National Health Surveillance Agency

MANUAL FOR SUBMISSION OF DOSSIER OF CLINICAL DRUG DEVELOPMENT (DDCM) AND SPECIFIC CLINICAL TRIAL DOSSIER

General Medicines Management - GGMED

Coordination of Clinical Research in Medicines

e Biological Products – COPEC

2017

MANUAL FOR SUBMISSION OF DOSSIER OF CLINICAL DRUG DEVELOPMENT (DDCM) AND SPECIFIC CLINICAL TRIAL DOSSIER

This Manual aims to guide professionals in the field with information on how to apply Resolution RDC/Anvisa No. 09 of February 20, 2015, contributing to the development of safe actions, providing relevant and updated information that can be better clarified through the Manual instrument.

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

MANUAL FOR SUBMISSION OF CLINICAL DEVELOPMENT DOSSIER OF MEDICATION (DDCM) AND SPECIFIC CLINICAL TRIAL DOSSIER

Circulation: 3rd edition

Organization - Anvisa
General Medicines Management

Technical Review – Anvisa
Adriane Alves de Oliveira
André Luís Carvalho Santos Souza
Bruno by Paula Coutinho
Bruno Zago Franca Diniz
Candida Luci Pessoa e Silva
Carla Abrahao Brichesi
Carlos Augusto Martins Netto
Carolina Pingret Cintra
Claudio Nishizawa
Fanny Nascimento Moura Viana
Fernando Casseb Flosi
Flávia Regina Souza Sobral
Janaina Lopes Domingos
Kellen of Malaman Dew
Leonardo Fabio Costa Filho
Miriam Motizuki Onishi
Patricia Ferrari Andreotti
Ricardo Eccard da Silva
Sonia Costa e Silva

Layout and Review
Anvisa Publisher

Graphic project
Anvisa Publisher

Catalog Sheet:
Manual for Submission of Clinical Drug Development Dossier (DDCM) and Specific Clinical Trial Dossier / Brasília. Anvisa 2017

27 p.
DDCM; Specific Dossier; Clinical Trials.

SUMMARY

1. SIGLARY

ATCC - Anatomical Therapeutic Chemical Code
BI – Investigator Brochure
CE – Special Communiqué
DDCM - Clinical Drug Development Dossier
IFA – Active Pharmaceutical Ingredient
ORPC - Clinical Research Representative Organization
RDC – Collegiate Board Resolution

2. INTRODUCTION

The publication of regulations on Clinical Trials with medicines in Brazil now evaluates Development Plans and not just isolated protocols. This manual is intended to provide guidance for the sponsor, sponsor-investigator or ORPC to submit Drug Clinical Development Dossiers (DDCM) and Specific Clinical Trial Dossiers appropriately.

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 legislation, and is not intended to expand or restrict established technical or administrative requirements.

3. BASE LEGAL

Anvisa Resolution - RDC nº 9, of February 20, 2015, which provides for the regulations for carrying out clinical trials with medicines in Brazil.

4. OBJECTIVE

Without prejudice to the provisions existing in the legal provisions, this manual aims to guide and explain in a complementary way the submissions of Dossiers for Clinical Development of Medicines (DDCM) and Specific Dossiers for Clinical Trials, as described in chapter III of RDC nº 09/2015 .

We recommend that the format is standardized in terms of order and content to facilitate assessment.

5. SUBMISSION OF THE DDCM AND SPECIFIC DOSSIERS FOR EACH CLINICAL TRIAL

5.1 DDCM SUBMISSION

According to RDC nº 09/2015, the Clinical Medicine Development Dossier (DDCM) is the compilation of documents to be submitted to Anvisa with the purpose of evaluating the steps inherent to the development of an experimental medicine in order to obtain information to subsidize the registration or post-registration changes of said product.

