Brazilian Health Surveillance Agency

MANUAL FOR SUBMISSION OF CHANGES, AMENDMENTS, SUSPENSIONS AND CANCELLATIONS

General Drug Management - GGMED
Coordination of Clinical Research in Drug Products and Biological Products - COPEC

2017
Brasília, 16/Aug/2018
This Manual aims to guide the professionals of the area with information on how to apply the Resolution RDC/Anvisa no. 09, dated February 20, 2015, thus contributing for the development of safe actions, in addition to making available relevant and updated information that can be better explained through the Manual.

The Manual does not create new obligations, and should be used by public and private agents as a reference for compliance of the already existing Legislation.
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1. ACRONYM

DDCM – Drugs Clinical Development Dossier
API – Active Pharmaceutical Ingredient
CRO – Contract Research Organization
RDC – Resolution of the Collegiate Board of Directors

2. INTRODUCTION

The publication of the regulation on Clinical Trials with drug products in Brazil provides changes, amendments, suspensions and cancellations as part of the clinical drug development. This manual has the purpose of supplying guidance for the sponsor, investigator-sponsor or CRO make these submissions adequately.

This is a regulatory measure of unbinding character used as complement to health legislation, with the purpose of guidance regarding routines and procedures for legislation compliance, not destined to the amplification or restriction of the established technical or administrative requirements.

3. LEGAL BACKGROUND

Anvisa Resolution - RDC no. 9, dated February 20, 2015, which provides for the regulation for the performance of clinical trials with drugs in Brazil.

4. PURPOSE

Without prejudice to the existing regulations in legal provisions, this manual aims to guide the submissions of modifications to the Drugs Clinical Development Dossier (DDCM), amendments to the clinical protocols, suspensions, and cancellations according to chapters IV, V, and VI of the RDC no. 09/2015.

The document is broken down into specific sections for each type of change. The changes are described in detail, with examples and their specific application subjects.

We emphasize that the situations and examples mentioned in this manual are illustrative, but by no means, exhaustive or restrictive. Each situation must be assessed on a case-by-case basis, and contexts lying outside the ones herein described shall be always followed by rationales.
5. CHANGES TO DDCM

Changes to DDCM, in the context of RDC 09/2015, are defined as any changes performed to the overall context of DDCM - specifically those related to the quality of the investigational product - or administrative changes, such as form updates.

All changes must be submitted to Anvisa. The substantial changes shall be filed as they are performed, and implementation must await manifestation, while the non-substantial changes shall be submitted as part of the safety update report regarding the experimental drug development. Details on the procedures for application are described below.

Substantial changes can be filed at any time after the initial DDCM submission, even before the final manifestation by Anvisa.

For the purposes of the Resolution, substantial changes are:

I - Inclusion of clinical trial protocol(s) not foreseen or different from that (those) previously established in the initial development plan;

II - Exclusion of clinical trial protocol(s);

III - Amendments that may potentially generate impact to the quality or safety of the investigational drug, active comparator, or placebo.

It is the sponsor’s responsibility to assess whether a change is considered substantial or not and its impact on the clinical development. This assessment should always be performed on a case-by-case basis, based on the aforementioned criteria and on the examples below.

The following are examples of substantial changes related to the quality or safety of the investigational product. We emphasize that the lists below are illustrative only, not exhausting all the possibilities.

1. Substantial changes:

   a. Changes related to the active pharmaceutical ingredient;
   b. Changes related to the quality control and stability of the active pharmaceutical ingredient and investigational drug;
   c. Changes related to the inactive ingredient quality control;
   d. Changes of description and composition of the investigational drug;
2. Non-substantial changes:

a. Update of DDCM Application Form;
b. Labeling change of the investigational product;
c. Any changes in placebos previously provided in the DDCM;
d. Test Drug Development Plan Update, whose change does not impact the clinical trials to be conducted in Brazil;
e. Spell check in documents;
f. Minor clarifications.
g. Changes of shelf lives not provided for in letter k of item 5, sub-item 1 of substantial changes.

For changes of any information contained in the Form, the submission of new form with updated information and document describing the reasons for each change is enough. The clinical trial amendment is not a change, as explained in the next section. It is recommended that substantial changes are accompanied by a comparative table, if applicable.
The applicant must update the forms whenever there is a change in the data therein contained (and not just at the time of submission of annual reports, for example), because this data reflect the advertising of clinical trials at Anvisa website and will be used to guide inspections in Good Clinical Practices. The update for this form does not depend on the Agency’s prior approval.

