DDCM.

IV – Investigator's Brochure (BI), containing:

a) the minimum information described in ICH E6 (R2) and its updates;

b) for phase 1 clinical trials involving the use of a medicinal product for the first time in humans (First-in-human, FIH), attach reports of toxicity and detailed pharmacokinetic and pharmacodynamic studies as a complement to the BI, as soon as they are available;

c) a section identified as Reference Safety Information;

d) in cases where clinical trials are intended to support a new therapeutic indication, an expansion of use to a new population, a new dosage regimen, new combinations or any post-marketing authorization change that requires clinical data, the updated version of the BI with the changes highlighted (track-change format) must be submitted, or a specific BI, by means of a secondary petition to the DDCM; and

e) Anvisa will issue a supplementary normative act to comply with the provisions of letter "b".

V – Investigational Medicinal Product Dossier (IMPD), including information regarding:

a) Active Pharmaceutical Ingredient – API

1. description of the API: nomenclature, structure, general properties (physical-chemical, organoleptic, and biological characteristics);

2. manufacturing process and in-process controls;

3. characterization, including impurities;

4. quality control of the API or active substance, including validation of the analytical methodology;

5. reference standards or materials;

6. packaging material;

7. results of stability studies.

b) investigational medicinal product

1. description of the pharmaceutical form and composition of the investigational medicinal product;

2. pharmacotechnical development;

3. manufacturing process and in-process controls;

4. quality control of excipients;

5. quality control of the investigational medicinal product;

6. reference standards/materials or chemical substances;

7. packaging material;

8. results of stability studies; and

9. documentation regarding the control of transmissibility of Transmissible Spongiform Encephalopathies (TSE), according to current health standards or justifications for exemption from this document.

c) placebo and modified comparator medicinal product

1. description of the pharmaceutical form and composition of the placebo or comparator medicinal product, when the latter is modified;

2. manufacturing process and analytical controls;

3. packaging material; and

4. results of stability studies.

VI – specific clinical trial dossier (DEEC, in Portuguese), containing:

a) clinical trial presentation form (FAEC, in Portuguese) duly completed, according to the model available on the Anvisa website;

b) clinical trial protocol containing the minimum information described in ICH E6 (R2) and its updates;

c) statistical analysis plan (PAE, in Portuguese), at least in draft version, in the case of phase 3 clinical trials and adaptive clinical trials;

d) scientific advisory opinion of any country/region, if any, on the clinical trial;

e) pediatric investigation plan of any country/region, if any;

f) model of the experimental medicinal product label;

g) proof of clinical trial record, in the same version as the clinical protocol submitted to Anvisa, in the record database of the International Clinical Trials Registry Platform/World Health Organization (ICTRP/WHO) or others recognized by the International Committee of Medical Journals Editors (ICMJE) and the World Health Organization (WHO); and

h) if the proof referred to in letter "g" is not available at the time of submission of the DEEC, it must be submitted together with the notification of the start of the clinical trial.

VII – Declarations of compliance with Good Clinical Practices (GCP), Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP)

a) declaration that the non-clinical trials presented to support the conduct of clinical trials in Brazil were carried out in accordance with GLP or equivalent standards, including the guidelines of the Organization for Economic Cooperation and Development (OECD), and justification for non-GLP trials;

b) declaration that the completed or ongoing clinical trials were conducted in accordance with the GCPs and that the clinical trials to be conducted in Brazil will also be conducted in accordance with the clinical protocol, this Resolution and the GCPs. If there is a GCP Certificate or equivalent document for the completed or ongoing clinical trials, it must be attached to the DDCM; and

c) declaration that the experimental medicinal product/placebo used in the completed or ongoing clinical trials were manufactured in accordance with the GMPs and that the experimental medicinal product/placebo to be used in the clinical trials in Brazil will also be manufactured in accordance with the GMPs, in accordance with the current GMP legislation for experimental medicinal products. If there is a GMP Certificate or equivalent document for the experimental medicinal product, it must be attached to the DDCM or to the request for substantial modification to the investigational product, if applicable.

