ANVISA
Agência Nacional de Vigilância Sanitária

DOSSIER SUBMISSION MANUAL CLINICAL DEVELOPMENT OF MEDICINE (DDCM) AND DOSSIER CLINICAL TRIALS SPECIFIC (DEEC)

COORDINATION OF CLINICAL RESEARCH IN MEDICINES AND BIOLOGICAL PRODUCTS (COPEC)

SECOND DIRECTORATE (DIRE2)

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MANUAL FOR SUBMISSION OF DOSSIERS CLINICAL DEVELOPMENT OF MEDICINE (DDCM) AND SPECIFIC DOSSIER CLINICAL TRIAL (DEEC)

4th

This Manual aims to guide professionals in the field with information on how to apply RDC No. 945, of November 29, 2024, contributing to the development of safe actions, in addition to providing relevant and updated information that can be better clarified through the Manual instrument.

The Manual does not create new obligations and should be used by public and private agents as a reference for compliance with existing legislation. existing.

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Summary

1. ACRONYM

Anvisa – National Health Surveillance Agency
AREE – Equivalent Foreign Regulatory Authority
BI – Researcher's Brochure
GCP – Good Clinical Practices
GMP – Good Manufacturing Practices
GLP – Good Laboratory Practices
DDCM – Clinical Drug Development Dossier
DEEC – Specific Clinical Trial Dossier
DI – Import Document
DOU – Official Gazette of the Union
DPI – Investigational Product Dossier
DSUR – *Development Safety* Update Report
Development of Experimental Drug)
FAEC – Clinical Trial Submission Form
ICH – *International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use* (ICH)
API – Active Pharmaceutical Ingredient
IMPD – *Investigational Medicinal Product Dossier*
IN – Normative Instruction
ORPC – Clinical Research Representative Organization
PAE – Statistical Analysis Plan
PDME – Investigational Drug Development Plan
RDC – Resolution of the Board of Directors
RSI – Reference Safety Information

2. INTRODUCTION

This manual is intended to provide guidance for the sponsor, sponsor-investigator or ORPC to instruct and submit the Clinical Drug Development Dossiers (DDCMs) and Specific Clinical Trial Dossiers (DEECs) in an appropriate manner.

This is a non-binding regulatory measure adopted as a complement to health legislation, with the educational purpose of providing guidance on routines and procedures for compliance with the legislation, and is not intended to expand or restrict established technical or administrative requirements.

3. LEGAL BASIS

Resolution of the Collegiate Board - RDC No. 945, of November 29, 2024, which provides on the guidelines and procedures for conducting clinical trials in the country with a view to subsequently granting drug registration.

Normative Instruction No. 338, of November 29, 2024, which establishes, under the terms of ANVISA Collegiate Board Resolution No. 945, of November 29, 2024, the list of Equivalent Foreign Regulatory Authorities (AREEs) and details the criteria for the adoption of the optimized analysis procedure by reliance and by risk and complexity assessment of petitions for DDCM, DEEC, substantial modifications to the product under investigation and substantial amendments to the clinical protocol, as amended by Normative Instruction No. 345, of February 20, 2025.

4. OBJECTIVE

Without prejudice to the provisions existing in the legal provisions, this manual aims to guide and explain in a complementary manner the submissions of Clinical Drug Development Dossiers (DDCM) and Specific Clinical Trial Dossiers (DEEC), as described in chapter III of RDC No. 945/2024.

We recommend that the submission format be standardized in terms of order and content of documents, aiming for speed in evaluation.

5. SUBMISSION OF DDCM AND DEEC

5.1 DDCM SUBMISSION

According to RDC No. 945/2024, the Drug Clinical Development Dossier (DDCM) is the compilation of documents to be submitted to Anvisa for the purpose of evaluating the stages inherent to the development of an experimental drug with a view to obtaining information to support the registration or post-registration changes of said product.

