NORMATIVE INSTRUCTION – IN NO. 338 OF 29 NOVEMBER 2024

Establishes, in accordance with Anvisa Collegiate Board Resolution RDC no. 945 of 29 November 2024, the list of Equivalent Foreign Regulatory Authorities (EFRAs) and details the criteria to adopt the optimized analysis procedure through regulatory reliance, as well as through risk and complexity assessment of applications for DDCM, DEEC, substantial alterations in the investigational product, and substantial amendments to the clinical protocol.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 7, item III, and Article 15, items III and IV, of Law no. 9,782 of 26 January 1999, and considering the provisions of Article 187, item VII, and Paragraphs 1 and 3 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Normative Instruction, as decided upon in a meeting held on 27 November 2024, and I, the Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Article 1. This Normative Instruction establishes, in accordance with Collegiate Board Resolution RDC no. 945 of 29 November 2024, the categories of risk and complexity of clinical trials, the complexity of investigational products, the identification of Equivalent Foreign Regulatory Authorities, and the optimized analysis procedure for Medicinal Product Clinical Development Dossier (DDCM, in Portuguese), Specific Clinical Trial Dossier (DEEC, in Portuguese), substantial alterations in the investigational product, and substantial amendments.

Article 2. The optimized analysis procedure is applicable to primary petitions for DDCM and DEEC and to secondary petitions for substantial alterations in the investigational product, and substantial amendments to the clinical protocol.

Article 3. For the purposes of this Normative Instruction, the following definitions are applicable:

I – Equivalent Foreign Regulatory Authority (EFRA): foreign regulatory authority or international entity with regulatory practices aligned with Anvisa's, which may be considered by Anvisa in regulatory reliance practice;

II – Low-Risk Clinical Trial Category: Phase 3 clinical trials with medicinal products or therapies with known safety profile, which represent a minimum additional risk to the safety of clinical trial participants, compared to the usual medical practice, in the following situations:

a) medicinal product used as established in the marketing authorization in Brazil or approved by an EFRA, without substantial alterations;

b) new therapeutic indication and/ or target population and/ or dosage regimen, supported by robust scientific literature evidence based on meta-analysis, systematic reviews of scientific articles published in an indexed journals including information on the safety and efficacy of the medicinal product or API;

c) fixed-dose combinations with active pharmaceutical ingredients granted marketing authorization and already used concomitantly in medical practice, in the same indication applied for, target population, and dosage regimen (without clinically significant pharmacokinetic interactions and/ or clinically significant pharmacodynamics);

III – Moderate-Risk Clinical Trial Category: clinical trials with medicinal products or therapies with known safety profile, or with approved DDCM, with substantial alterations, representing additional medium risk to the safety of clinical trial participants, compared to the usual medical practice, in the following situations:

a) new therapeutic indication and/ or target population and/ or dosage regimen;

b) new pharmaceutical form and/ or concentration;

c) new administration route;

d) biosimilar products;

e) medicinal product granted marketing authorization in Brazil or approved by an EFRA, altered to be used in the clinical trial;

f) fixed-dose combinations with active pharmaceutical ingredients granted marketing authorization and already used concomitantly in medical practice, in the same indication applied for, target population, and dosage regimen (with clinically significant pharmacokinetic and/ or pharmacodynamic interactions);

IV – High-Risk Clinical Trial Category: clinical trials with new medicinal products or therapies, representing high risk to the safety of clinical trial participants, in the following situations:

a) new medicinal products;

b) fixed-dose combinations with one or more active pharmaceutical ingredients not granted marketing authorization;

c) combinations of active pharmaceutical ingredients granted marketing authorization considering a new therapeutic indication;

V – Specific Clinical Trial Dossier (DEEC, in Portuguese): set of documents to be submitted to Anvisa with the purpose of obtaining information related to the clinical trials to be conducted in Brazil and that are part of the Experimental Medicinal Product Development Plan;

VI – Medicinal Product Clinical Development Dossier (DDCM, in Portuguese): set of documents to be submitted to Anvisa with the purpose of assessing the stages inherent to the development of an experimental medicinal product with a view to obtaining information to support marketing authorization or post-marketing authorization alterations in that product;

VII – Clinical trial: any interventional clinical study with humans aiming at finding or confirming clinical and/ or pharmacological effects and/ or any other pharmacodynamic effects of the experimental medicinal product and/ or identifying any adverse reaction to the experimental

medicinal product and/ or studying absorption, distribution, metabolism, and excretion of the experimental medicinal product to verify its safety and/ or efficacy;

VIII – Complex clinical trial: unconventional clinical trial meaning it has elements, characteristics, methods, or their combination, including new approaches, which provide complexity to its design, conduction, analyses, or reports, as in the following cases:

a) trials that study multiple therapies or multiple indications in a single clinical trial, called master protocols (Basket trials, Umbrella trials, Platform trials);

b) new designs of adaptive trials that allow alterations planned in the study protocol to occur in pre-specified moments during the life cycle of a trial;

c) Phase 1 clinical trials, where the experimental medicinal product is being used for the first time in humans (First in Human – FIH);

d) Phase 1, 2, and 3 clinical trials integrated in a single protocol;

e) clinical trials with interim analyses;

f) pragmatic clinical trials or clinical trials with real world data (RWD);

g) clinical trials with vulnerable populations, such as children, pregnant women, and lactating women.