Substantial changes should be a secondary application to the primary application of DDCM submission for the experimental drug, except for change by inclusion of clinical trial protocol not provided for in the initial development plan, which is a primary petition. The inclusion and exclusion of clinical trials have their own subjects, namely:

- **10818 - CLINICAL TRIALS - DDCM Change - Inclusion of clinical trial protocol not provided in the initial development plan**
  - The inclusion of the clinical trial protocols that were already provided in the initial development plan should be performed using specific subject according to the Manual for Submission of Drug Clinical Development Dossier (DDCM) and Specific Clinical Trial Dossier.

- **10819 - CLINICAL TRIALS - DDCM Change - Exclusion of clinical trial protocol**

The changes that potentially generate impact on the quality or safety of the investigational drug, active comparator or placebo, as examples above, should use the application subject **10820 - CLINICAL TRIALS - DDCM Change - Changes that may potentially generate impact on the quality or safety of the investigational product. (Comparative) Documentation of the initial situation and of the proposal must be submitted along with technical rationale and any additional documents required to prove that the change will not impact on the clinical development of the product.**

It is noteworthy to highlight that it is the sponsor’s responsibility to evaluate and classify the changes prior to submission to the Agency, so that a risk/benefit analysis and the need for supporting documentation is performed. As a suggestion for greater flexibility and ease of submitting the changes to analysis, the Attachment I of this manual, available in DOC version at Anvisa website, can be optionally completed and submitted along with other documents.
The shelf-life change should use the subject 10849 - CLINICAL TRIALS - DDCM Change - Shelf-life Change. As suggestion for more agility and ease in the analysis of this type of application, it can be completed and submitted along with the other documents, optionally, the Attachment III of this manual, available in version DOC at the Anvisa website. In addition, it is recommended for this subject of application:

- To submit rationales for any changes of analytical method that have occurred since the last submission, including a brief summary of their characteristics and validation status of the new method;
- To investigate and justify any deviation of the specifications that has been verified, even if it has occurred only in the accelerated study conditions;
- To submit stability study after dilution or reconstitution, for applicable products;
- To submit photostability study or rationale for its absence;
- For files that have been updated since the previous submission, submit version with tracked changes; and
- In cases where there were multiple manufacturing plants for API and finished product, the submitted files should allow easily the identification of the referred manufacturing plants.

Non-substantial changes do not have a specific application subject and should be integrated to the application 10825 - CLINICAL TRIALS - Update Safety Report of the Investigational Drug Development.
6. AMENDMENTS TO PROTOCOL

Amendments, in the context of RDC 09/2015, are defined as any changes made to the clinical protocol, whether they are substantial or not.

All amendments must be submitted to Anvisa. Substantial amendments shall be filed, when their performance and implementation must await manifestation, while non-substantial changes must be submitted as part of the annual report of the clinical trial. Details on the procedures for filing will be described below.

Substantial amendments may be filed at any time after the inclusion of the first clinical protocol to DDCM, even before the final manifestation by Anvisa.

Substantial changes are those where one or more of the following criteria are met:

- Changes in the clinical trial protocol affecting the safety, physical or mental integrity of individuals;
- Change in the scientific value of the clinical trial protocol;

Conceptually, a clinical trial has scientific value if:

a. It assesses a therapeutic or diagnostic intervention that can lead to improvements in health and quality of life; or
b. It is a preliminary etiologic, pathophysiological, or epidemiological study to develop such intervention; or

It tests a hypothesis that can generate important knowledge about the structure or the functioning of human biological systems, even if this knowledge has no immediate practical ramifications.

It is the sponsor’s responsibility to assess whether an amendment is considered significant or not and its impact on clinical development. This assessment should always be performed on a case-by-case basis, based on the aforementioned criteria.

Here are some examples for each category of amendments, including examples of situations that do not constitute an amendment. Note that the list below is illustrative only, not exhausting all possibilities.
1. **Substantial Amendments:**

   a. Change of the primary objective of the clinical protocol;
   
   b. Change of the primary endpoints;
   
   c. Using new parameter to measure the primary endpoint;
   
   d. Removing the Independent Data Monitoring Committee originally planned for the study;
   
   e. Change in the sample size calculation provided for the study.