For the electronic petition of a DDCM at Anvisa, the regulated sector must inform one of the following primary petition subjects:

- 10750 - CLINICAL TRIALS - Approval in Process of the Dossier Clinical Drug Development (CDDD) – Synthetics
- 10754 - CLINICAL TRIALS - Approval in Process of the Dossier Clinical Drug Development (CDDD) – Biological Products
- 10752 - CLINICAL TRIALS - Approval in Process of the Dossier Clinical Drug Development (DDCM) – Phytotherapeutics, Specific, Dynamized, Medical gases
- 10748 - CLINICAL TRIALS - Approval in Process of the Dossier Clinical Drug Development (CDDD) – Radiopharmaceuticals

- 10751 - CLINICAL TRIALS - Approval in Process of Dossier Clinical Drug Development (CDDD) of ORPCs – Synthetic
- 10755 - CLINICAL TRIALS - Approval in Process of the Dossier Clinical Drug Development (CDDD) of ORPCs – Products Biological
- 10753 - CLINICAL TRIALS - Approval in Process of the Dossier Clinical Drug Development (CDDD) of ORPCs – Phytotherapeutics, Specific, Dynamized, Medical gases
- 10749 - CLINICAL TRIALS - Approval in the process of the Dossier Clinical Drug Development (CDDD) of ORPCs – Radiopharmaceuticals

The specific *checklist* for the aforementioned subjects can be consulted on the Anvisa website and follows the description of the items contained in the current regulation.

Consultations - National Health Surveillance Agency

The applicant must submit a DDCM to Anvisa only if he/she intends to conduct clinical trials with drugs that will have all or part of their clinical development in Brazil for registration purposes. The DDCM applies only to the development of an experimental drug. For the purposes of DDCM analysis, at least one specific clinical trial dossier (DEEC) to be conducted in Brazil must be filed.

The documents of a DDCM must be filed electronically with Anvisa, according to a specific checklist for the subject in question.

5.2 DEEC SUBMISSION

According to RDC No. 945/2024, the Specific Clinical Trial Dossier (DEEC) is the 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 Drug Development Plan (PDME).

DEECs must be submitted as primary petitions and, therefore, will have a process number, with specific subjects for each clinical trial that is to be carried out in Brazil and that have not yet been submitted to Anvisa.

DEECs can be submitted to Anvisa as one of the following subjects:

- 10482 - CLINICAL TRIALS – Approval in Clinical Research Process – Synthetic Medicines
- 10479 - CLINICAL TRIALS – Approval in Clinical Research Process – Biological Products
- 10476 - CLINICAL TRIALS – Approval in Clinical Research Process – Phytotherapeutics, Specific, Dynamized, Medicinal gases
- 10773 - CLINICAL TRIALS – Approval in Clinical Research Process – Radiopharmaceuticals

- 10483 - CLINICAL TRIALS – Approval in the Clinical Research Process of ORPCs – Synthetic Medicines
- 10478 - CLINICAL TRIALS – Approval in the Clinical Research Process of ORPCs – Organic Products
- 10477 - CLINICAL TRIALS – Approval in the Clinical Research Process of ORPCs – Phytotherapeutics, Specifics, Dynamized, Medicinal gases
- 10774 - CLINICAL TRIALS – Approval in the Clinical Research Process of ORPCs – Radiopharmaceuticals

DEECs can be petitioned by institutions with CNPJs different from those informed in the DDCM.

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To petition for the aforementioned matters, the DDCM process number to which the petition for Approval in Clinical Research Process must be linked must be provided, as the system does not allow these matters to be petitioned without belonging to a DDCM.

The specific *checklist* for each subject mentioned can be consulted on the Anvisa website and it follows the description of the items required by the current regulation.

The petition and protocol must be filed electronically. For each item contained in the checklist of these petitions, the applicant will be required to attach at least one file. For greater clarity, we recommend that the protocol attachment be identified as "Protocol version XX of DD/MM/YYYY".

It should be noted that only DEECs for clinical trials to be conducted in Brazil should be petitioned. Only dossiers that already have clinical and non-clinical basis for initiation should be filed. If an Experimental Drug Development Plan (PMDE) is submitted in full, containing phase 1, 2 and 3 clinical trials, but studies are still being conducted in the initial phases, which are not capable of supporting later phase clinical trials, the phase 3 clinical trial, for example, should not be initially petitioned at Anvisa. This clinical trial may be petitioned when there is already sufficient clinical and non-clinical basis for its initiation. It may be included later as a petition according to the subject codes listed above.

