



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

**Drugs General Management – GGMED
Clinical Research Coordination in Drugs
and Biological Products – COPEC**



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

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This Manual aims at guiding the professionals of the area with information on how to apply Resolution RDC/Anvisa no. 09, dated February 20th, 2015, contributing to the development of safe actions, in addition to providing relevant and updated information that can be better clarified by the Manual instrument.

The manual does not create new obligations, and it shall be used by public and private agents as a reference for complying with the existing Legislation.



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

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Adriane Alves de Oliveira

André Luís Carvalho Santos Souza

Bruno de 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 do Rocio Malaman

Leonardo Fabio Costa Filho

Miriam Motizuki Onishi

Patrícia Ferrari Andreotti

Ricardo Eccard da Silva

Sônia Costa e Silva

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1. ACRONYMS

ATCC - Anatomical Therapeutic Chemical Code
IB – Investigator's Brochure
CE - Special Communication
DDCM - Drug Clinical Development Dossier
API - Active Pharmaceutical Ingredient
CRO - Contract Research Organization
RDC - Board of Directors Resolution

2. INTRODUCTION

The publication on the regulation about Clinical Trials with drugs in Brazil starts evaluating Development Plans and not only single protocols. This manual aims at providing guidance for the sponsor, investigator-sponsor or CRO to appropriately submit the Drugs Clinical Development Dossiers (DDCM) and Specific Dossiers for Clinical Trials.

It is a non-binding regulatory measure adopted as a complement to the health legislation, with the educational purpose of orientation regarding routines and procedures for compliance with the legislation, not aimed at the extension or restriction of the established technical or administrative requirements.

3. LEGAL BASIS

Anvisa Resolution – RDC no. 9, dated February 20th, 2015, that provided for the regulation for performing clinical trials with drugs in Brazil.

4. OBJECTIVE

Without prejudice to the determinations existing in the legal provisions, this manual aim is to complementarily guide and explain the submissions of the Drug Clinical Development Dossiers (DDCM) and Specific Dossiers for Clinical Trials, as described in the chapter III of RDC no. 09/2015.

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



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

5.1 DDCM SUBMISSION

According to RDC no. 09/2015 the Drug Clinical Development Dossier (DDCM) is a collection of documents to be submitted to Anvisa in order to assess the steps inherent to the development of an experimental drug with the aim to obtain information to support either the registration or post-registration changes of the referred product.

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

- 10750 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) - Synthetic Products
- 10754 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) - Biological Products
- 10752 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) - Herbal Products
- 10748 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) - Radiopharmaceutical products
- 10751 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) of CROs - Synthetic Products
- 10755 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) of CROs - Biological Products
- 10753 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) of CROs - Herbal Products
- 10749 - CLINICAL TRIALS - Process for Approval of Drug Clinical Development Dossier (DDCM) of CROs - Radiopharmaceutical Products

The specific checklist for the above-mentioned subjects can be checked at Anvisa's website and they strictly follow the description of the items included in the regulations.

The applicant must submit a DDCM to Anvisa only if he/she intends to conduct clinical trials with drugs in Brazil. DDCM is only applicable for the development of experimental



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drugs. For DDCM analysis purposes, at least one specific dossier for the clinical trial to be conducted in Brazil must be filed.

Upon electronic petition for one of the DDCM's subjects, the applicant must answer the following question: "Are there approval processes filed at Anvisa to be linked to the DDCM?". If positive, the one responsible for the petition must inform the process numbers of the approval subjects related to the experimental drug in the DDCM, already petitioned at Anvisa (and they may have already been analyzed, accepted, refused, canceled, pending or waiting for technical analysis), which are part of the product clinical Development Plan. Thus, the approval processes already submitted to Anvisa must be linked to a single DDCM per experimental drug.

The following subjects previously petitioned at Anvisa can be linked to a DDCM:

- 10482 - CLINICAL TRIALS - Clinical Research Approval Process - Synthetic Drugs
- 10479 - CLINICAL TRIALS - Clinical Research Approval Process - Biological Products
- 10476 - CLINICAL TRIALS - Clinical Research Approval Process - Herbal Products
- 10483 - CLINICAL TRIALS - CRO's Clinical Research Approval Process - Synthetic Drugs
- 10478 - CLINICAL TRIALS - CRO's Clinical Research Approval Process - Biological Products
- 10477 - CLINICAL TRIALS - CRO's Clinical Research Approval Process - Herbal Products
- 102 – CLINICAL TRIALS - Clinical Research Approval Process – Drugs
- 1650 – CLINICAL TRIALS – CRO's Clinical Research Approval Process – Drugs
- 550 – CLINICAL TRIALS - Clinical Research Notification – Phase IV/Observational linkable to the DDCM

The documents of a DDCM must be manually filed at Anvisa, according to the specific checklist for the subject in question, except Specific Dossier(s) for each Clinical Trial, which will be a new process, electronically petitioned and filed.