Article 29. Anvisa shall issue a supplementary normative act regarding the quality requirements of the API or active substance and the investigational product to comply with the provisions of item V of Article 28, regarding the IMPD.

Sole paragraph. If the experimental medicinal product has already been granted marketing authorization in Brazil, the presentation of the documentation described in item V, Article 28, regarding the IMPD is waived. However, in cases where there is a substantial change in the quality of the experimental medicinal product in relation to the medicinal product granted marketing authorization, all documentation and information that support the change(s) must be presented in the DDCM.

Article 30. The information in the IMPD must be presented in accordance with a logical structure that facilitates technical analysis, and it is recommended that it be in the format of Module 3 of the Common Technical Document (CTD), provided for in ICH M4 and its updates.

Article 31. In the case of associations or combinations of Active Pharmaceutical Ingredients (APIs) in Fixed Dose that require pharmacokinetic interaction assessment or in applicable cases of studies with biosimilar products, the Relative Bioavailability or Bioequivalence studies must be presented to the responsible area, in accordance with specific guidelines and regulations.

CHAPTER IV

PROCEDURES AND REQUIREMENTS FOR THE AUTHORIZATION OF SUBSTANTIAL CHANGES TO THE INVESTIGATIONAL PRODUCT AND SUBSTANTIAL AMENDMENTS TO THE CLINICAL PROTOCOL

Section I

Substantial modifications to the Investigational product

Article 32. Substantial modifications to the investigational product refer to changes that potentially impact the quality or safety of the experimental medicinal product, active comparator, or placebo and must be filed electronically, as a secondary petition linked to the corresponding DDCM.

Article 33. The petition for substantial modification to the investigational product must contain a copy of the previously approved IMPD, containing the proposed modifications highlighted (track-changes format) and a table comparing the current situation with the proposed changes, the justifications for each change and the assessment of the impacts of the modifications on clinical development.

Sole paragraph. In addition to the documentation described in the caption of this article, the Petition Form for Substantial Modification to the Investigational Product and other information in accordance with each proposed modification must be attached to the petition, in accordance with specific instructions available on the Anvisa website.

Article 34. Anvisa shall issue a supplementary normative act to comply with the provisions above regarding modifications to the investigational product considered substantial and non-substantial.

Article 35. Non-substantial modifications to the investigational product must be submitted to Anvisa always in the next petition for substantial modification to the investigational product or as part of the DSUR, whichever occurs first.

Section II

Substantial Amendments to the Clinical Protocol

Article 36. An amendment to a clinical trial protocol shall be considered substantial when it meets at least one of the following criteria:

I – change in the clinical trial protocol that interferes with the safety or physical or mental integrity of the participants; or

II – change that is likely to have an impact on the reliability or robustness of the data produced in the clinical trial.

Article 37. Petitions for substantial amendments to clinical trial protocols must be filed electronically, as a secondary petition, linked to the corresponding DEEC and must contain a copy of the previously approved clinical protocol with the proposed modifications highlighted (track-changes format) and a table comparing the current situation with the proposed changes, the justifications for each change and the assessment of the impacts on clinical development.

Sole paragraph. In addition to the documentation described in the caption of this article, the updated Clinical Trial Submission Form (FAEC, in Portuguese) in a clean version and a version with highlighted changes (track-changes format) and the new clean version of the clinical protocol must be attached to the petition.

Article 38. Anvisa shall issue a supplementary normative act to comply with the provisions above on amendments to the clinical protocol considered substantial and non-substantial.

Article 39. Non-substantial amendments to the clinical trial protocol must always be submitted to Anvisa in the next substantial amendment petition or as part of the final clinical trial protocol monitoring report in cases where there are no substantial amendments by the end of the clinical trial.

CHAPTER V

OPTIMIZED PROCEDURE FOR ANALYZING DDCM, DEEC AND SUBSTANTIAL MODIFICATIONS TO THE INVESTIGATIONAL PRODUCT AND SUBSTANTIAL AMENDMENTS TO THE CLINICAL PROTOCOL

Section I

Based on regulatory reliance practices

Article 40. The optimized analysis procedure may be applied, when requested by the sponsor, in accordance with this resolution, to the following petition subjects:

I – Approval of the Process of the Clinical Medicinal Product Development Dossier (DDCM, in Portuguese);

II – Approval of the Clinical Research Process (DEEC);

III – Substantial modification to the investigational product;

IV – Substantial amendment to the Clinical Protocol.