Although the submission of a DEEC petition to Anvisa is only for clinical trials that will be conducted in Brazil, in the PDME (described in detail in section 6) all trials planned for that experimental drug, whether they will be conducted in Brazil or not, must be described.

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6. DDCM DOCUMENTS

For the submission of DDCM, Section II of Chapter III of RDC No. must be followed. 945/2024. We recommend that all documentation be submitted in Portuguese, especially the clinical protocol, the PMDE and the investigator's brochure, as established in RDC 947/2024, which provides for the procedures for filing documents within the scope of the National Health Surveillance Agency –
Anvisa, the technical area evaluator may issue a requirement requesting a free translation of the documentation presented. What is expected of some documents that make up the DDCM to assist in the submission of the dossier is described in the following sections.

6.1 EXPERIMENTAL MEDICINE DEVELOPMENT PLAN (PDME)

The preparation of a PDME by the study sponsor allows the definition of objectives and methodologies that make it possible to identify critical stages and challenges of the process and plan monitoring actions based on established indicators. The information available on the experimental drug should support the proposed clinical indication, the target population and the types of designs proposed for the clinical trials.

The PDME must explain the steps necessary for the clinical investigation of the experimental drug. In short, this plan must demonstrate the rationale for the
development of the drug, foreseeing all the steps already executed, in progress and those intended for the clinical investigation of the drug. The PDME must also indicate the clinical trials that were, are being or will be carried out outside Brazil.

The Development Plan must begin with a brief description of the experimental drug, stating the API or active substance, drug category, therapeutic class, pharmaceutical form, concentration and route of administration. The indication(s) must be technically justified by means of the mechanism of action of the experimental drug, demonstrating that it is directly or indirectly involved in the therapeutic or diagnostic effect. In addition, it must be stated whether the mechanism of action is innovative. This topic should only present the indication(s) proposed in the Development Plan.

The sponsor must also inform the general objectives, listing all intended indications for the experimental drug, even those that are not yet being investigated in the submitted Development Plan. It is important to note that the PDME must address the entire clinical development of the experimental drug and not be restricted to the protocol submitted to the DDCM. Therefore, the technical justification must be described for the clinical development as a whole. In addition, the expected duration of the proposed clinical development must be informed.

Additionally, the sponsor must submit a list, in tabular form, of the countries where clinical development has been submitted, including details on the regulatory and ethical approval status, and respective clarifications or justifications in the

cases of approval under reservation, rejection, interruption or cancellation of clinical development in any of the countries where it was submitted.

It is recommended that a table or schematic drawing containing all clinical trials planned for clinical development over a given period be submitted, as well as the progress of these trials (completed, ongoing or planned).

In the Plan, the Sponsor must also report on the receipt, if any, of scientific advisory opinions from any foreign regulatory authority, regarding the clinical development of the experimental drug. The respective opinions must be attached to the PDME. It is important to note that if there are specific scientific advisory opinions for the DEEC that will be petitioned to the DDCM, these must be sent in the DEEC dossier and not in the PDME, as per item “d” of section VI of Art. 28 of RDC 945/2024.

To make things easier, Anvisa has developed a PDME model to be used when submitting the DDCM, as per Annex 1 of this Manual.

Anvisa recognizes that the PDME is not static and that it can be changed throughout the development of the experimental drug.

An updated version of the PDME must always be requested from Anvisa with the subject code “12373 - CLINICAL TRIALS - Notification of Update of Experimental Drug Development Plan” in cases of inclusion of new clinical trials not previously foreseen in the PDME and which will be the subject of DEECs to be linked to a DDCMs and exclusion of protocols cited in the PDME in which the corresponding DEECs were not submitted.

Updates should be submitted with the changes highlighted.

Regarding primary petitions for DDCMs or DEECs and secondary petitions for which there has not yet been a decision from Anvisa published in the Official Gazette of the Union (DOU), if the company is no longer interested in the evaluation, it must submit the Withdrawal request using the specific subject code.