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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, they will have process number, with specific subjects for each clinical trial intended to be conducted in Brazil and that have not been submitted to Anvisa yet.

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

- 10482 - CLINICAL TRIALS - Clinical Research Approval Process - Synthetic Drugs
- 10479 - CLINICAL TRIALS - Clinical Research Approval Process - Biological Products
- 10476 - CLINICAL TRIALS - Clinical Research Approval Process - Herbal Products
- 10773 - CLINICAL TRIALS - Clinical Research Approval Process - Radiopharmaceutical Products
- 10483 - CLINICAL TRIALS - CRO's Clinical Research Approval Process - Synthetic Drugs
- 10478 - CLINICAL TRIALS - CRO's Clinical Research Approval Process - Biological Products
- 10477 - CLINICAL TRIALS - CRO's Clinical Research Approval Process - Herbal Products
- 10774 - CLINICAL TRIALS - CRO's Clinical Research Approval Process - Radiopharmaceutical Products
- 550 - CLINICAL TRIALS - Clinical Research Notification - Phase IV/Observational linkable to the DDCM

The Specific Dossiers for each Clinical Trial can be petitioned by Institutions with CNPJ (Corporate Taxpayer's Registry) different from that informed in the DDCM. For petitioning the above subjects, the DDCM process number to which the Clinical Research Approval Process petition shall be bound, must mandatorily be informed, because the system does not allow these subjects to be petitioned if not inserted in any DDCM.



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The specific checklist for each of the above-mentioned subjects can be checked at Anvisa's website and they strictly follow the description of the items required by the regulation in force.

The petitioning and filing processes must be done electronically. For each item in these petitions' checklist, the applicant is required to attach at least one PDF file that allows text search. It is possible to attach up to 5 750 kb size files. For greater clarity, we recommend that the attachment related to the protocol is identified as "Protocol".

To continue the petition process, each attached file must be viewed. After the petitioning is completed, a transaction number is generated. For tax collection cases, no changes in the submitted dossier are possible after the tax is paid. Any later change can be done through a specific subject code.

It is important to note that only dossiers for clinical trials to be conducted in Brazil shall be petitioned. Only dossiers already containing clinical and non-clinical justification to be initiated must be filed, since the CE issued for the DDCM will only contain clinical trials that Anvisa considers feasible to be initiated. If the Development Plan is fully presented containing phase 1, 2 and 3 clinical trials, but early-stages clinical trials are still ongoing, and are not able to support clinical trials in later stages, the phase 3 clinical trial, for instance, must not be petitioned in Anvisa initially. This clinical trial may be petitioned when there is enough clinical and non-clinical justification for its initiation. It can be included later as a petition of the Specific Dossiers for Clinical Trial subjects, if not different from that presented in the Development Plan or as a petition for Substantial DDCM Modification (10818 - CLINICAL TRIALS - DDCM Modification - Inclusion of clinical trial protocol not foreseen in the initial development plan) for cases that have changes in the Development Plan.

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



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6. DDCM DOCUMENTS

For DDCM submission, Section II of Chapter III from RDC no. 09/2015 must be followed. We recommend that all documentation be submitted in Portuguese, especially the clinical protocol and the investigator's brochure, because as established in RDC 50/2013, the technical evaluator may issue a query requesting the free translation of the presented documentation. Here follows the description of some documents to facilitate DDCM submission.

6.1 DRUG DEVELOPMENT PLAN

The preparation of a Development Plan by the study sponsor allows the definition of objectives and methodologies, which enable the identification of critical stages and process challenges and planning of monitoring actions, from the established indicators. The available information on the experimental drug must support the proposed clinical indication, the target population and the proposed designs types for the clinical trials.

The drug Development Plan must explain the necessary steps for the experimental drug clinical investigation. In short, this plan shall present all the drug development rationale, anticipating all steps already completed, in progress and those intended for the drug clinical investigation. The Development Plan must present, also, the clinical trials that have been, are being or will be conducted outside Brazil.

It is recommended to send a table or a chart containing all planned clinical trials for the clinical development during a specific period, as well as the progress of such trials (completed, in progress or planned).

