National Health Surveillance Agency

MANUAL FOR SUBMISSION OF MODIFICATIONS, AMENDMENTS, SUSPENSIONS AND CANCELLATIONS

General Medicines Management - GGMED

Coordination of Clinical Research on Medicines and Products Biological – COPEC

Brasilia, 04/26/2021

MANUAL FOR SUBMISSION OF MODIFICATIONS, AMENDMENTS, SUSPENSIONS AND CANCELLATIONS

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

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

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SUMMARY

1. CONFIDENTIAL

BCM - Master Cell Bank

COPEC - Coordination of Clinical Research in Medicines and Biological Products

DDCM - Clinical Drug Development Dossier

DEEC - Specific Clinical Trial Dossier

API – Active Pharmaceutical Ingredient

ORPC - Representative Clinical Research Organization

RDC - Resolution of the Collegiate Board of Directors

2. INTRODUCTION

The publication of the regulation on Clinical Trials with drugs in Brazil provides for modifications, amendments, suspensions and cancellations as part of the clinical development of drugs. This manual is intended to provide guidelines for the sponsor, investigator-sponsor or CRO to make these submissions properly.

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, 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 regulation for conducting clinical trials with drugs in Brazil.

4. OBJECTIVE

Without prejudice to the existing provisions in the legal provisions, this manual aims to guide the submission of modifications to the Clinical Drug Development Dossier (DDCM), amendments to clinical protocols, suspensions and cancellations,
as described in chapters IV, V and VI of RDC No. 09/2015.

The document breaks down into specific sections for each type of change. The changes are described in detail, with examples and the respective specific petition subjects.

We emphasize that the situations and examples contained in this manual are illustrative and not restrictive or exhaustive. Each situation must be evaluated on a case-by-case basis, and contexts that differ from those described here must always be accompanied by justifications.

5. MODIFICATIONS TO THE DDCM

Modifications to the DDCM, in the context of RDC No. 09/2015, are defined as any changes made in the global context of the DDCM, especially those related to the quality of the investigational product or administrative changes, such as form updates, for example.

All changes must be submitted to Anvisa. Substantial modifications must be filed when they are carried out and their implementation must await manifestation, while non-substantial modifications must be presented as part of the safety update report on the development of the investigational drug.
Details on the petitioning procedures will be described below.

Substantial changes can be filed at any time after the initial submission of the DDCM, including before Anvisa's final statement.

For the purposes of the Resolution, the substantial changes consist of:

- Inclusion of unforeseen or different clinical trial protocol(s)
from the one(s) previously established in the initial development plan;

II - Exclusion of clinical trial protocol(s);

III - Changes that potentially generate an impact on the quality or safety of the investigational drug, modified active comparator, or placebo.

A clinical trial protocol is considered as provided for in the plan when all information about the phase, design, objectives, outcomes, comparator, dosage of the investigational drug and comparators, pharmaceutical form of the investigational drug, population, hypothesis, sample size and planning statistics are fully presented in the initial Development Plan or when there is no change in this information. The petition with this development plan must be

granted by Anvisa.

Below are the modifications considered substantial, non-substantial and changes that do not constitute a modification that potentially impact the quality or safety of the investigational drug, modified active comparator or placebo.

Cases not listed may be discussed with the Agency through the formal contact channels available, if necessary.

1. Substantial Modifications:

The. Modifications related to **Active Pharmaceutical Ingredient - API / Active Substance (biological products),** as described below:

i. Replacement/Inclusion of a new manufacturing site or manufacturing steps;

ii. Alteration of the synthesis route (synthetic/semi-synthetic);

iii. Change in the manufacturing process of the active substance of biological products:

iii.1 Change in cell banks, involving:

iii.1.1 Generation of a new Master Cell Bank (BCM) from the same expression construct with the same cell lineage or highly similar cell lineage; or

iii. 1.2 Generation of new BCM from a different expression construct with the same coding sequence and the same cell lineage; or iii. 1.3 Adaptation of a new BCM in a new culture medium;

Where

iii.1.4 Generation of new BCM for a recombinant product or viral vaccine.