If Anvisa's decision on primary petitions for DDCMs or DEECs and secondary petitions has already been published in the Official Gazette of the Union (DOU) and the company is not interested in continuing with clinical development, it must request cancellation of the petition by the specific subject code.

The results of clinical trials already carried out should not be presented in the Development Plan. These results should be presented in the Investigator's Brochure.

If the experimental drug is already registered in Brazil, only the information that supports the proposed post-registration changes must be submitted in the PDME.

6.2 INVESTIGATOR'S BROCHURE (BI)

The Investigator's Brochure (IB) is a document that contains a compilation of non-clinical and clinical data on an investigational medicinal product that are relevant to the study in humans. Its purpose is to provide investigators and others involved in the conduct of the clinical trial with information regarding the dose, dosage regimen, methods of administration and safety monitoring procedures. The IB also provides support for monitoring clinical trial participants during the course of the trial. The information should be presented in concise, clear, simple and objective language to better guide investigators in conducting the clinical trial.

Depending on the development phase of the experimental drug and its category, the level of detail of the information available may vary. If a drug already on the market is being investigated for a new therapeutic indication, an expansion of use to a new population, a new dosage regimen, new combinations or any post-registration change that requires clinical data, the BI must contain information that justifies and supports this new condition.

The BI must contain the minimum information described in item 7 of ICH Guide E6(R2) and its updates.

The Brochure is expected to have a section identified as “Reference Safety Information” , as per item “c” of section IV of Art. 28 of RDC 945/2024. If this is not the case, the sponsor must submit this list attached to the BI. The main purpose of the Reference Safety Information (RSI) is to serve as a basis for assessing whether or not ‘suspected’ serious adverse reactions are expected and therefore subject to immediate notification to the agency.

For phase 1 clinical trials involving the use of an experimental drug for the first time in humans (First-*in-human,* FIH), the applicant must attach reports of toxicity studies and detailed pharmacokinetics and pharmacodynamics, as a complement to the BI, as soon as they are available. These reports may be submitted separately or in the BI itself, as long as they are duly highlighted.
It is recommended to use the report template available in the CTD ICH M4S guide.
Other models may be used, as long as they contain the information described in this ICH guide. Furthermore, it is necessary to clearly justify and support the choice of dose that will be used in this study in the BI.

During clinical development, for any clinical trial that aims at a new therapeutic indication, a new population, new dosage regimen, new associations or any change not previously studied, the updated version of the BI must be submitted with the changes highlighted (track-*changes format),* or a specific BI, through a secondary petition to the DDCM (subject code 10821 - CLINICAL TRIALS - Notification of Investigator's Brochure Update).

6.3 INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

The documents related to items a, b and c of the DPI/IMPD described in RDC No. 945/2024 will be addressed in a Normative Instruction (IN) dedicated to this topic. Until this IN is published, the quality dossier submission manuals currently available on Anvisa's website related to RDC 09/2015 may be used.

6.4 SPONSOR STATEMENTS

The following sponsor statements must be submitted in the DDCM:

a) Declaration of commitment to distribute and use investigational products only after authorization of the initial and subsequent DDCM and DEEC(s) corresponding (item II of Art. 28 of RDC 945/2024). This document should only be attached to the DDCM if the sponsor is interested in receiving the Import Document (DI) before the analysis and approval of the DDCM. If the company has attached the aforementioned declaration to the DDCM, the DI will be issued for advance import both for the initial clinical trials (DEECs) submitted together with the DDCM and for the clinical trials submitted after the approval of the DDCM.

b) 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 (item a of item VII of Art. 28 of RDC 945/2024);

c) Declaration that the completed or ongoing clinical trials were conducted in accordance with GCP and that the clinical trials to be conducted in Brazil will also be conducted in accordance with GCP.

with the clinical protocol, with this Resolution and with the GCP. If there is a GCP Certificate or equivalent document for completed or ongoing clinical trials, this must be attached to the DDCM (item b of item VII of Art. 28 of RDC 945/2024;

d) Declaration that the experimental drug/placebo used in completed or ongoing clinical trials were manufactured in

compliance with GMP and that the experimental drug/placebo to be used in clinical trials in Brazil will also be manufactured

in accordance with GMP, in accordance with current GMP legislation for experimental drugs. If there is a GMP Certificate or equivalent document for the experimental drug, it must be attached to the DDCM or to the petition for substantial modification to the

product under investigation, if applicable (item c of section VII of Art. 28 of RDC 945/2024).