To electronically petition a DDCM to Anvisa, the regulated sector must inform one of the following primary petition subjects:

- 10750 - CLINICAL TRIALS - Consent in Process of the Dossier of Clinical Drug Development (DDCM) – Synthetics
- 10754 - CLINICAL TRIALS - Consent in Process of the Dossier of Clinical Drug Development (DDCM) – Biological Products
- 10752 - CLINICAL TRIALS - Consent in Process of the Dossier of Clinical Drug Development (DDCM) – Phytotherapeutics
- 10748 - CLINICAL TRIALS - Consent in Process of the Dossier of Clinical Drug Development (DDCM) – Radiopharmaceuticals
- 10751 - CLINICAL TRIALS - Consent in Process of the Dossier Clinical Drug Development (DDCM) of ORPC`s – Synthetics
- 10755 - CLINICAL TRIALS - Consent in Process of the Dossier of Clinical Drug Development (DDCM) of ORPC`s – Products Biological
- 10753 - CLINICAL TRIALS - Consent in Process of the Dossier of Clinical Development of Medicines (DDCM) of ORPC`s – Phytotherapeutics
- 10749 - CLINICAL TRIALS - Consent in the process of the Dossier of Clinical Drug Development (DDCM) of ORPC`s – Radiopharmaceuticals

The specific checklist for the subjects mentioned above can be consulted on the Anvisa website and they strictly follow the description of the items contained in the norma.

The applicant must submit a DDCM to Anvisa only if they intend to carry out clinical trials with medicines in the national territory. The DDCM applies

only to the development of an experimental medicine. For the purposes of analyzing the DDCM, at least one specific clinical trial dossier to be carried out in Brazil.

When submitting an electronic petition for one of the DDCM matters, the applicant must answer the following question: “Are there consent processes filed with Anvisa to be linked to the DDCM?” If so, the person responsible for the petition must inform the process numbers of the consent matters related to the DDCM experimental medicine, already petitioned at Anvisa (which may have already been analyzed, granted, rejected, canceled, are in demand or awaiting technical analysis), which are part of the product's Clinical Development Plan. Therefore, the consent processes already submitted to Anvisa must be linked to a single DDCM per experimental drug.

The following matters previously petitioned to Anvisa may be linked to um 200:

- 10482 - CLINICAL TRIALS – Consent in the Clinical Research Process – Synthetic Medicines
- 10479 - CLINICAL TRIALS – Consent in the Clinical Research Process – Biological Products
- 10476 - CLINICAL TRIALS – Consent in the Clinical Research Process – Phytotherapeutics
- 10483 - CLINICAL TRIALS – Consent in the Clinical Research Process of ORPC's – Synthetic Medicines
- 10478 - CLINICAL TRIALS – Consent in the Clinical Research Process of ORPC's – Biological Products
- 10477 - CLINICAL TRIALS – Consent in the Clinical Research Process of ORPC's – Phytotherapeutics
- 102 - CLINICAL TRIALS - Consent in the Clinical Research Process - Medicines
- 1650 - CLINICAL TRIALS - Consent in the Clinical Research Process of ORPC's – Medicines
- 550- CLINICAL TRIALS - Notification in Clinical Research - Phase IV/Observational linkable to DDCM

The documents for a DDCM must be filed manually with Anvisa, in accordance with a specific checklist for the subject in question, except for the Dossier(s)

Specific for each Clinical Trial, which will be a new process, petitioned and filed electronically.

5.2 SUBMISSION OF SPECIFIC DOSSIERS FOR EACH CLINICAL TRIAL

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

Specific Dossiers for Clinical Trials can be submitted to Anvisa as one of the following subjects:

- 10482 - CLINICAL TRIALS – Consent in the Clinical Research Process – Synthetic Medicines
- 10479 - CLINICAL TRIALS – Consent in the Clinical Research Process – Biological Products
- 10476 - CLINICAL TRIALS – Consent in the Clinical Research Process – Phytotherapeutics
- 10773 - CLINICAL TRIALS – Consent in the Clinical Research Process – Radiopharmaceuticals
- 10483 - CLINICAL TRIALS – Consent in the Clinical Research Process of ORPC's – Synthetic Medicines
- 10478 - CLINICAL TRIALS – Consent in the Clinical Research Process of ORPC's – Biological Products
- 10477 - CLINICAL TRIALS – Consent in the Clinical Research Process of ORPC's – Phytotherapeutics
- 10774 - CLINICAL TRIALS – Consent in the Clinical Research Process of ORPC's – Radiopharmaceuticals
- 550- CLINICAL TRIALS - Notification in Clinical Research - Phase IV/Observational linkable to DDCM

Specific Dossiers for each Clinical Trial can be requested by institutions with a CNPJ different from that informed in the DDCM. To petition the above matters, the DDCM process number must be informed to which the petition for Consent in the Clinical Research Process must be linked, as the system does not allow these matters to be petitioned without belonging to a DDCM.