2. **Non-substantial amendments:**

   a. Change, addition, or removal of exploratory endpoints;
   
   b. Proposals for extending or continuing research with the same enrolled participants, without change in the design, methods and objectives of the original project. In the case any of these changes takes place, another research protocol must be submitted, not an amendment;
   
   c. Addition of preventive safety monitoring, not related to any issued safety notifications.
   
   d. New data or interpretation about pharmacological or toxicological data;
   
   e. Change in criterion established for protocol termination, even though this has already been completed;
   
   f. Change in the inclusion and exclusion criteria;
   
   g. Reduction in the number of scheduled visits;
   
   h. Change in diagnostic procedures or medical monitoring;
   
   i. Change in the secondary or exploratory endpoints;
   
   j. Minor clarifications to the protocol;
   
   k. Spell check;

The applicant must update the Clinical Trial Presentation Form whenever there is a change in the data contained therein (and not just at the time of submission of annual reports, for example), because this data reflects the advertising of clinical trials at the Anvisa website and will be used to guide inspections for Good Clinical Practices. The update for this form does not depend on prior approval of the Agency, except when there is:

- Change in the title or in the code of the clinical trial protocol;
- Inclusion or exclusion of the investigational products to be imported
- Change in storage conditions and shelf-life of the investigational products.
For these cases, a new version of the CE (special notification) will be issued.

3. **Examples that do not constitute amendments to the protocol:**

   a. Investigator’s Brochure update. This should be filed as 10821 - CLINICAL TRIALS - Investigator’s Brochure Update, unless it also substantiates changes to the clinical protocol. In this case, the change must be evaluated by the Sponsor and rated as substantial or not, and respective procedures must be followed.

   b. Changes in the DDCM submission form or in attached documents. These should be filed as 10822 - CLINICAL TRIALS - Change of DDCM Application Form.

   c. Changes in the submission form of the clinical protocol. These should be filed as 10823 - CLINICAL TRIALS - Change of Clinical Trial Presentation Form.

   1. The applicant should update the Clinical Trial Presentation Form whenever there is change in the contained data, since this data reflects the advertising of the clinical trials at the Anvisa website and will be used to direct inspections in Good Clinical Practices. Updating of this form does not depend on Agency’s previous manifestation, except when there is:

      i. Change in the title or code of the clinical trial protocol;

      ii. Inclusion or exclusion of investigational products to be imported;

      iii. Change in the storage conditions and shelf-life of the investigational products.

   For these cases, a new version of CE will be issued.

   d. Proposal to extend the clinical protocol in which change in design, methods or objectives are expected. For this type of change, a new clinical protocol should be added to DDCM, not fitting amendment to the protocol already submitted, as explained in the examples of non-substantial amendments.

   e. Exclusion, cancellation, suspension, or reactivation of clinical trial protocol.

Substantial amendments should be a secondary application to the primary application that entered the clinical protocol in DDCM for the investigational drug. As a suggestion for
greater flexibility and ease of submitting amendments to the analysis, the Attachment II of this manual can be optionally completed and submitted along with other documents. The specific subject of application is 10824 - CLINICAL TRIALS - Substantial Amendment to Clinical Protocol.

Non-substantial amendments do not have a specific application subject and should be integrated into the application in 1391 - CLINICAL TRIALS - Annual Follow-up Report for Clinical Trial Protocol with the same documents required for substantial amendments.
7. SUSPENSIONS AND CANCELLATIONS

- For DDCM:

A DDCM may be canceled or suspended. These situations have their own application subjects and should not constitute any of the applications of the aforementioned changes. After suspension or cancellation decision, the sponsor must notify Anvisa within 15 calendar days.

If the cancellation occurs through company’s request, including cancellation cases for safety reasons, the application subject 10826 - CLINICAL TRIALS - DDCM cancellation at request should be used; if cancellation occurs for global transfer of responsibility, the application subject is 10827 - CLINICAL TRIALS – Global Responsibility Transfer on DDCM. It is important to remember that cancellations under RDC 09/2015 are definitive, with no possibility of subsequent reactivation, and that once a DDCM is cancelled, no clinical trials related thereto may be continued in the country. In the specific case of the DDCM cancellation at request, requirements to be submitted to the follow-up plan and for measures to minimize/mitigate the risk of participants in clinical trials already ongoing are detailed in the Manual for Adverse Event Notification and Safety Monitoring in Clinical Trials.