Subsection I

Documents subject to the optimized analysis procedure through reliance

Article 41. The documents required for the instruction of each type of petition or process, in accordance with this resolution, may be partially or fully exempted from technical analysis through the optimized analysis procedure through reliance.

Sole paragraph. Anvisa shall issue a supplementary normative act to establish the criteria and documents that may be partially or fully exempted from technical analysis through the optimized analysis procedure (reliance).

Subsection II

Requirements for the admissibility of the optimized analysis procedure through reliance

Article 42. Official proof issued by the EFRA regarding the approval, in the same versions submitted to Anvisa, of the clinical protocol or amendment to the clinical protocol, DPI, or IMPD of the DDCM or of the substantial modification of the investigational product must be presented.

Paragraph 1. In the absence of the official document described in the caption of this article, a statement signed by the legal and technical representatives of the sponsor must be presented with due justification and additional information, if applicable.

Paragraph 2. In cases of non-compliance with the admissibility criteria for the optimized analysis procedure, Anvisa shall inform the applicant about the non-acceptance and the reason for such.

Article 43. The sponsor must inform Anvisa about any commitment or conditional approval terms assumed with EFRA and details about the respective pending issues and referrals, if applicable.

Article 44. By opting for the optimized analysis procedure through regulatory reliance, the sponsor confirms its automatic consent for Anvisa to communicate directly with the EFRA about the details of the clinical development process under analysis, when necessary.

Article 45. The request for analysis through the optimized procedure may be requested by the sponsor at any time, by means of a secondary petition, before the start of the analysis of the petition that is the object of the request.

Article 46. The admissibility of the optimized analysis procedure does not imply prioritization of petition analysis, but Anvisa may create specific queues for the allocation and analysis of such petitions.

Article 47. Anvisa shall be responsible for the decision on the acceptance of the request for analysis through the optimized procedure, including the decision to opt for the ordinary analysis of the petition, regardless of the decision rendered by the EFRA.

Article 48. Anvisa may carry out additional monitoring actions, such as audits or GCP inspections to monitor DDCMs, DEECs, and secondary petitions approved through the optimized analysis procedure.

Sole paragraph. Monitoring actions include the evaluation of information regarding the safety profile, based on national and international alerts, and other duly justified actions, at Anvisa's discretion, that may contribute to maintaining the approved conditions.

Subsection III

Equivalent Foreign Regulatory Authorities (EFRAs)

Article 49. For the purposes of admissibility of the optimized procedure for analyzing primary and secondary petitions, the related documents must have been approved by at least one of the EFRAs recognized by Anvisa.

Paragraph 1. To comply with the provisions in the caption of this article, Anvisa shall issue a complementary normative act to define the recognized authorities (EFRA).

Paragraph 2. The manufacturing process of the API and the investigational product/experimental medicinal product approved by the EFRA must comply with the guidelines and principles described in the current ICH guides, where applicable, according to the clinical development phase.

Section II

Based on risk assessment supported by the experience of using the investigational product

Article 50. The optimized analysis procedure based on risk assessment may be applied, when requested by the sponsor, in accordance with this resolution, to the following petition subjects:

I – Approval of the Process of the Clinical Medicinal Product Development Dossier (DDCM);

II – Substantial modification to the investigational product.

Subsection I

Documents subject to the optimized analysis procedure based on risk assessment

Article 51. The documents required for the submission of each type of petition or process, in accordance with this resolution, may be partially or fully exempted from technical analysis, through the optimized analysis procedure, according to the risk and complexity of the clinical trial.

Paragraph 1. Anvisa shall issue a complementary normative act to establish the criteria of risk and complexity of the clinical trial and the cases in which the analysis may be waived.