The specific checklist for each subject mentioned above can be consulted on Anvisa's website and they strictly follow the description of the items required by current regulations.

Petitioning and filing must be carried out electronically. For each item contained in the checklist of these petitions, the requester will be required to attach at least one PDF file, which allows textual search. It will be possible to attach up to 5 files measuring 750 Kb. For greater clarity, we recommend that the annex referring to the protocol be identified as "Protocol".

For the petition process to continue, each attached file must be viewed. After completing the petition, a number of
transaction. In cases of fee payment, it is not possible to make any changes to the submitted dossier after the fee has been paid. Any subsequent changes can be made using a specific subject code.

It should be noted that only dossiers of clinical trials to be carried out in Brazil should be requested. Only dossiers that already have a clinical and non-clinical basis for initiation must be filed, as the CE issued for the DDCM will only contain clinical trials that Anvisa considers capable of being initiated. If a Development Plan is presented in complete form containing phase 1, 2 and 3 clinical trials, but studies are still being carried out in early phases, which are not capable of supporting later phase clinical trials, the phase 3 clinical trial , for example, should not be initially filed with Anvisa. This clinical trial may be requested when there is already sufficient clinical and non-clinical basis for its initiation. It may be included later as a petition for the subjects of the Specific Dossiers for Clinical Trial, if it is not different from what has already been presented in the Development Plan or with a petition for Substantial Modification of DDCM (10818 – CLINICAL TRIALS – Modification of DDCM – Inclusion clinical trial protocol not foreseen in the initial development plan) for those cases in which there is a change in the Development Plan.

The above provisions are not applicable to the Drug Development Plan (described in detail in section 6), where all trials planned for that experimental drug, whether to be conducted in Brazil or not, must be described.

6. DDCM DOCUMENTS

To submit the DDCM, Section II of Chapter III of RDC no.
09/2015. We recommend that all documentation be submitted in Portuguese, especially the clinical protocol and the investigator's brochure, as, as established in RDC 50/2013, the technical area evaluator may make a requirement requesting a free translation of the documentation presented. Below is a description of some documents to facilitate the submission of the DDCM.

6.1 DRUG DEVELOPMENT PLAN

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

The drug Development Plan must explain the steps necessary for the clinical investigation of the experimental drug. In short, this plan must demonstrate the entire rationale for developing the medicine, foreseeing all the steps already carried out, in progress and those intended for the clinical investigation of the medicine. The Development Plan must also indicate clinical trials that have been, are being or will be carried out outside Brazil.

It is recommended to send a table or a schematic drawing containing all clinical trials planned for clinical development over a certain period of time, as well as the progress of these trials (completed, ongoing or planned).

The Development Plan must begin with a brief description of the experimental drug, informing the IFA or active substance, drug category, therapeutic class, according to the ATCC - Anatomical Therapeutic Chemical Code classification and route of administration. The indication(s) must be technically justified through the mechanism of action of the experimental medicine, demonstrating that it is directly or indirectly involved in the therapeutic or diagnostic effect. Including whether the mechanism of action is innovative. Only the indication(s) proposed in the Development Plan must be presented in this topic.

The sponsor must also inform the general objectives, listing all intended indications for the experimental medicine, even those that are not yet being investigated in the Development Plan presented. A technical justification for clinical development must also be described. Furthermore, the expected duration of the proposed clinical development must be informed.

Additionally, the sponsor must present a brief description for all clinical trials contained in the Development Plan, containing information about the phase, design, outcomes, comparators, objectives, population to be studied, hypothesis(es) s) to be tested, estimated number of participants and statistical planning.

It is recommended to use the development plan template available on the
Annex I of this Manual.

Anvisa recognizes that the Development Plan is not static and that it can be changed throughout the development of the experimental medicine.