iii.2 Change in seed banks, involving:

iii. 2.1 Establishment of a new Master Seed Bank (BSM);

Where

iii. 2.2 Extension of the number of passes of the Seed Bank of Work (BST) beyond the approved level.

iii.3 Changing the place of manufacture of the cell bank or bank of seeds;

iii.4 Alteration of the fermentation process or viral propagation or cell, fractionation or extraction:

iii.4.1 Critical change (change with high potential to impact the quality of the active substance or finished product, for example, incorporation of disposable bioreactor technology);

iii.4.2 Change with moderate potential to impact the quality of the active substance or finished product (eg extension of *in vitro* cell age beyond validated parameters).

iii.5 Change in the purification process:

iii.5.1 Critical change (change with high potential to impact the quality of the active substance and finished product, for example, a change that could potentially impact the

viral removal/inactivation capacity or impurity profile of the active substance);

iii.5.2 Change with moderate potential to impact the quality of the active substance and the finished product (eg change in chemical separation method, such as switching from ion exchange HPLC to reverse phase HPLC).

iii.6 Change in the scale of the manufacturing process:

iii.6.1 In the stage of fermentation or viral or cellular propagation;

iii.6.2 In the purification step.

iv. Change, inclusion or exclusion of API/active substance production equipment with different design and operating principle;

v. Modifications in the physicochemical properties of the API/Active substance that influence the quality of the investigational drug (for example, particle size distribution, polymorphism, etc.);

saw. Modifications related to quality control, such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters such as quantification of content and impurities, provided that the method is not equivalent or superior to the original method .

B. Modifications related to the **Experimental Drug,** as described below:

i. Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for immediate/conventional release synthetic and semi-synthetic drugs; ii. Modifications impacting the release of the API or active substance of the investigational drug or critical quality parameters, including stability and impurities, and:

ii.1 Qualitative changes in composition;

ii.2 Change in the manufacturing process and inclusion or exclusion of equipment with different design and operating principle; ii.3 Increase in the lot size above 10 (ten) times the initially approved lot size;

ii.4 Change of primary packaging;

iii. Modifications related to quality control such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters, provided that the method is not equivalent or superior to the original method;

iv. Extension of the shelf life and/or change in conservation care, provided that there has been a change in the previously established stability assessment criteria, that the values are not within the ranges

allowed or that the validity period is defined based on reduced stability study plan models (grouping and matrixing); v. Inclusion of a new presentation that will require new stability studies; saw. Inclusion of a new concentration; vii. Inclusion of a new pharmaceutical form; viii.Inclusion of a new route of administration with a change in the pharmaceutical form;

ç. Modifications related to **Placebo or Modified Active Comparator,** as Described below:

i. Inclusion of placebo and/or unanticipated modified active comparator formerly not DDCM.

2. Insubstantial Modifications:

The. Change in the corporate name of the API/active substance or investigational drug manufacturing site;

B. Exclusion of an additional manufacturer of the API/active substance or investigational drug for reasons not related to safety/quality;

ç. Replacement/Inclusion of a new manufacturing site or manufacturing steps of an immediate/conventional synthetic and semi-synthetic experimental drug;

d. Changes related to the secondary and tertiary packaging of the API/active substance or experimental drug;

and. Replacement/Inclusion of API/active substance quality control site or experimental drug;

f. Inclusion of an additional analytical test to evaluate the same process control parameter, quality control and stability of API/active substance or investigational drug;

g. Narrowing specification limits of in-process control tests, quality control and stability of the API/active substance or investigational drug;

H. Alteration, inclusions or exclusions of the analytical method for purposes of adaptation to an official compendium recognized by Anvisa regarding in-process control, quality control and stability of the API/active substance or experimental drug;

i. Quantitative and quality control changes of excipients of the investigational drug;

j. Increase in batch size of less than ten (10) times the batch size initially approved for synthetic or semi-synthetic drugs;

k Increase in lot size less than 10 (ten) times the initially lot size

approved for biological medicines, provided that the conditions below are fully met:

1. The proposed scale uses equipment(s) equivalent to the approved equipment(s).

2. Changes to the manufacturing process or in-process controls are only those necessary for the change in lot size (eg the same formulation, controls and standard operating procedures are used).