Paragraph 2. In cases where the placebo, when used, is identical to the experimental medicinal product granted marketing authorization, differing from it only by the absence of the API, and/or the active comparator is identical to the medicinal product granted marketing authorization, the analysis of the documents present in the IMPD may also be optimized.

CHAPTER VI

DEADLINES FOR THE AUTHORIZATION OF CLINICAL TRIALS, MODIFICATIONS, AND SUBSTANTIAL AMENDMENTS

Article 52. After regular receipt of the primary petitions for DDCM and DEEC, Anvisa shall evaluate them within 90 (ninety) business days, counting from the date of issuance of the DEEC document.

Paragraph 1. If Anvisa does not respond within the period provided for in the caption of this article, the DDCM and respective DEEC shall be released due to the expiration of the term, by means of a Resolution-RE published in the Federal Official Gazette (DOU, in Portuguese), and the clinical development may begin after the pertinent ethical approvals.

Paragraph 2. The provisions of Paragraph 1 also apply to primary petitions for new DEECs subsequently linked to the DDCM and to secondary petitions for substantial modifications to the investigational product and substantial amendments to the clinical protocol.

Paragraph 3. Substantial modifications to the investigational product and substantial amendments to the clinical protocol arising from recommendations or safety alerts issued by health authorities that aim to eliminate immediate risks to the safety of clinical trial participants must be petitioned before implemented and may be implemented regardless of Anvisa's prior opinion.

Article 53. The act of releasing primary petitions for DDCMs and DEECs and secondary petitions due to the expiration of the term does not exempt any entity involved in the clinical trial from its responsibilities and from the obligation to fully comply with the provisions of this Resolution, where applicable.

Article 54. Anvisa may request, once only, by means of a technical requirement, additional clarifications and documents during the analysis of primary petitions for DDCM and DEEC and secondary petitions for substantial modification to the investigational product or substantial amendment to the clinical protocol, which will result in the suspension of the analysis deadlines, with interruption prohibited.

Sole paragraph. The deadline for compliance with the technical requirement, as described in the caption of this article, is 30 (thirty) business days, starting from the date of confirmation of receipt of the requirement by the sponsor.

CHAPTER VII

MONITORING AND NOTIFICATION OF SAFETY INFORMATION ON CLINICAL TRIALS

Section I

Safety Monitoring

Article 55. The sponsor must systematically collect, monitor, and evaluate all adverse events, including non-serious ones, that occur throughout the clinical development and be responsible for the safety of the clinical trial participants.

Sole paragraph. Safety information from other countries where clinical development is taking place must be communicated to Anvisa if it implies a change in the benefit-risk profile of the experimental medicinal product, including safety actions taken by other regulatory authorities.

Article 56. The sponsor must inform the investigators involved in the clinical trial about SUSARs (Suspected Unexpected Serious Adverse Reactions) and adopt procedures to update the investigator's brochure, in addition to reassessing the risks and benefits for the participants.

Article 57. Investigators must monitor and report to the sponsor, in accordance with the GCP and study protocol, the occurrence of all adverse events, including those that come to their attention after the end of the clinical trial. They must also provide any requested information and express their opinion regarding the causality between the adverse event and the investigational product.

Article 58. The sponsor must establish a monitoring plan to detect late adverse events, justifying the proposed period, which considers aspects of the investigational product, the participants, and the clinical trial.

Article 59. Throughout the clinical development of the experimental medicinal product, the sponsor and the investigator must adopt immediate safety measures to protect the clinical trial participants in the event of a serious adverse reaction or event.

Article 60. The clinical trial participant affected by an adverse event must receive care and appropriate safety measures must be taken until their clinical condition is resolved or stabilized, as described in the clinical protocol.

Article 61. It is desirable that an Independent Data and Safety Monitoring Committee (DSMB) be established.

Sole paragraph. The data collected by the sponsor must be submitted to the DSMB, if established, and the results of such assessment must be presented to Anvisa in the Development Safety Update Report (DSUR) of the experimental medicinal product and at any time, upon request by Anvisa.

Article 62 Anvisa shall issue a supplementary normative act on the safety monitoring of clinical trials.