In the Development Plan, it is not necessary to present the results of clinical trials already carried out. The results of clinical trials must be presented in the Investigator's Brochure.

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

6.2 INVESTIGATOR'S BROCHURE

The Investigator's Brochure (BI) is a document that contains the compilation of non-clinical and clinical data of 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 dose, dosage regimen, methods of administration, and safety monitoring procedures. BI also provides support for monitoring clinical trial participants during the trial. In the meantime, information must be presented in concise, clear, simple and objective language to better guide investigators in conducting the clinical trial.

This item of the manual aims to explain the minimum information that must be
included in a BI. According to the drug development phase
experimental and its category, the degree of detail of the information available may vary. If an already marketed drug is being investigated for

a new indication or in a new population, the BI must contain information that justifies and supports this new condition.

The BI must contain a brief description of the experimental medicine; chemical characterization; biological activity; the formulation; the characterization of the pharmacological and toxicological effects of the experimental medicine on animals and humans, when applicable; information on safety and efficacy in humans obtained from clinical trials already carried out; as well as any critical information regarding the experimental medicine. The BI must present the data already known, the available results of non-clinical and clinical studies, as well as ongoing studies and their preliminary data, when they exist.

The BI must clearly describe the possible risks and adverse events related to the experimental drug, based on previous experiences, as well as precautions, safety alerts or special monitoring, including from other regulatory authorities, to be followed during development, to better guide investigators who will conduct the study.

6.3 EXPERIMENTAL MEDICINE DOSSIER

The documents referring to items a, b, c, d, and f of the experimental drug dossier described in RDC nº 09/2015 will be covered in a specific guide for the technical evaluation of the products under investigation. Therefore, this item will only address items g and h of Section II, Chapter III - Content and Format of the Request - of RDC nº 09/2015.

The critical analysis of non-clinical studies must consider the following aspects:

I - Give reasons for the choice of types of tests and animal models chosen, and discuss the possible methodological limitations of the tests already carried out. The tests must support the clinical indication to be studied, route of administration and equivalent dose in humans.

II - Discuss findings in animal models, identifying target organs and possible implications of these findings in humans. It must also demonstrate that the safety profile of the experimental medicine, based on the results of pharmacological and toxicological studies, is acceptable for clinical research.

III - Evaluate the possible benefits and risks involved to support the clinical development of the experimental medicine.

IV - Present information about the locations where the studies were conducted, as well as where their records are available for consultation, including a statement that each
study was carried out in accordance with Good Laboratory Practices or
justification for absence.

The critical analysis of clinical trials already carried out must foresee the following aspects:

I - Discuss the scientific quality of clinical trial data based on the level of evidence and degree of recommendation of the available evidence. Furthermore, discuss the possible methodological limitations of clinical trials already carried out and the procedures used to control systematic errors.

II - Based on data from non-clinical tests, present a discussion on monitoring safety in clinical development.

III - Substantiate the choice of safety and efficacy outcomes used in previous studies. These outcomes must be in line with the objectives and hypotheses.

IV - In case of post-registration changes, such as expansion of use, new therapeutic indication, new pharmaceutical form or others, justify the choice of type of design, study population, dose schedules and other relevant aspects related to the change .

V - Risk management must be guided by the results of previous studies such as death or other serious adverse events, type of sequelae arising from these events, evaluations and recommendations of the Independent Safety Monitoring Committee, tolerability, toxicological findings, pharmacological safety (cardiovascular system , respiratory and nervous), among others. Furthermore, recommendations from other agencies for the proposed study or experimental drug must be taken into consideration.

VI - Present the assessment of the balance between the possible benefits and the risks involved to support the continued clinical development of the experimental medicine.

7. ISSUANCE OF THE SPECIAL COMMUNICATION (CE) AND DOCUMENT FOR IMPORTATION OF PRODUCT(S) UNDER INVESTIGATION OF THE CLINICAL DRUG DEVELOPMENT DOSSIER (DDCM)

According to RDC nº 09/2015, Special Communication (CE) is the authorizing document, issued by Anvisa, after analysis and approval by the DDCM, and can be used in import or export requests for a clinical trial. In CE
All clinical trials authorized to be conducted in Brazil are described.
Therefore, only clinical trials listed in the EC can be started in the country, respecting other ethical approvals.