It is important to remember that, for a DDCM, cancellation can occur at any time, even though it has not yet been assessed.

For suspensions, the subject to be used is 10828 - CLINICAL TRIALS - Temporary suspension of DDCM. By definition, these have a temporary character and can be reversed with the application subject 10829 - CLINICAL TRIALS - Reactivation of suspended DDCM. Reactivation is subject to prior approval by Anvisa.

- For a Clinical Trial:

As well as the DDCM, an individual clinical trial can also be canceled or suspended. These situations have their own application subjects and should not constitute any of the applications of the aforementioned amendments. After suspension or cancellation decision, the sponsor must notify Anvisa within 15 calendar days, except in cases of temporary suspension as an immediate safety measure, when the deadline is 7 calendar days from the date of suspension. In addition, cancellations, in the terms of RDC 09/2015, are definitive with no possibility of subsequent reactivation.
It is important to remember that the cancellation only applies to clinical trial protocols that have been initiated by the sponsor. If the protocol is provided in DDCM, but has not been started yet, the protocol exclusion should be performed, as provided in the previous section.

If the cancellation occurs as the company's request, including cancellation cases for safety reasons, the application subject 10767 - CLINICAL TRIALS - Clinical Trial Protocol Cancellation at request should be used; if cancellation occurs for global transfer of responsibility, the application subject 10053 - CLINICAL TRIALS - Global Responsibility Transfer on Clinical Trial Protocol. In the specific case of the cancellation at request, the requirements to be submitted to the monitoring plan and for measures to minimize/mitigate the risk of trial participants are detailed in the Manual for Adverse Event Notification and Safety Monitoring in Clinical Trials.

For suspensions, the subject to be used is 10830 - CLINICAL TRIALS - Temporary suspension of Clinical Trial Protocol. By definition, these have a temporary character and can be reversed with the application subject 10831 - CLINICAL TRIALS - suspended Clinical Trial Protocol Reactivation. Reactivation is subject to prior approval by Anvisa.
8. **GLOSSARY**

I- Drug Clinical Development Dossier (DDCM) – compilation of documents to be submitted to Anvisa with the purpose of evaluating the steps inherent to the development of a test drug aiming to gather information to subside the registration or post-registration changes of the mentioned product;

II- Specific Dossier for each Clinical trial - compilation of documents to be submitted to Anvisa with the purpose of obtaining information relative to the clinical trials, to be conducted in Brazil, which make part of the Test Drug Development Plan;

III- Clinical trial protocol amendment – any proposed change in an original clinical trial protocol, submitted always with the rationale that motivated it, and such amendment can be substantial or not;

IV- Clinical trial – research conducted in human beings with the purpose of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamics effect of the test drug and/or identifying any adverse reaction to the test drug and/or studying the absorption, distribution, metabolism and excretion of the test drug to verify its safety and/or efficacy;

V- Test drug – tested pharmaceutical product, purpose of the DDCM, to be used in the clinical trial, with the purpose of obtaining information for its registration or post-registration;

VI- Contract Research Organization (CRO) – every company regularly installed in national territory hired by the sponsor or by the investigator-sponsor, which assumes partial or totally, along with Anvisa, the sponsor’s attributions;

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

VIII- Investigational product – Test drug, placebo, active comparator or any other product to be used in the clinical trial;

IX- Clinical Trial Protocol – document describing the purposes, design, methodology, statistical considerations and trial organization. It also provides the context and the rationale of the clinical trial;
9. REFERENCES


10. ATTACHMENTS

The attachments of this manual are also available in DOC format at the Anvisa Electronic Portal > Drugs > Clinical Research > Forms.