Subsection I

Notification of SUSARs to Anvisa

Article 63. The sponsor is responsible for notifying adverse events to Anvisa, and the delegation of such activity to the Clinical Research Representative Organization (CRO) is permitted.

Article 64. The sponsor must notify all Suspected Serious and Unexpected Adverse Reactions (SUSARs) through the electronic notification system made available by Anvisa.

Sole paragraph. Regarding the assessment of causality, if the investigator's interpretation is different from that of the sponsor, both must be submitted with their respective justifications.

Article 65. The notification of SUSARs must be made independently of the submission of the Investigator's Brochure, amendments, reports, or early termination of the clinical trial.

Article 66. The notifications must be sent individually and contain all the information requested in the fields present in the electronic notification system and as provided for in ICH-E2A and its updates.

Article 67. If there is a possibility that an event is a SUSAR, the sponsor must break the blinding for notification to Anvisa and the break must be only in relation to the allocation of the participant who was affected by the serious and unexpected adverse reaction.

Paragraph 1. If after breaking the blinding the event is classified as a SUSAR, follow the provisions of Article 64 and the allocation of the participant in the arm of the clinical trial must be informed in the SUSAR notification to Anvisa.

Paragraph 2. Whenever possible, blinding must be maintained for those responsible for analyzing and interpreting the study results and for those responsible for continuing the clinical trial, such as study managers, monitors, and investigators.

Article 68. When an event is related to the disease and represents a primary efficacy outcome of a clinical trial, the protocol must clearly define the event in question, and it will not be subject to notification.

Sole paragraph. If the event described in the caption of this article is characterized as a SUSAR, that is, when there is a reasonable possibility of a causal relationship between the event and the experimental medicinal product or active comparator, this must be notified, as it may be a possible change in the safety profile.

Article 69. Medication errors, pregnancy, or uses not provided for in the protocol, including misuse and abuse of the investigational product, are subject to the same notification obligations as adverse reactions.

Sole paragraph. In the case of pregnancy, the investigator and the sponsor must monitor the mother and child.

Subsection II

Deadlines for Notification of SUSARs

Article 70. The investigator must inform the sponsor about serious adverse events within 24 (twenty-four) hours from the date of knowledge of the event.

Article 71. Notifications of SUSARs that are fatal or life-threatening must be reported to Anvisa within a maximum period of 7 (seven) calendar days from the date the sponsor becomes aware of the case.

Sole paragraph. Additional information on the monitoring of SUSAR events mentioned in the caption of this article must be forwarded within 8 (eight) calendar days from the date of notification.

Article 72. Any other SUSARs, which are not fatal or life-threatening, must be notified to Anvisa within 15 (fifteen) calendar days counting from the sponsor becoming aware of the case.

Section II

Monitoring Reports

Subsection I

Annual Clinical Trial Monitoring Reports

Article 73. The sponsor must send Anvisa annual monitoring reports containing the following information, in tabulated form, for each clinical trial protocol:

I – title of the clinical trial and protocol code;

II – recruitment status and breakdown of the number of participants recruited per center in Brazil and worldwide;

III – number of centers in Brazil and worldwide and their respective status; and

VI – number of SAEs per participant and per center in Brazil, including the description of SAEs related to the experimental medicinal product or comparator, ADRs, SUSARs and whether or not the blinding was broken.

Paragraph 1. The annual clinical trial protocol monitoring report must be submitted to Anvisa in the form of a secondary petition attached to the process of the respective protocol to which it is linked.

Paragraph 2. The annual report must be filed within a maximum period of 60 (sixty) calendar days, with the annual reference being the start date of the clinical trial in Brazil.

Paragraph 3. After submitting the annual report containing all information up to the end of the clinical trial in Brazil, only the final clinical trial report must be submitted.

Subsection II

Final Clinical Trial Reports

Article 74. After the completion of the activities of a clinical trial in all participating countries, for whatever reason, the sponsor must submit to Anvisa a final report containing at least the following information:

I – title of the clinical trial and protocol code;

II – final recruitment status and breakdown of the number of participants recruited per center in Brazil and worldwide;

III – final number of centers in Brazil and worldwide;

VI – final number of SAEs per participant and per center in Brazil, including the description of SAEs related to the experimental medicinal product or comparator, ADRs, SUSARs and whether or not the blinding was broken;

VIII – reason for termination of the study and rationale for premature termination of development in Brazil or worldwide, when applicable.