The Development Plan must start with a brief description of the experimental drug, informing its API or active substance, drug category, therapeutic class, according to the ATCC – Anatomical Therapeutic Chemical Code and route of administration. The indication(s) must be technically justified by the experimental drug mechanism of action, showing that it is directly or indirectly involved in the therapeutic effect or diagnosis. Also inform if the mechanism of action is innovative. Only the indication(s) proposed in the Development Plan must be presented in this topic.



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The Sponsor must also inform the general objectives listing all indications intended for the experimental drug, even those that are not yet under investigation in the presented Development Plan. A technical justification for the clinical development must also be described. Moreover, the expected duration of the proposed clinical development must be informed.

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

It is recommended to use the development plan template available in the Attachment I of this Manual.

Anvisa is aware that the Development Plan is not statistic and it can be changed during the experimental drug development.

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

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

6.2 INVESTIGATOR'S BROCHURE

The Investigator's Brochure (IB) is a document containing the collection of non-clinical and clinical data of an experimental drug, which are relevant for the study in human beings. Its objective is to provide Investigators and other personnel conducting the clinical trial with information related to dose, posology, administration methods and safety monitoring procedures. The IB also provides support for the assessment of clinical trial participants during its progress. In the meantime, the information must be presented in a clear, concise, simple and objective language to better guide the investigators conducting the clinical trial.

This guidance item aims to explain the minimal information that must be included in an IB. Depending on the experimental drug development phase and its category, the level of details of the information available may vary. If an already marketed drug is



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being investigated for a new indication or in a new population, the IB must contain information justifying and supporting this new condition.

The IB must contain a brief description of the experimental drug; chemical characterization; biological activity; formulation; characterization of the experimental drug toxicological and pharmaceutical effects in animals and human beings, where applicable; safety and efficacy information on human beings obtained from already conducted clinical trials; as well as any critical information regarding the experimental drug. The IB must present already known data, results available from non-clinical and clinical studies, as well as the studies in progress and their preliminary data, if any.

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

6.3 EXPERIMENTAL DRUG DOSSIER

The documents related to items a, b, c, d and f of the experimental drug dossier described in RDC no. 09/2015 will be addressed in a specific guide for technical assessment of the products under investigation. Thus, in this item, only the subheads g and h of Section II, of Chapter III - Application Content and Format – of RDC no. 09/2015, will be addressed.

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

I - Justify the choice of test types and chosen animal models, and discuss the possible methodological limitations of already performed tests. The test must support the clinical indication to be studied, route of administration and equivalent dosage in human beings.

II - Discuss the findings in animal models, with identification of target organs and possible implications of such findings in human beings. It must also show that the experimental drug safety profile, from pharmacological and toxicological studies results, is acceptable for clinical investigation.

III - Assess possible benefits and risks involved in order to support the conduction of the experimental drug clinical development.



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IV - Present information on the study conduction sites, as well as where their records are available for consultation, including a statement that each study was conducted in compliance with the Good Laboratory Practices or justify the lack of it.

The critical analysis of already conducted clinical trials must describe the following aspects:

I - Discuss the scientific quality of clinical trials data based on the level of evidence and recommendation rate of available evidences. Additionally, discuss possible methodological limitations of already conducted clinical trials and procedures used to control systematic errors.

II - From non-clinical tests data, present an argument on safety monitoring in the clinical development.

III - Justify the choice of safety and efficacy endpoints used in previous studies. These endpoints must be consistent with the objectives and hypotheses.

IV - For post-registration changes, for instance, usage expansion, new therapeutic indication, new pharmaceutical form or others, justify the choice of the type of design, study population, dosage regimen and other relevant aspects related to the change.

V - Risk management must be guided by previous results such as death or serious adverse events, type of sequels due to such events, assessments and recommendations from the Independent Safety Monitoring Committee, tolerability, toxicological findings, pharmacological safety (cardiovascular, respiratory and nervous systems) among others. And also, recommendations from other agencies for the proposed study or for the experimental drug must be taken into consideration.

VI - Present assessment of the balance between possible benefits and risks involved in order to support the experimental drug clinical development continuation.



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

According to RDC 09/2015, Special Communication (CE) is an authorization document, issued by Anvisa, after DDCM analysis and approval, and it can be used in importing and exporting requests for a clinical trial. In the CE, all clinical trials authorized to be conducted in Brazil are described. Hence, only the clinical trials listed in the CE can be initiated in the country, respecting other ethical approvals.