**ATTACHMENT I**

APPLICATION FORM FOR SUBSTANTIAL CHANGE OF THE DRUG CLINICAL DEVELOPMENT DOSSIER (DDCM)

<table>
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<th>Document Identification</th>
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<td>File (Day/ Month/ Year)</td>
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**Company Data**

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<td>Number of Authorization/Registration</td>
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**DDCM Data**

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<tr>
<td>7</td>
<td>Change Type:</td>
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<tr>
<td></td>
<td>a) Inclusion of clinical trial protocol(s) not provided or different from those previously established in the initial development plan?</td>
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<td>b) Exclusion of clinical trial protocol(s)?</td>
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<td></td>
<td>c) Changes that may potentially generate impact to the quality or safety of the investigational product?</td>
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<td>a. If so, see item 9.</td>
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<td>d) Change from recommendations or alerts issued by health authorities?</td>
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<td>8</td>
<td>Reasons for Substantial Change:</td>
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<tr>
<td></td>
<td>a) Changes related to the active pharmaceutical ingredient?</td>
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<td>b) Changes related to the quality control and stability of the active pharmaceutical ingredient and investigational product?</td>
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<td>c) Changes related to the inactive ingredient quality control?</td>
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<td></td>
<td>d) Description and composition changes of the investigational product?</td>
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<td>Changes related to the manufacturing site of the investigational product?</td>
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<td>e</td>
<td>( ) Yes ( ) No</td>
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**ATTACHMENT II**  
APPLICATION FORM FOR SUBSTANTIAL CHANGE TO THE  
CLINICAL TRIAL PROTOCOL

Brazilian Health Surveillance Agency Clinical Research Application  
Form for Substantial Change of the Drug Clinical Development Dossier  
(DDMC)

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**Clinical Trial Protocol Data**

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<th>8 Generator Factor (datavisa)</th>
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<tr>
<th>9 Title and Code of the Clinical Trial Protocol</th>
<th>10 Protocol number (version and date)</th>
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<th>11 Trial Phase</th>
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| I | II | III | IV |

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<tr>
<th>12 Reasons for Substantial Amendment:</th>
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<tr>
<th>a) Change of the primary objective of the clinical protocol;</th>
<th>a) ( ) Yes ( ) No</th>
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<td>b) Change of the primary endpoints;</td>
<td>b) ( ) Yes ( ) No</td>
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<td>c) Using new parameter to measure the primary endpoint;</td>
<td>c) ( ) Yes ( ) No</td>
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<td>d) Removing the Independent Data Monitoring Committee originally planned for the study;</td>
<td>d) ( ) Yes ( ) No</td>
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<tr>
<td>e) Change in the sample size calculation provided for the study.</td>
<td>e) ( ) Yes ( ) No</td>
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ATTACHMENT III
TEMPLATE FOR SUBMISSION OF UPDATED STABILITY INFORMATION
LONG-TERM STABILITY STUDY (30°C ± 2°C / RH 75 ± 5% RH)

Product:
Active ingredient:
API Manufacturer’s Name and Address:
Finished Product Manufacturer’s Name and Address:
Primary package:
Dosage form:
Date of Manufacturing:
Quantity of samples analyzed by period:

Study Start Date:
Study End Date:
Batch:
API Batch:
Batch sizes (API and Finished Product):
Dosage:
Batch destination:
Package Position:

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<tr>
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<th>24 months</th>
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*Also inform whether it is from pharmacopeia or not

**Rationales should be submitted for any methods that will not be or were not performed in all the analysis times.
## 11. HISTORY OF CHANGES