Paragraph 1. The final report of the clinical trial protocol must be submitted to Anvisa in the form of a secondary petition attached to the process of the respective protocol to which it is linked.

Paragraph 2. The final report must be filed within 12 (twelve) months of the date of completion of the clinical trial.

Paragraph 3. In the year in which the final report is filed, the annual report may be waived.

Section III

Safety Update Report of the Development of the Experimental Medicinal Product

Article 75. The Safety Update Reports on the Development of the Experimental Medicinal Product (DSUR) must be sent annually to Anvisa, until the end of the clinical development of the experimental medicinal product in Brazil.

Sole paragraph. The safety update reports on the development of the experimental medicinal product (DSUR) must be prepared in accordance with the format described in the current version of ICH E2F and must be filed within a maximum period of 60 (sixty) calendar days, with the annual reference being the date of approval of the clinical trial in any country.

CHAPTER VIII

GOOD CLINICAL PRACTICE (GCP) INSPECTIONS

Article 76. In order to ensure the protection of the rights, safety, and well-being of clinical trial participants, as well as the accuracy and reliability of the data to be obtained or submitted for health marketing authorization, Anvisa may conduct GCP inspections at clinical trial centers, sponsors, CROs, laboratories, and other institutions involved in the development of the experimental medicinal product to verify the degree of adherence to current Brazilian legislation and compliance with GCP, in addition to ensuring the rights and duties of the scientific community and the State.

Sole Paragraph. GCP inspections shall follow the harmonized guidelines of ICH E6 (R2) and its updates, in addition to specific GCP inspection standards issued by Anvisa.

Article 77. Alternatively, Anvisa may carry out the inspection in a completely remote or hybrid manner, replacing the completely in-person health inspection, for the purpose of verifying compliance with Good Clinical Practices (GCP).

Paragraph 1. Remote inspection shall be carried out by means of videoconferencing and data transmission technologies or others to be defined by Anvisa in specific complementary procedures and guidelines.

Paragraph 2. Establishments inspected remotely may be inspected in person at any time by Anvisa.

Article 78. Depending on the result of the GCP inspection, Anvisa may determine:

I – the temporary suspension of the clinical trial;

II – the definitive cancellation of the clinical trial at the center in question;

III – the definitive cancellation of the clinical trial at all centers in Brazil;

IV – the invalidation of data from centers, sponsors, CROs, and clinical trials that are not in compliance with the GCP;

V – the temporary suspension of the activities of the center, sponsor, or CRO related to clinical trials;

VI – the definitive cancellation of the clinical trial(s) conducted by the sponsor/CRO.

Paragraph 1. For the purposes described in the caption of this article, the sponsor will be notified and Anvisa may open an administrative or investigation process, in accordance with current legislation.

Article 79. Anvisa may inspect any clinical trials that subsidized or subsidize the clinical development or marketing authorization of the medicinal product in Brazil, including those conducted outside the country.

CHAPTER IX

INSPECTIONS OF GOOD MANUFACTURING PRACTICES OF EXPERIMENTAL MEDICINAL PRODUCTS (GMP)

Article 80. Anvisa may conduct GMP inspections of the experimental medicinal product produced by the sponsor in order to verify the information and data presented in the DDCM and whether the experimental medicinal product is sufficiently safe to be administered to the participants of the clinical trial.

Sole paragraph. The scope of the caption of this article includes the GMP of experimental medicinal products involving a production stage by ionizing radiation (radiopharmaceuticals).

CHAPTER X

IMPORT OF INVESTIGATIONAL PRODUCTS

Article 81. The import of investigational products for exclusive use in clinical trials shall be subject to the registration of licenses, permits, certificates, and other documents on the Single Foreign Trade Portal, and shall be subject to inspection by the health authority, and shall comply with Chapter XXVI of RDC No. 81 of 5 November 2008, its updates or any other version that may replace it.