The CE also contains the list of products to be imported, referring to each clinical trial, as well as storage conditions and expiration date. This information is provided by the applicant by completing the "Clinical Trial Submission Form". If new clinical trials are included or excluded, products to be imported are included or excluded or storage conditions and shelf life are changed, an update to the CE must be issued.

Information regarding the inclusion of Clinical Trials not foreseen in the Development Plan must be provided to Anvisa through the subjects: 10818-
CLINICAL TRIALS – Modification of DDCM – Inclusion of a clinical trial protocol not foreseen in the initial development plan. In cases of inclusion of protocol(s) already foreseen in the initial Development Plan, only submission will be necessary through the subject(s) listed in item 5.2 of this Manual. Regarding the deletion of protocols, information will be provided through subject 10819 -
CLINICAL TRIALS – Modification of DDCM – Exclusion of clinical trial protocol.
For changes to information regarding the products under investigation, such as storage conditions and expiration date, subject 10823 - CLINICAL TRIALS – Change of Clinical Trial Presentation Form must be requested. We emphasize that changes to the validity period are considered substantial modifications and must be sent as explained in the Modifications, Amendments, Suspensions and Cancellations Submission Manual.

For cases in which there is no manifestation from Anvisa in accordance with RDC nº 09/2015, a "Document for import of Product(s) under investigation from the Clinical Medicine Development Dossier (DDCM)" is sent so that it is possible to import of products necessary to conduct Clinical Trials. This document contains the same information as the CE regarding Clinical Trials and products to be imported. Therefore, in cases of changes to these

information, the same criteria and subjects presented for changes to the EC must be followed. After the applicant has sent relevant documentation for the changes, a "Document for import of Product(s) under investigation from the Drug Clinical Development Dossier (DDCM)" will be issued.

updated.

8. SECONDARY PETITIONS

Secondary petitions must be linked to the respective specific processes, that is, secondary petitions related to a DDCM must be filed with the Drug Clinical Development Dossier Consent (DDCM) process. Some examples of DDCM petitions are: DDCM Modification Matters, DDCM Petition Form Amendment, Investigational Drug Development Safety Update Report, DDCM Cancellation on Request, Global Transfer of Responsibility for DDCM, Temporary Suspension of DDCM , Reactivation of Suspended DDCM.

Likewise, petitions related to Clinical Trial Dossiers must be linked to the respective clinical trial processes. Some examples of Clinical Trial Dossier petitions are: Change of Clinical Trial Presentation Form, 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.

Linking 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 requester will need to attach at least one PDF file, which allows textual search. It will be possible to attach up to 5 files measuring 750 Kb.

For the petition process to continue, each attached file must be viewed. After completing the petition, a transaction number will be generated. In cases of fee payment, it will not be possible to make any changes to the dossier submitted after payment of the fee. Any subsequent changes may be made using a specific subject code.

9. GLOSSARY

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

II - Investigator's Brochure - compiled of clinical and non-clinical data on the experimental medicine(s), which are relevant to its study in human beings;

III - Independent Safety Monitoring Committee - independent committee, established to monitor specific safety data collected from one or more clinical trials at defined intervals. Recommends to the sponsor whether a study should be continued, modified, or stopped;

IV - Special Announcement (CE) - document of an authorizing nature, issued by the Anvisa, after analysis and approval of the DDCM, can be used in import or export requests for a clinical trial;

V - Clinical Medicine Development Dossier (DDCM) – compiled of documents to be submitted to Anvisa with the purpose of evaluating the steps inherent to the development of an experimental medicine with a view to obtaining information to support the registration or post-registration changes of the said product;

VI - Specific Dossier for each Clinical Trial - compiled of documents to be submitted to Anvisa with the purpose of obtaining information regarding clinical trials, to be conducted in Brazil, which are part of the Experimental Medicine Development Plan;

VI - Document for Import of Product(s) under investigation in the Dossier of Clinical Development of Medicines (DDCM): Document issued by Anvisa, necessary to request import or export for a clinical trial, in cases of non-compliance with the DDCM;