<table>
<thead>
<tr>
<th>Version</th>
<th>Changes performed</th>
<th>Explanation and Rationale</th>
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<tbody>
<tr>
<td>1st Edition</td>
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<tr>
<td>2nd Edition</td>
<td>• Inclusion of the title 6. History of Changes <em>(Page 15)</em></td>
<td>• Insertion of comparative table of the writings between versions for a more transparent follow-up of the updates performed.</td>
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<tr>
<td></td>
<td>2. Non-substantial changes.</td>
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<tr>
<td></td>
<td>▪ a. DCCM Application Form Update <em>(Page 4)</em></td>
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<tr>
<td>2nd Edition</td>
<td>• Changes to the DDCM</td>
<td>• Exclusion of the example &quot;a&quot;, once the form update is a secondary application with proper subject, and should not be integrated to the annual report in the non-substantial change situation.</td>
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<td>2. Non-substantial changes.</td>
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<tr>
<td></td>
<td>▪ b. Update of the Experimental Drug Development Plan <em>(Page 4)</em></td>
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</tr>
<tr>
<td>2nd Edition</td>
<td>• Changes to the DDCM</td>
<td>• Inclusion of the &quot;Update of the Experimental Drug Development Plan&quot; as example of non-substantial change. The plan update is only required when the application of substantial changes, but its update should be possible at the sponsor’s discretion.</td>
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<td>2. Non-substantial changes.</td>
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<td></td>
<td>▪ c. Update of comparator drug package insert <em>(Page 4)</em></td>
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<tr>
<td>2nd Edition</td>
<td>• Changes to the DDCM</td>
<td>• Exclusion, for further clarity, of the example &quot;c&quot; after receipt of contribution, considering that the update of comparator drug package insert is not an item included by RDC no. 09/2015.</td>
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<td>2. Non-substantial changes.</td>
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<td></td>
<td>▪ c. Update of comparator drug package insert <em>(Page 4)</em></td>
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<tr>
<td>2nd Edition</td>
<td>Changes to the DDCM</td>
<td>In consonance with the first change, the excerpt was removed because it mentioned the possibility of submission of updated form in the non-substantial change situation, since the form update is a secondary application with proper subject.</td>
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<td>• The applicant must update the forms whenever there is a change in the data therein contained (and not just at the time of submission of annual reports, for example), because this data reflects the advertising of clinical trials at Anvisa website and will be used to guide inspections in Good Clinical Practices. The update for this form does not depend on the Agency’s prior approval. (Page 5)</td>
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| 2nd Edition | Amendments to the Protocol  
    • c. Change in the documentation used by the study team to collect and record the data. (Page 9) |
|  | • Exclusion of the example “c” after receipt of contributions reporting that the type of track change is not present in the clinical protocol. For all the purposes, any change in the documentation or media used during the protocol can be verified at the time of an inspection in GCP. |
| 2nd Edition | Amendments to the Protocol  
    • g. Clinical Trial Presentation Form Update. (Page 9) |
|  | • Exclusion of the example “g”, once the form update is a secondary application with proper subject, and should be integrated to the annual report in the situation of non-substantial amendment. |
| 2nd Edition | Amendments to the Protocol |
|  | • Excluded the excerpt that mentioned the possibility of the submission of updated form in the non-substantial change situation, since the form update is a secondary application with proper subject. |
The applicant must update the Clinical Trial Presentation Form whenever there is a change in the data contained therein (and not just at the time of submission of annual reports, for example), because this data reflects the advertising of clinical trials at the Anvisa website and will be used to guide inspections for Good Clinical Practices. The update for this form does not depend on prior approval of the Agency, except where there is:

- Change in the title or in the code of the clinical trial protocol;
- Inclusion or exclusion of the investigational product to be imported;
- Change in storage conditions and shelf-life of the investigational products.

For these cases, a new version of the CE will be issued. (Page 10)

| 2nd Edition | • Changed the name of the application subject to: 10827 – CLINICAL TRIALS – Global Responsibility Transfer on DDCM (page 14). | • Change of the application subject name. |
| 2nd Edition | • Changed the name of the application subject to: 10053 – CLINICAL TRIALS - Global Responsibility Transfer on Clinical Trial Protocol (page 15). | • Change of the application subject name. |
| 2nd Edition | • Title of the item 1 of the Form contained in the attachments I and II
• Exclusion of the item 7 of the Form contained in the attachments I and II | • As the process number request is already performed in the header, the field no. 7 was removed to avoid redundancies and the title of the field 1 was explained for each form. |
<table>
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<th>Edition</th>
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| 2nd     | • Added Attachment III, "Template for submission of updated stability information"
         | • Changes to the DDCM:
         |   o "The shelf-life change should use the subject 10849 - CLINICAL TRIALS - DDCM Change - Shelf-life Change. As suggestion for faster agility and facility in the analysis of this type of application, it can be completed and submitted along with the other documents, optionally, the Attachment III of this manual" |
| 3rd     | • Changes to the DDCM
         |   o 1. Substantial Changes
         |     ▪ New item “q”: Inclusion of placebo not previously provided in the DDCM; |
|         | • A new item was inserted exclusively relative to the placebo to be a counterpoint to the new sub-item “c”, item 2. Non-substantial changes. Attachments of the Manual were updated to reflect this change. |
| 3rd     | • Changes to the DDCM
         |   o 2. Non-substantial changes
         |     ▪ New item “c”: Any changes in placebos already provided previously in DDCM; |
|         | • Based on a risk analysis performed by COPEC, it was chosen to explicitly exemplify that changes regarding previously provided placebos are no longer considered as substantial. A counterpoint was added to the item 1 of the same section to perform this situation the inclusion of placebos that were not included in the initial analysis. The attachments of the Manual were updated to reflect this change. |
## 3rd Edition