Sole paragraph. Investigational products subject to special control of lists A1, A2, A3, B1, B2, C3, D1, E, and F of SVS/MS No. 344 of 12 May 1998 and its updates, in addition to complying with

Chapter XXVI of RDC 81/2008 and its updates or any other that may replace it, must comply with Procedure 1 or 1A of the aforementioned regulation, as well as with RDC No. 659 of 30 March 2022 and its updates or any other that may replace it.

Article 82. Information on investigational products to be imported for use in clinical trials will be included in the Import Document (ID).

Paragraph 1. Changing the import purpose of the goods and products covered by this Resolution is prohibited without due authorization from Anvisa.

Paragraph 2. Any change to the information on investigational products contained in the ID may only be made upon request to the clinical research technical area.

Article 83. A single Import Document (ID) shall be issued per DDCM, mentioning all clinical trials to be conducted in Brazil.

Paragraph 1. Only authorized clinical trials, as published in the Federal Official Gazette, may be initiated in the country, respecting other pertinent ethical approvals.

Paragraph 2. Anvisa shall issue the ID within 30 business days from the date of filing of the DEEC petition for the import of investigational products necessary for carrying out the clinical development before the approval or rejection of the DDCM and DEEC petitions published in the Federal Official Gazette. The import of products prior to publication in the Federal Official Gazette is at the discretion and responsibility of the sponsor.

Paragraph 3. In the case of Paragraph 2, the investigational products must be stored in a protected area, under the control of the sponsor, and may only be distributed to the locations where they will be used after the approval of the DDCM and DEEC petitions published in the Federal Official Gazette.

Paragraph 4. The use of any investigational product imported by means of ID before the approval of DDCM and DEEC petitions published in the Federal Official Gazette constitutes a health violation and subjects the offender to the penalties provided for in Law No. 6,437 of 20 August 1977, and in specific health regulations, without prejudice to applicable civil and criminal sanctions.

Paragraph 5. In the event of rejection of the DDCM and corresponding DEEC and prior import of the investigational products, the sponsor must submit, by means of a petition to amend the DDCM process, a document informing the destination or destruction of the investigational products. This document must be submitted to Anvisa within a maximum period of 60 business days from the publication of the rejection of the DDCM and respective DEEC and must contain information on the destination given to the investigational products and their respective quantities compatible with what was previously imported.

CHAPTER XI

START AND END, SUSPENSION OR CANCELLATION OF CLINICAL TRIAL OR DDCM

Article 84. Forms indicating the start and end date of the clinical trial in Brazil must be filed in the form of a secondary petition to the corresponding DEEC process, within 30 (thirty) business days after each start and end date.

Article 85. The sponsor may suspend or cancel an approved DDCM or clinical trial at any time, provided that the appropriate justifications are submitted, as well as a plan for monitoring participants, in case the clinical trial has been initiated.

Paragraph 1. Once a DDCM has been canceled, no clinical trial related to it may be continued in Brazil.

Paragraph 2. If a DDCM or clinical trial is canceled for safety reasons, the sponsor must describe the reasons for the cancellation and present the measures to minimize/mitigate risk to the clinical trial participants.

Paragraph 3. Suspensions and cancellations must be filed with Anvisa, in the form of a secondary petition attached to the respective process within 15 (fifteen) business days after the decision to suspend or cancel a clinical trial or DDCM.

Paragraph 4. In cases of temporary suspension of the clinical trial or DDCM, as an immediate safety measure, the sponsor must notify Anvisa within 7 (seven) calendar days from the date of suspension, justifying the reasons.

Paragraph 5. The reasons, scope, interruption of treatment, and suspension of participant recruitment must be clearly explained in the notification of temporary suspension.

Paragraph 6. The request to reactivate a suspended clinical trial protocol or DDCM must be accompanied by the appropriate justifications and the sponsor must await authorization from Anvisa to restart the clinical trial.

Article 86. At any time, the sponsor may request the cancellation of secondary requests for substantial modifications to the investigational product and substantial amendments to the approved clinical protocol, presenting the appropriate justifications and clarifications on any impact of this decision on the related primary requests.