The CE also contains a list of products to be imported, related to each clinical trial, as well as storage conditions and shelf life. This information is provided by the applicant by filling out the "Clinical trial presentation 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, a CE update must be issued.

Information related to Clinical Trial inclusion not foreseen in the Development Plan must be provided to Anvisa through the following subjects: 10818 - CLINICAL TRIALS - DDCM Modification - Inclusion of clinical trial protocol not foreseen in the initial development plan. For the inclusion of protocol(s) already foreseen in the initial Development Plan, only the submission through the subject(s) listed in item 5.2 of this Manual will be required. Regarding exclusion of protocols, the information will be provided through subject 10819 - CLINICAL TRIALS - DDCM Modification - Exclusion of clinical trial Protocol. For changes in information related to study products, such as storage conditions and shelf life, subject 10823 - CLINICAL TRIALS - Clinical Trial Presentation Form Change must be petitioned. We emphasize that shelf life changes are considered substantial changes and they must be submitted as explained in the Manual for Submission of Changes, Amendments, Suspension and Cancellations.

For cases with no manifestation from Anvisa according to new RDC no. 09/2015, a "Document for importation of the Study Product(s) from the Drug Clinical Development Dossier (DDCM)" is submitted, allowing the importation of products required for to conduct of Clinical Trials. This document contains the same CE information related to Clinical Trials and products to be imported.



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Thus, for cases in which such information is changed, the same criteria and subjects presented for CE changes must be followed. Upon submission of documents pertaining to the changes by the applicant, an updated "Document for Importation of the Study Product(s) from the Drug Clinical Development Dossier (DDCM)" will be issued.

8. SECONDARY PETITIONS

Secondary petitions must be linked to their respective specific processes, i.e., secondary petitions related to a DDCM must be filed along with the process for Approval of Drug Clinical Development Dossier (DDCM). Some examples of DDCM petitions are: DDCM Modification Subjects, DDCM Petition Form Change, Safety Update Report of the Experimental Drug Development, DDCM Cancellation upon Request, Global Transfer of Responsibility over DDCM, DDCM Temporary Suspension, Reactivation of Suspended DDCM.

Likewise, petitions related to Clinical Trial Dossiers must be linked to their respective clinical trial processes. Some examples of petitions of Clinical Trial Dossiers are: Clinical Trial Presentation Form Change, Substantial Amendment to Clinical Protocol, Clinical Trial Protocol Annual Follow-up Report, Clinical Trial Protocol Cancellation upon Request, Global Transfer of Responsibility over Clinical Trial Protocol, Clinical Trial Protocol Temporary Suspension, Reactivation of Suspended Clinical Trial Protocol.

The binding of secondary petitions to their correspondent processes are crucial for their analyses and tracking in Anvisa's electronic systems.

Secondary petitions must be electronically filed. For each item in those petitions' checklist, the applicant is required to attach at least one PDF file that allows text search. It is possible to attach up to 5 750 kb size files.

To continue the petition process, each attached file must be viewed. After the petitioning is completed, a transaction number is generated. For tax collection cases, no changes in the submitted dossier are possible after the tax is paid. Any later change can be done through a specific subject code.



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9. GLOSSARY

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

II – Investigator's Brochure – collection of clinical and non-clinical data about the experimental drug(s), which are relevant to its study in human beings;

III – Independent Safety Monitoring Committee – independent committee, formed for monitoring specific safety data collected from one or more clinical trials in defined intervals. It recommends to the sponsor if a study must be continued, changed or interrupted;

IV - Special Communication (CE) - authorization document, issued by Anvisa, after DDCM analysis and approval, and it can be used in importing and exporting requests for a clinical trial.

V - Drug Clinical Development Dossier (DDCM) - collection of documents to be submitted to Anvisa in order to assess the steps inherent to the development of an experimental drug with the aim to obtain information to support either the registration or post-registration changes of the referred product.