7. DEEC DOCUMENTS

According to section VI of Art. 28 of RDC 945/2024, the following documents must make up the DEEC:

a) duly completed clinical trial presentation form (FAEC), in accordance with the model available electronically from Anvisa (https://www.gov.br/anvisa/pt- br/assuntos/medicamentos/pesquisaclinica/formularios-1); from the

b) clinical trial protocol containing the minimum information described in item 6 of ICH Guide E6 (R2) and its updates;

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

d) opinion of the scientific advisory board of any country/region, if any, on the clinical trial. If such opinion is available after approval by the DEEC, it must be submitted in the annual clinical trial monitoring report;

e) pediatric investigation plan of any country/region, if any. If such a plan is available after approval by DEEC, it must be submitted in the annual clinical trial monitoring report;

f) model of the experimental drug label, in accordance with IN No. 136/2022, which *provides for Good Manufacturing Practices complementary to Experimental Drugs.*

g) proof of registration of the clinical trial, in the same version as the clinical protocol submitted to Anvisa, in the registration database of the *International Clinical Trials Registration Platform* / World Health Organization (ICTRP/WHO) or others recognized by the *International Committee of Medical Journals Editors* (ICMJE) and the World Health Organization (WHO). If this proof is not available at the time of submission of the DEEC, it must be submitted together with the notification of start of the clinical trial.

8. ISSUANCE OF THE DOCUMENT FOR IMPORTATION OF PRODUCT(S) UNDER INVESTIGATION FROM THE DRUG CLINICAL DEVELOPMENT DOSSIER (DDCM)

The approval or rejection of petitions submitted to Anvisa and the release due to the expiration of the petition deadline, as per § 1° of Art. 52 of RDC 945/2024, will be published in the Official Gazette of the Union (DOU).

As described in Chapter X of RDC 945/2024, for each DDCM submitted, an Import Document (DI) will be issued, which is a document to be used in requests for import or export of investigational products, when necessary. The DI lists the investigational products to be imported for use in each clinical trial linked to the DDCM.

The DI will be issued by Anvisa within 30 business days from the date of filing of the DEEC petition, and may be before the approval or rejection of the DDCM petitions and respective initial DEECs, published in the DOU. The import of products before publication in the DOU is at the discretion and responsibility of the sponsor.

For the purposes of complying with the provisions of §1 of Art. 52 of RDC 945/2024, it is necessary for the company to have attached the declaration cited in item II, Art. 28 of RDC No. 945/2024, without which the Import Document (DI) will not be issued by Anvisa. Therefore, if the company is interested in anticipating the DI, it must attach the aforementioned declaration together with the DDCM documentation.

The advance issuance of the Import Document (DI), according to §2°, Art. 83 of RDC No. 945/2024, applies to the DDCM and DEECs submitted together with the DDCM. Therefore, this measure does not apply to cases of DEECs submitted after the approval of the DDCM.

According to §5° of Art. 83 of RDC 945/2024, in the event of rejection of the DDCM and corresponding DEEC or subsequent DEECs and prior importation of the products under investigation, the sponsor must submit to Anvisa a document informing the destination or destruction of the products under investigation and their respective quantities compatible with what was previously imported. 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 or subsequent DEECs, using the subject code “10046 - CLINICAL TRIALS - Notification of destruction of products under investigation”

9. SECONDARY PETITIONS

Secondary petitions must be linked to the respective specific processes, that is, secondary petitions related to a DDCM must be filed

along with the Clinical Drug Development Dossier Approval (DDCM) process. Some examples of DDCM petitions are:

- Substantial Modification to the Product Under Investigation;
- Investigational Drug Development Safety Update Report (DSUR);

- Cancellation of DDCM on Request;
- Global Transfer of Responsibility for DDCM;
- Temporary Suspension of DDCM;
- Reactivation of Suspended DDCM;
- PDME Update Notification;
- BI Update Notification.