VII - Amendment to the clinical trial protocol - any proposal to modify an original clinical trial protocol, always presented with the justification that motivated it, and such amendment may be substantial or not;

VIII - 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 absorption , distribution, metabolism and excretion of the experimental drug to verify its safety and/or effectiveness;

IX - Active Pharmaceutical Ingredient (IFA) - 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 other direct effects on the diagnosis, cure, treatment or prevention of a disease, and may also affect the structure and functioning of the human body;

X - Investigator - person responsible for conducting a clinical trial at the location 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;

XI - Patrocator Investigator - Individuals responsible for conducting and coordinating clinical trials, in isolation or in a group, carried out by their immediate direction independently, developed with financial resources and materials proper to the researcher, national or international development entities to research, from private entities and other non-profit entities;

XII - Experimental medicine - pharmaceutical product being tested, object of the DDCM, to be used in the clinical trial, with the purpose of obtaining information for its registration or post-registration;

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

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

XV - Placebo – formulation without pharmacological effect, administered to the clinical trial participant for the purpose of masking or being a comparator;

XVI - Product under investigation - experimental medicine, placebo, active comparator or any other product to be used in the clinical trial;

XVII - 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;

XVIII - Annual Monitoring Report - annual document containing specific information about the conduct of a specific clinical trial in centers in Brazil, in accordance with the clinical protocol and the GCP;

XIX - Safety update report on the development of an experimental medicine - harmonized periodic report containing information on the safety and development of an experimental medicine;

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

10. BIBLIOGRAPHICAL REFERENCES

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2. GUIDELINE FOR GOOD CLINICAL PRACTICE. ICH E6(R1). Available in: <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf> Accessed on: 02 Sep. 2016.

11. CHANGE HISTORY

Version	Changes made	Explanation and Justification
1st edition		
2nd Edition	• Replacement throughout the document of Resolution that provides for the Health Regulations for carrying out clinical trials with medicines in Brazil" by **"RDC nº 09/2015"**	• As the first edition of the Manual of Submission had been completed before the publication of the new standard, there was still no definition of the number of the new DRC. That was corrected in this first revision.
2nd Edition	• Changed the name of the subject of petition for: Global Transfer of Responsibility on DDCM (page 15).	• Changing the name of the subject of petition.
2nd Edition	• Changed the name of the subject of petition for: Global Transfer of responsibility for Clinical Trial Protocol (page 15).	• Changing the name of the subject of petition.
2nd Edition	• Removed section "Provisions Transient"	• With more than one year of experience implementation of RDC 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 whether the mechanism of action is innovative.”	• Information about innovation in the mechanism of action is important to evaluate the rationale of the clinical development.
3rd Edition	• Inclusion of the following sentence in 5th paragraph in item 6.1: “A	• To better understand which is the technical justification for the

	technical justification for the clinical development as well must be described."	clinical development.
3rd Edition	• Inclusion of the following paragraph in the item 6.1: "It is recommended to use of the plan template development available in Annex I of this Manual."	• Due to various problems identified in plans development evaluated until the moment, COPEC developed a plan template to facilitate analysis of the document by Anvisa.
3rd Edition	• Change to item "6.2. Dossier of Experimental Medicine" for item 6.3	• Correction of numbering
3rd Edition	• Inclusion of Annex I	• Provision of a model of development plan for facilitate document analysis by Anvisa

ANNEX I: Development plan template

MODELv1 - Development Plan – Drug XXX – Version XX of xx/xx/xxxx

Sponsor: XXXXX

1) IFA or active substance

Provide a brief description of the IFA or active substance. For example: name of the API, physical-chemical and biological characteristics.

2) Category of medicine

Inform whether the medicine is synthetic, biological, herbal or radiopharmaceutical

3) Therapeutic class

Inform the therapeutic class of the medication

4) Route of administration

Inform the studied and intended routes of administration

In this item, you can also inform the pharmaceutical forms and dosages of the experimental medicine. For example: 10 mg coated tablet for oral administration and 5 mg granules for oral suspension.

5) Mechanism of action

Briefly state the mechanism of action and explain whether the mechanism is innovative. Submit a technical justification for this clinical development of this medicine.