- Amendments to the Protocol
  - Substantial Amendments – transposition of the following examples that are not present as example of NON-substantial amendments:
  d. New data or interpretation about pharmacological or toxicological data, passive of impact on the risk analysis;
  e. Change in criterion established for end of the protocol, even though this has already been completed;
  f. Inclusion of experimental arms or placebo group;
  g. Change in the inclusion and exclusion criteria;
  h. Reduction in the number of scheduled visits;
  i. Change in diagnostic procedures or medical monitoring;
  j. Change in the investigational product;
  k. Change in the investigational product dosage;
  l. Change in the administration route of the investigational product;
  m. Change in the clinical protocol design;
  n. Change in the secondary or exploratory endpoints;

Clinical trial Presentation Form Update.

## 4th Edition

- Cover page: inclusion of the effective date.

- Item 5, sub-item 1. Substantial Modifications: The letters "b," "d" to "i" had the term "investigational product" changed to "experimental drug".

- The change was made to comply with the terms of RDC 09/2015.

- Based on a risk analysis performed by COPEC, it was chosen to relate these items as examples of NON-substantial amendments from the 3rd edition. The Manual attachments were updated to reflect this change.
| 4th Edition | Item 5, sub-item 1: Substantial Modifications
k. Changes related to the shelf life provided that there has been a change in the previously established stability assessment criteria, that the values are not within the permitted ranges, or that the shelf life is defined based on reduced stability study plan models (grouping and Matrixing)? Changes related to shelf life or conservation care of the investigational product. |
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<tr>
<td>4th Edition</td>
<td>The text has been modified to reduce situations where the change in the shelf life should be considered as a substantial change.</td>
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</table>
| 4th Edition | Item 5, sub-item 2: Substantial modifications
\[10pt\]d. Updating of the Experimental Drug Development Plan, whose change does not impact the clinical trials to be conducted in Brazil. |
| 4th Edition | Sentence was included to clarify that in cases of substantial modification by inclusion of protocol not provided for in the plan, an updated development plan must be provided. For other cases, the update is considered as non-substantial. |
| 4th Edition | Item 5, sub-item 2: Substantial modifications
\[10pt\]e. Update of the comparison drug package insert. The remaining items were renumbered from "f" and "g" to "e" and "f". |
| 4th Edition | The example has been removed to avoid confusion in the understanding as per question 3.2.8 of the Questions and Answers document version 2. |
| 4th Edition | Item 5, sub-item 2: Substantial modifications
\[10pt\]g. Changes of shelf lives not provided for in letter k of item 5, sub-item 1 of substantial modifications. |
| 4th Edition | Inclusion was performed to reflect the reduction in cases where the change in shelf life should be considered as substantial modification. |
| 4th Edition | Item 5 - Modifications to DDCM Substantial modifications should constitute a secondary petition to the primary petition for submission of the experimental drug DDCM, except for modification by inclusion of clinical trial protocol not provided for in the initial development plan, which is a primary petition. |
| 4th Edition | Inclusion of the sentence was performed to indicate that the substantial modification by inclusion of a protocol not provided for in the initial development plan is a primary petition because it represents the Specific Clinical Trials Dossier (DEEC) itself, which is a primary petition. |
### Item 5, sub-item 2, Substantial Amendments
- **c. Change in documentation used by the study team to capture and record data:**
  - Subsequent letters were renumbered from "d" to "l" to "c" to "k".

### Annex I, item 8
- **k. Changes related to the shelf life provided that there has been a change in the previously established stability assessment criteria, that the values are not within the permitted ranges, or that the shelf life is defined based on reduced stability study plan models (grouping and Matrixing)?**
  - Changes related to shelf-life or conservation care of the investigational product

### Annex II, item 12: item exclusion
- The subsequent item was renumbered from "13" to "12".

### Other modifications?
- **If yes, specify:**