Similarly, petitions related to DEECs should be linked to the respective clinical trial processes. Some examples of Clinical Trial Dossier petitions are:

- Change of Clinical Trial Submission Form (FAEC);
- Substantial Amendment to Clinical Protocol;
- Annual Clinical Trial Protocol Monitoring Report;
- Cancellation of Clinical Trial Protocol on Request;
- Global Transfer of Responsibility for Clinical Trial Protocol;
- Temporary Suspension of Clinical Trial Protocol;
- Reactivation of Suspended Clinical Trial Protocol

The correct linking of secondary petitions to the corresponding processes is essential for their analysis and traceability in Anvisa's electronic systems.

Secondary petitions must be filed electronically. For each item contained in the *checklist* of these petitions, the applicant will be required to attach at least one file.

In cases where the DDCM or DEEC have been prioritized, under the terms of RDC No. 204/2017 and RDC No. 205/2017 (Rare diseases) and their updates, the prioritization does not automatically extend to secondary petitions. The company must request prioritization of analysis at the time of filing each secondary petition, if applicable.

10. REQUEST FOR APPLICATION OF THE OPTIMIZED ANALYSIS PROCEDURE

The optimized analysis procedure may be applied based on regulatory confidence *(Reliance)* or based on experience in using the experimental drug.

The optimized procedure concerns the documentation that may be exempted from technical analysis, when the criteria described in IN No. 338/2024 are met for each of the specific situations. In the case of application of the optimized analysis procedure by regulatory confidence, these documents are: the Investigator's Brochure (BI), the Active Pharmaceutical Ingredient (API) and Investigational Product (DPI) Dossier and the clinical trial protocol. In the case of application of this procedure, based on the risk assessment by user experience, they are the same documents, except for the clinical protocol.

However, all documents required for the instruction of each type of petition or process must be submitted.

The optimized analysis procedure does not assume analysis prioritization.

10.1 BASED ON REGULATORY RELIANCE PRACTICES

According to IN No. 338/2024, the sponsor may request the application of the optimized analysis procedure based on regulatory trust practices *(reliance).* To do so, the applicant must file a secondary petition with one of the subject codes described below in the petition in which the optimized analysis procedure is requested:

12102 - CLINICAL TRIALS - Optimized analysis procedure for Approval in Clinical Research Process (DEEC)

12103 - CLINICAL TRIALS - Optimized analysis procedure for Amendment Substantial to the Clinical Protocol

12104 - CLINICAL TRIALS - Optimized analysis procedure for Approval in Clinical Drug Development Dossier (CDDD) Process

11634 - CLINICAL TRIALS – Optimized analysis procedure for Modification Substantial to the Product Under Investigation

Since these are secondary petitions, and considering that the petitioning system does not allow the linking of a secondary petition to another secondary petition, in the cases of petitions for amendment to a clinical protocol and modification of the product under investigation, the requests (codes 12103 and 11634) must be linked to the primary petitions of the DEEC and DDCM, respectively.

The request for the application of the optimized analysis procedure based on regulatory reliance practices *may* be filed by the sponsor at any time before the analysis of the corresponding petition begins.

In the case of a petition for DDCM and linked DEEC(s), for both to be analyzed in accordance with the optimized procedure, it is necessary to do the following:

requested in parallel and individually for each of the petitions (codes 12102 and 12104), including for each related secondary petition, if applicable.

As described in item II, Art. 6 of IN No. 338/2024, there are no restrictions on the application of the optimized analysis procedure for the Active Pharmaceutical Ingredient (API) and Investigational Product (DPI) Dossier or *Investigational Medicinal Product Dossier* (IMPD). Therefore, even in the case of complex clinical trials, prophylactic and therapeutic vaccines, and biosimilar products, the company may request the application of this procedure for the API and DPI Dossier of the DDCM or secondary petition, using subject codes 12102 and 11634, respectively, if they have been approved by at least one of the AREEs listed in IN No. 338/2024.