IX – Pragmatic clinical trial: type of clinical trial designed to compare an intervention and a comparator in participants more similar to those affected by the conditions in routine clinical practice environments.

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

XI – Complex investigational product: product that involves formulations and/ or pharmaceutical inputs or active substances with physico-chemical or biological characteristics that provide complexity, as in the following cases:

a) active substances or complex active pharmaceutical inputs, including monoclonal antibodies (mAbs), conjugated antibodies or fractions of conjugated antibodies, hormones, substances derived from recombinant DNA (rDNA) technology, mRNAs, blood coagulation factors, products derived from human tissues, polymeric compounds, complex mixtures of natural origin (herbal medicines), synthetic nucleotides, peptides or oligopeptides, synthetic substances of high molecular weight, enzymatic products;

b) complex pharmaceutical forms, including liposomes, microspheres, nanocrystals, polymeric particles, nanosuspensions and nanoemulsions, injectable implants;

c) combination of medicinal products with medical devices, such as injection pens, filled syringes, and other devices;

d) biosimilar products;

e) prophylactic and therapeutic vaccines.

XII – Reliance: act through which Anvisa may consider and give significant weight to the analyses carried out by a reliable Equivalent Foreign Regulatory Authority (EFRA), as single or complementary reference, to support its decisions.

CHAPTER II

APPLICATION OF THE OPTIMIZED ANALYSIS PROCEDURE

Article 4. The optimized analysis procedure may be applied based on regulatory reliance practices and based on the risk assessment supported by the Experimental Medicinal Product use experience.

Sole paragraph. For an adequate identification of the situations where the optimized analysis procedure may be applied, the sponsor shall fill up a specific form of petition characterization made available by Anvisa.

Section I

Based on regulatory reliance practices

Article 5. For the application of the optimized analysis procedure based on regulatory reliance practices, the versions of the Investigational Medicinal Product Dossier (IMPD), the clinical protocol, or the substantial amendment to the clinical protocol submitted to Anvisa must be the same versions approved by at least one of the following EFRAs:

1 – European Medicines Agency (EMA) and its member countries;

2 – Health Canada (HC);

3 – Swiss Agency for Therapeutic Products (Swissmedic);

4 – United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA);

5 – US Food and Drug Administration (FDA);

6 – Japan Pharmaceuticals and Medical Devices Agency (PMDA).

Sole paragraph. Exclusion or inclusion of new EFRAs shall be decided upon by Anvisa Collegiate Board (DICOL, in Portuguese).

Article 6. Among the documents required to submit each type of petition, in accordance with Collegiate Board Resolution – RDC no. 945 of 29 November 2024, the optimized analysis procedure based on regulatory reliance practices may be applied to the following documents:

I – investigator's brochure, except in the cases of complex clinical trials, prophylactic and therapeutical vaccines, and biosimilar products;

II – Active Pharmaceutical Input Dossier and Investigational Medicinal Product Dossier;

III – clinical trial protocol, except in the cases of complex clinical trials, prophylactic and therapeutical vaccines, and biosimilar products.

Article 7. The petition for optimized analysis procedure based on regulatory reliance practices may be submitted by the sponsor at any time, via secondary petition, before the correspondent petition analysis starts.

Paragraph 1. If the requirements to apply the optimized analysis procedure based on regulatory reliance practices are complied with, the status of the secondary petition shall be updated to "Approved".

Paragraph 2. In case of non-compliance with the requirements to apply the optimized analysis procedure based on regulatory reliance practices, the status of the secondary petition shall be updated to "Not approved", and the full analysis of all documents related to the petition shall be carried out, as provided for in Collegiate Board Resolution – RDC no. 945 of 29 November 2024.

Paragraph 3. In the case described in Paragraph 2, a letter shall be sent to the company with the respective justification.

Section II

Based on the risk assessment supported by the Experimental Medicinal Product use experience

Article 8. Among the documents required to submit each type of petition, in accordance with Collegiate Board Resolution – RDC no. 945 of 29 November 2024, the optimized analysis procedure based on risk assessment may be applied to the following documents:

I – investigator's brochure, in the case of risk categories as defined in item II, letters "a" and "c" of Article 3;

II – Investigational Medicinal Product Dossier, in the case of low-risk clinical trials categories and item III, letter "a" of Article 3.

Sole paragraph. For the purposes of the provisions in the caption of this article, in the cases of medicinal products granted marketing authorization in Brazil or approved by an EFRA, medicinal products altered to be used in clinical trials, and fixed-dose combinations with active pharmaceutical ingredients granted marketing authorization and already used concomitantly in medical practice, in the same indication applied for, target population, and dosage regimen (without clinically significant pharmacokinetic interactions and/ or clinically significant pharmacodynamics), the IMPD information related to the alterations made shall be analyzed.

CHAPTER III

FINAL PROVISIONS

Article 9. Adoption of the optimized analysis procedure as established in this Normative Instruction does not bar Anvisa from reassessing petitions, at any time, through ordinary analysis.

Article 10. Anvisa is exclusively responsible for the decisions on petitions submitted through the optimized analysis procedure based on regulatory reliance practices, and such decisions are not bound to decisions and conditions approved by the EFRA.

Article 11. Failure to comply with the provisions contained in this Normative Instruction constitutes a health infraction, in accordance with Law no. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 12. This Normative Instruction enters into force 30 days after its publication.

ANTONIO BARRA TORRES

Director-President