VI – Specific Dossier for each Clinical Trial - collection of documents to be submitted to Anvisa in order to get information regarding the clinical trials to be conducted in Brazil, which are part of the Experimental Drug Development Plan;

VI - Document for importation of the Study Product(s) from the Drug Clinical Development Dossier (DDCM): Document issued by Anvisa, necessary for requesting importation or exportation for a clinical trial, in the cases of lack of manifestation about the DDCM;

VII – Amendment to the clinical trial protocol – any proposal for change in an original clinical trial protocol, always presented with the justification that led to it, and it can be substantial or not;

VIII – Clinical trial – research conducted in human beings with the objective of finding out 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;



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IX – Active Pharmaceutical Ingredient (API) – any substance introduced in the formulation of a pharmaceutical form that, when administered in a patient, acts as active ingredient. Such substances may have a pharmacological activity or another direct effect in the diagnosis, cure, treatment or prevention of a disease, and it may also affect the structure and functioning of the human body;

X – Investigator – person responsible for the conduction of a clinical trial in 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 principal investigator;

XI – Investigator-Sponsor – individual person responsible for the conduction and coordination of clinical trials, alone or in a group, performed towards his/her immediate independent direction, developed with financial and material resources from the investigator him/herself, national or international research-fostering entities, private entities and other non-profit entities;

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

XIII – Contract Research Organization (CRO) – every company regularly set up in Brazil contracted by the sponsor or investigator-sponsor, that takes partial or full responsibility over the sponsor's attributions, towards Anvisa;

XIV – Sponsor – person, company, institution or organization responsible for starting, administering, controlling and/or funding a clinical trial;

XV – Placebo – formulation with no pharmacological effect, administered to the clinical trial participant with the purpose of masking or being the comparator;

XVI – Study product – experimental drug, placebo, active comparator or any other product to be used in the clinical trial;

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

XVIII - Annual Follow-up Report – annual document containing specific information on the conduction of a certain clinical trial in Brazilian sites, according to the clinical trial protocol and the GCP;

XIX – Safety update report of the experimental drug development – harmonized periodic report containing safety and development information of an experimental drug;



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



10. REFERENCES

1. BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Resolução RDC nº 09, de 20 de Fevereiro de 2015, publicada no D.O.U. de 03 de Março de 2015. Dispõe sobre o regulamento para a realização de ensaios clínicos com medicamentos no Brasil. Diário Oficial da União; Poder Executivo, de 03 de Março de 2015. [Resolution RDC No. 09, of February 20, 2015, published in D.O.U. of 03 March 2015. Provides for the regulation for conducting clinical trials with drugs in Brazil. Official Diary of the Union; Executive Power, March 03, 2015].

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



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11. HISTORY OF CHANGES

Version	Performed changes	Explanation and Justification
1 st Edition		---
2 nd Edition	<ul style="list-style-type: none"> Replacement in the whole document from "Resolution that provides for the Health Regulation for conducting clinical trials with drugs in Brazil" to "RDC no. 09/2015" 	<ul style="list-style-type: none"> As the 1st edition of the Submission Manual had been finished before the publication of the new rule, the new RDC number had not been defined yet. This was corrected in this first review.
2 nd Edition	<ul style="list-style-type: none"> The petition subject name was changed to: Global Transfer of Responsibility over DDCM (page 15) 	<ul style="list-style-type: none"> Petition subject name was change.
2 nd Edition	<ul style="list-style-type: none"> The petition subject name was changed to: Global Transfer of Responsibility over Clinical Trial (page 15) 	<ul style="list-style-type: none"> Petition subject name was change.
2 nd Edition	<ul style="list-style-type: none"> Section "Transitional Dispositions" was removed 	<ul style="list-style-type: none"> With over one year from the implementation of RDC no. 09/2015, these transitional dispositions lost their objective and are no longer applicable.
3 rd Edition	<ul style="list-style-type: none"> Inclusion of the following sentence in the 4th paragraph of item 6.1: "Also inform if the mechanism of action is innovative." 	<ul style="list-style-type: none"> The information on the innovation of the mechanism of action is important to assess the clinical development rationale.
3 rd Edition	<ul style="list-style-type: none"> Inclusion of the following sentence in the 5th paragraph of item 6.1: "A technical justification for the clinical development must also be described." 	<ul style="list-style-type: none"> For better understanding which is the technical justification for the clinical development.



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3 rd Edition	<ul style="list-style-type: none"> Inclusion of the following paragraph on item 6.1: "It is recommended to use the development plan template available in the Attachment I of this Manual." 	<ul style="list-style-type: none"> Due to problems identified in development plans assessed so far, COPEC developed a template plan to facilitate the document analysis by Anvisa.
3 rd Edition	<ul style="list-style-type: none"> Change of item "6.2 Experimental Drug Dossier" to item 6.3 	<ul style="list-style-type: none"> Numbering correction
3 rd Edition	<ul style="list-style-type: none"> Inclusion of Attachment I 	<ul style="list-style-type: none"> Provision of a development plan template to facilitate the document analysis by Anvisa