Instructions and details on documents to be submitted and situations in which *reliance* is applicable must be verified in RDC 945/2024 (Arts. 40 to 49) and in IN nº 338/2024.

10.2. BASED ON RISK ASSESSMENT SUPPORTED BY EXPERIENCE IN USE OF THE PRODUCT UNDER INVESTIGATION

According to IN nº 338/2024, the sponsor may request the application of the optimized analysis procedure based on the risk assessment supported by the experience of using the product under investigation.

There is no specific subject code for the request for application of the simplified analysis procedure based on the risk assessment supported by the experience of using the Experimental Drug (Section II, Art. 50 of RDC No. 945/2024 and Section II, Art. 8 of IN No. 338/2024).

Therefore, based on the description in the Sole Paragraph, Art. 4 of IN No. 338/2024, the company may request the application of the optimized analysis procedure by marking the option “(X) We request the application of the optimized analysis procedure, in accordance with Art. 8 of IN No. 338/2024” in the corresponding field of the Clinical Trial Submission Form (FAEC), or by answering “yes” to the question “Request for application of the optimized analysis procedure (based on the risk assessment supported by the experience of using the product under investigation), in accordance with Art. 8 of IN No. 338/2024” in the Petition Form for Substantial Modification of the Product under Investigation.

During this transition period, the technical area will screen the information provided by the sponsor in the Clinical Trial Submission Form (FAEC) and in the Petition for Substantial Modification of the Investigational Product Form to verify which petitions will meet the criteria for the application of the optimized procedure and analysis. Petitions that meet the criteria of IN No. 338/2024 will be subject to the optimized analysis procedure.

In the future, if necessary, the technical area may provide a specific subject code to request the application of the optimized analysis procedure based on the risk assessment.

12. GLOSSARY

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

II - Investigator's Brochure - compilation of clinical and non-clinical data on the experimental drug(s) that are relevant to their study in human beings;

III - Clinical Drug Development Dossier (DDCM) - compilation of documents to be submitted to Anvisa for the purpose of evaluating the stages inherent to the development of an experimental drug with a view to obtaining information to support the registration or post-registration changes of said product;

IV - Specific Clinical Trial Dossier (DEEC) - 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 Development Plan of the
Experimental Drug;

V - Import Document (DI) - document issued by Anvisa, used in requests for import or export of products under investigation, when necessary;

VI - 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;

VII - Clinical trial - research conducted on human beings with the aim of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental drug and/or identifying any adverse reaction to the experimental drug and/or studying the absorption, distribution, metabolism and excretion of the experimental drug to verify its safety and/or efficacy;

VIII - Active Pharmaceutical Ingredient (API) - any substance introduced into the formulation of a pharmaceutical form that, when administered to a patient, acts as an active ingredient. Such substances may exert pharmacological activity or another direct effect on the diagnosis, cure, treatment or prevention of a disease, and may also affect the structure and functioning of the human organism;

IX - 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 principal investigator;

X - Investigator-Sponsor - natural person responsible for conducting and coordinating clinical trials, alone or in a group, carried out under his/her immediate direction independently, developed with financial and material resources owned by the investigator, by national or international research funding entities, by private entities and other non-profit entities;

XI - Experimental drug - pharmaceutical product under test, subject to the DDCM, to be used in the clinical trial, with the purpose of obtaining information for its registration or post-registration;

XII - Clinical Research Representative Organization (ORPC) - any company regularly installed in national territory contracted by the sponsor or by the investigator-sponsor, which partially or fully assumes, with Anvisa, the sponsor's attributions;

XIII - Sponsor - person, company, institution or organization responsible for initiating, administering, controlling and/or financing a clinical study;

XIV - Placebo - formulation without pharmacological effect, administered to the clinical trial participant for the purpose of masking or acting as a comparator;

XV - Product under investigation - product used as an experimental medicine, active comparator or placebo or any other product to be used in a clinical trial;

XVI - Clinical Trial Protocol - 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;

XVII - Annual Clinical Trial Monitoring Report - annual document containing specific information on the conduct of a given clinical trial in centers in Brazil, in accordance with the clinical protocol and the
BPC;

XVIII - Development Safety Update Report *(DSUR)* - harmonized periodic report containing information on the safety and development of an investigational drug;

XIX - Active substance - is the substance with a pharmacological effect for the intended therapeutic activity, used in the production of a given biological product.