6) Indications to be studied

Inform the therapeutic indications of the experimental medicine that have been studied and those that are intended to be evaluated in this clinical development.

7) General objectives and planned duration for clinical development

Inform the general objectives of clinical development and send a technical justification for this clinical development of this medicine

Inform the expected duration of development. For example: The estimated duration of clinical development is expected to be 2025.

In this section, it can also be informed whether the medicine has already been sent to the Anvisa registration area and for which indications/ pharmaceutical forms/ populations.

In this section, it can also be informed whether the experimental medicine has already been submitted for registration in other countries and is awaiting manifestation of other agencies. inform pharmaceutical forms, populations for which indications/ cases that the registration was submitted.

8) Clinical trials

8.1. List of completed, ongoing and planned clinical trials

Protocol	Status	Start	End	Phase	Number of participants	Participation of Brazil
A	Finished	01/01/2010	20/12/2010	1	30	No

Fill:

- ***Protocol:*** *inform the protocol code*
- ***Status:*** *inform whether the study has been completed, is in progress or is planned*
- ***Start:*** *inform the date the study began. If it is a planned study, place the expected start of the clinical trial*
- ***End:*** *inform the date that the study was completed. If it is a planned study, place the anticipated closure of the clinical trial*
- ***Phase:*** *inform whether it is phase 1, 2, 3, etc.*
- ***Participation of Brazil:*** *inform whether the study was/ is being/ will be conducted in Brazil*

8.2. Description of clinical trials

8.2.1. Completed or ongoing clinical trials

Planned clinical trial	Protocol code:
Participation of Centers in Brazil	Try ( ) No ( )
Estimated number of participants	
Status	Completed ( ) In progress ( )
Phase	
Design	
Goals	
Outcomes	

Comparators	
Dosage of the experimental drug Dosage	
of comparators	
Pharmaceutical form of the investigational drug	
Population	

Note: If there is a clinical trial that is ongoing outside Brazil, but is planned to be conducted in Brazil, include the study in “planned clinical trials”.

8.2.2. Planned clinical trials

8.2.2.1. Clinical trial A

Planned clinical trial	Protocol code:
Participation of Centers in Brazil	Try ( ) No ( )
Estimated number of participants	
Status	Global Start Forecast: Expected Start in Brazil: End Forecast:
Phase	
Design	
Goals	
Outcomes	
Comparators	
Dosage of the experimental drug	
Dosage of comparators	
Pharmaceutical form of experimental medicine	
Population	
Hypothesis	
Statistical planning	

8.2.2.2 Clinical Trial B

Planned clinical trial	Protocol code:
Participation of Centers in Brazil	Try ( ) No ( )
Estimated quantity of	

participants	
Status	Global Start Forecast: Expected Start in Brazil: End Forecast:
Phase	
Design	
Goals	
Outcomes	
Comparators	
Dosage of the experimental drug	
Dosage of comparators	
Pharmaceutical form of the investigational drug	
Population	
Hypothesis	
Statistical planning	

8.2.2.3 Clinical Trial C

Planned clinical trial	Protocol code:
Participation of Centers in Brazil	Try ( ) No ( )
Estimated number of participants	
Status	Global Start Forecast: Expected Start in Brazil: End Forecast:
Phase	
Design	
Goals	
Outcomes	
Comparators	
Dosage of the experimental drug	
Dosage of comparators	
Pharmaceutical form of the investigational drug	
Population	
Hypothesis	
Statistical planning	

Fill:

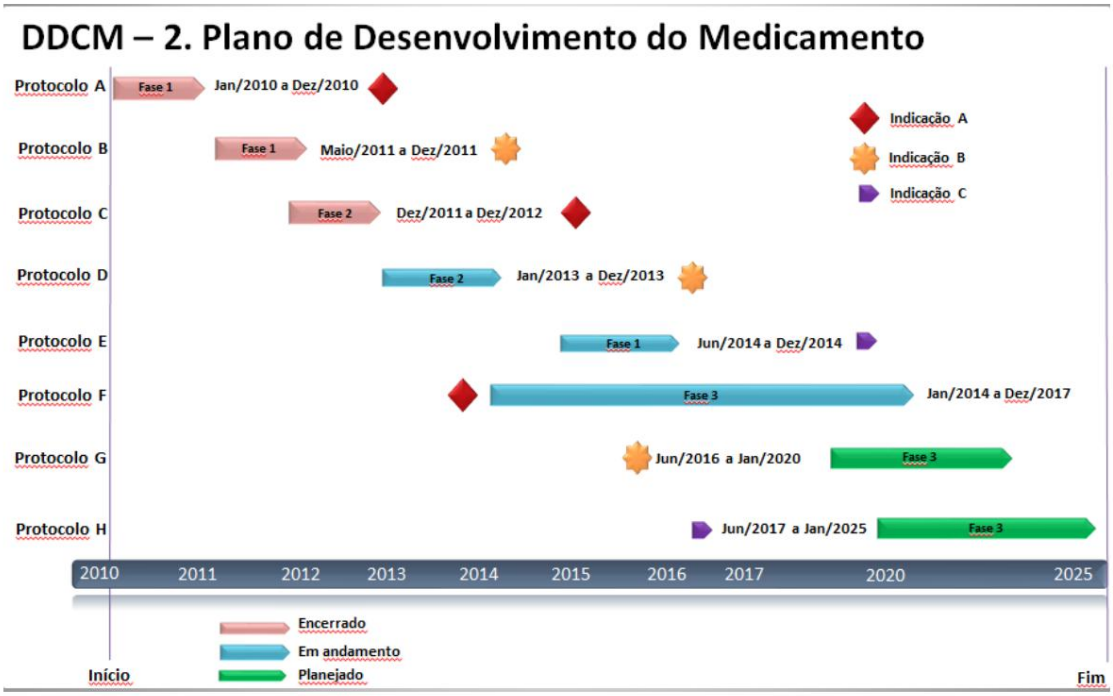
- ***Planned clinical trial:*** *inform the protocol code*
- ***Participation of centers in Brazil:*** *answer whether or not the participation of the Brazil in this clinical trial*
- ***Estimated number of participants:*** *inform the number of expected participants in the study*
- ***Status:*** *inform the expected date for the study to begin in Brazil and worldwide (if applicable) and the expected end date*
- ***Phase:*** *inform whether it is phase 1, 2, 3, etc.*
- ***Design:*** *the title of the study can be provided*
- ***Objective:*** *include at least the primary and secondary objectives*
- ***Outcome:*** *include, at least, the outcomes referring to the primary and secondary objectives*
- ***Comparator:*** *inform the name of the active comparator or indicate whether it is placebo (or placebo + basic therapy) and justify the rationale for choosing the comparator. In the case of open studies, justify the rationale.*
- ***Dosage of the experimental drug:*** *inform the dose and treatment schedule*
- ***Dosage of comparators:*** *inform the dose and treatment schedule*
- ***Pharmaceutical form of the experimental drug:*** *inform the pharmaceutical form used in this clinical trial*
- ***Population:*** *inform the profile of the population (age group, gender, disease, etc.) •*

Hypothesis: *inform whether there is a hypothesis for the clinical trial. If yes, please state what the hypothesis is. be tested*

- ***Number of participants:*** *inform the number of expected or recruited participants in the study*
- ***Statistical planning:*** *inform, at least, the determination of the sample size, description of efficacy and safety analyses.*

9) Timeline with all clinical trials of the drug's development.

Example:



GENERAL OBSERVATIONS:

ÿ The plan must preferably be written in Portuguese.
ÿ For each new update of the plan, change the document version, highlight the changes made and send a change tracking history.
ÿ There is no need to include the results of clinical trials in this document. You Results must be presented in the Investigator's Brochure.
ÿ The development plan is the first technical document to be analyzed, as it provides an overview of the DDCM. This way, the more complete and clear the document is, the faster the analysis of the DDCM as a whole will be. Other documents can be referenced in this document, however, the brief description of each item facilitates analysis, as it allows you to quickly verify the clinical development of the medicine.

ÿ It is clarified that Anvisa understands that the Development Plan is a dynamic document, which may be changed throughout clinical development. However, such information is still fundamental for the first moment of analyzing the DDCM and understanding the general idea of the development of the experimental medicine.