Article 87. Anvisa may, at any time, cancel or suspend the DDCM or any linked clinical trial or related secondary petitions, when:

Paragraph 1. It deems that the conditions for approval have not been met or if there are reports of safety, quality, or efficacy that significantly affect the participants of the clinical trial or affect the reliability or robustness of the data obtained from the clinical trial.

Paragraph 2. The participants are being exposed to significant and unreasonable risks.

Paragraph 3. The sponsor violates the rules described in this Resolution or fails to comply with the principles of Good Clinical Practices (GCPs) and GMP of the experimental medicinal product; and

Paragraph 4. To comply with the provisions in the caption of this article, Anvisa will notify the sponsor about the suspension or cancellation of the DDCM or clinical trial and will open an administrative and/or investigative process, in accordance with current legislation, when applicable.

Article 88. The sponsor may, at any time, request that Anvisa discontinue the analysis of DDCM, DEEC, and secondary petitions.

Sole paragraph. The request for discontinuance described in the caption of this article must be accompanied by the appropriate justifications and applies only to petitions on which Anvisa's decision has not yet been published in the Federal Official Gazette (DOU, in Portuguese).

Article 89. The temporary suspension, cancellation, reactivation, and discontinuation of DDCM, DEEC, and secondary petitions may only be implemented after Anvisa has issued a statement, which shall be issued within 30 (thirty) business days, by publishing its decision in the DOU. In the situations described in Paragraph 4 of Article 85, implementation must be immediate, and the analysis shall be carried out within 10 calendar days.

CHAPTER XII

FINAL AND TRANSITIONAL PROVISIONS

Article 90. The approval of DDCM, DEEC, and secondary petitions filed with Anvisa prior to the publication of this Resolution and still awaiting technical analysis shall be assessed in accordance with the rules and requirements in force at the time of submission, and the petitions may be requested to be included in the optimized analysis procedure, as established in this Resolution.

Article 91. Anvisa shall issue standards, guides, or manuals with additional guidelines for compliance with this Resolution, such as procedures that allow for greater speed in the analysis of primary and secondary clinical development petitions, including a continuous submission procedure to allow for the analysis of data as they are generated and submitted to Anvisa, without prejudice to the rules for prioritizing analysis established in regulations and without compromising the safety of clinical trial participants.

Article 92. Anvisa may, at any time, request other information that it deems necessary for the evaluation and monitoring of the clinical development.

Article 93. The clinical trial and/or experimental medicinal product approved through the optimized analysis procedure based on regulatory reliance practices or based on the experience of using the experimental medicinal product or released due to the lapse of time, may be inspected on site, which may result in a change in the decision, request for additional evidence, and any other necessary health measure, without prejudice to other applicable legal measures.

Article 94. In the case of clinical development involving genetically modified organisms – GMOs or derivatives, the interested party must consult the responsible body, the Brazilian Technical Commission on Biosafety (CTNBio, in Portuguese), in accordance with current legislation.

Article 95. Anvisa's decisions regarding authorization or non-authorization, cancellation or suspension, and reactivation of DDCM and/or clinical trials must be published in the Federal Official Gazette (DOU, in Portuguese) and publicized on Anvisa's website, with their respective status.

Article 96. Failure to comply with the provisions of this Resolution and the Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP) standards for experimental medicinal products constitutes a health violation, and the offender shall be subject to the penalties provided for in Law No. 6,437 of 20 August 1977, without prejudice to applicable civil and criminal sanctions.

Article 97. Omissions shall be resolved considering other Brazilian standards and international guidelines.

Article 98. The following are hereby revoked:

I – Collegiate Board Resolution – RDC No. 9 of 20 February 2015, published in the Federal Official Gazette No. 41 of 3 March 2015, Section 1, page 69; and

II – Collegiate Board Resolution – RDC No. 449 of 15 December 2020, published in the Federal Official Gazette No. 241 of 17 December 2020, Section 1, page 173.

Article 99. This Resolution shall come into force 30 days after the date of its publication.

ANTONIO BARRA TORRES

Director-President