13. BIBLIOGRAPHICAL REFERENCES

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6. GUIDELINE FOR GOOD CLINICAL PRACTICE. ICH E6(R3). Available at: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf> Accessed on: 17/01/2025.

14. CHANGE HISTORY

Version	Changes made	Explanation and Justification
1st Edition	---	
2nd Edition	• Replacement throughout document of " Resolution that provides about the Regulation Sanitary for the conducting tests clinical with medicines in the Brazil" by **"RDC No. 09/2015"**	• Like the first edition from the Submission Manual had been finalized before the publication of the new standard, there was no still the definition of number of the new RDC. This has been fixed in this first review.

2nd Edition	• Changed the name of the petition subject to: Transfer Global Responsibility about DDCM (page 15).	• Change of name of subject of petition.
2nd Edition	• Changed the name of the petition subject to: Transfer Global Responsibility on Protocol of Clinical Trial (page 15).	• Change of name of subject of petition.
2nd Edition	• Removed section "Provisions "Transient"	• With more than a year of implementation of the DRC No. 09/2015, these transitional provisions lost their objects and no longer apply.
3rd Edition	• Inclusion of the following sentence in the 4th paragraph in item 6.1: “Inform, including, if the mechanism of action is innovative.”	• Information about the mechanism innovation of action is important to evaluate the rational of development clinical.
3rd Edition	• Inclusion of the following sentence in the 5th paragraph in item 6.1: “A technical justification for the development	• For the better understanding of what is the technical justification for development clinical.

	clinical must also be described."	
3rd Edition	• Inclusion of the following paragraph in item 6.1: "It is recommended that use of the model of plan of development available in Annex I of this Manual."	• Due to various problems identified in plans of development evaluated until the moment, COPEC developed a model of plan to facilitate document analysis by Anvisa.
3rd Edition	• Change of item "6.2. Dossier of the Medication Experimental" for item 6.3	• Correction of numbering
3rd Edition	• Inclusion of Annex I	• Provision of a plan template development for facilitate the analysis of document by Anvisa
4th Edition	• Section 1 Update - Acronym	• Exclusion of acronyms not used and inclusion of new acronyms
4th Edition	• Section 2 Update - Introduction	• Text reduction to bring more clarity
4th Edition	• Updates throughout the document	• Change of RDC 09/2015 for DRC 945/2024 and inclusion of IN 338/2024
4th Edition	• Section 5.1	• Description update of the subject codes

		10752, 10753, 10476 and 10477 • Paragraph deletion about petitioning electronic • Deletion of codes subject 10752, 10753, 10476 and 10477 •
4th Edition	• Section 5.2	• Description update of the subject codes 10476 and 1047 • Deletion of the code subject 550 • Minor changes in text for better clarity • Clarifications on the PDME
4th Edition	• Section 6.1, 6.2 and 6.3	• Text update to reflect the DRC requirements 945/2024
4th Edition	• Section 6.4	• Inclusion of new section relating to the declarations from the sponsor to reflect the requirements of RDC 945/2024
4th Edition	• Section 7	• Inclusion of new section related to documentation of the DEEC to reflect the

		DRC requirements 945/2024
4th Edition	• Section 8	• Text update to reflect the as changes described in the RDC 945/2024
4th Edition	• Section 10	• Inclusion of new section for detailing the optimized procedure analysis based on trust practices regulatory
4th Edition	• Section 11	• Inclusion of new section for detailing the optimized procedure analysis based on risk assessment supported by experience of use of the Product under investigation
4th Edition	• Section 12	• Update of definitions
4th Edition	• Section 13	• Update of references

ANNEX 1: Model Development Plan

Experimental Medicine (PDME)

https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/pesquisaclinica/formularios-1/modelo-v3-plano-de-desenvolvimento-rdc-945.docx