3. The change is not due to recurring events arising during manufacturing or stability issues.

4. There is no change in the principle of the sterilization procedures of the finished product.

6. The change does not affect the lyophilization step.

l. Alteration of equipment used in the API/active substance manufacturing process or experimental drug, keeping the principle of operation (purpose) unchanged;

m. Reduction of the expiration date of the API/active substance or investigational drug;

no. Extension of the validity period without any type of change or inclusion of method and/or specification;

The. Substantial modification of the registered investigational drug, whose modification has already been approved by the registration area;

P. Update of the DDCM Petition Form;

q. Alteration of the labeling of the investigational drug; a. Any changes in placebo previously provided for in the DDCM; s. Small clarifications.

To modify any information contained in the Form, it is sufficient to submit a new form with the updated information and a document describing the justifications for each change.

The applicant must update the forms whenever there is a change in the data contained therein (and not just at the time of submission of annual reports, for example), as these data reflect the advertising of clinical trials on Anvisa's website and will be used to guide inspections in Good Clinical Practice. Updating this form does not depend on the Agency's prior manifestation.

Amendment to the clinical trial does not constitute a modification to the DDCM, as explained in the next section.

Substantial modifications must constitute a secondary petition to the primary petition for submission of the DDCM of the investigational drug, with the exception of the modification by inclusion of a clinical trial protocol not provided for in the initial development plan, which is a

primary petition. The inclusion and exclusion of clinical trials and the change that potentially impacts the quality or safety of the investigational drug, modified comparator drug and placebo have their own issues, namely:

- 10818 - CLINICAL TRIALS - Modification of DDCM - Inclusion of a clinical trial protocol not provided for in the initial development plan
- 10819 - CLINICAL TRIALS - Modification of DDCM - Exclusion of Protocol of clinical trial
- 10820 - CLINICAL TRIALS - Modification of DDCM - Alteration that potentially impacts the quality or safety of the product under investigation

Clinical trial protocols that were already provided for in the initial Development Plan must be submitted according to the specific subjects described in the Manual for Submission of Clinical Drug Development Dossier (DDCM) and Specific Clinical Trial Dossier (DEEC).

For cases of changes that potentially impact the quality or safety of the investigational drug, comparator drug or placebo, a comparative table must be presented between the current approved situation and the proposed change, accompanied by the respective technical justifications, and any additional documents
necessary to prove that the change will not impact the clinical development of the product.

It is the sponsor's responsibility to evaluate and classify the modifications prior to the submission to the Agency, so that a risk/benefit analysis is carried out and as to the need to present supporting documentation. As a suggestion for greater agility and ease in submitting the changes to analysis, Annex I of this manual, available in DOC version on Anvisa's website, can be filled out and submitted together with the other documents, optionally.

The change in the expiration date of the investigational drug classified as a substantial modification according to item 1.b.iv must use the subject code 10849 – CLINICAL TRIALS – Modification of DDCM – Change of Shelf Life.

As a suggestion for greater agility and ease in the analysis of this type of petition, Annex III of this manual, available in DOC version on Anvisa's website, can be filled out and submitted together with the other documents, optionally. In addition, it is recommended for this petition subject:

- Submit justifications for any analytical method changes that have occurred since the last submission, including a brief summary of its characteristics and validation status of the new method;

- Investigate and justify any deviation from the specifications that has been verified, even if it has only occurred under accelerated study conditions;

- Submit a stability study after dilution or reconstitution, for products applicable;
- Present a photo stability study or justification for its absence;
- For files that have been updated since the previous submission, send a version with highlighted changes; and
- In cases where there are multiple manufacturing plants for API and for finished product, the files sent must easily allow the identification of the manufacturing plants to which they refer.

The change in the expiration date of the investigational drug classified as non-substantial according to item 2.m and 2.n, as well as all other non-substantial changes, do not have a specific petition subject, and must be integrated into petition 10825 - CLINICAL TRIALS - Report of Experimental Drug Development Safety Update.

The FAEC must be updated with the new expiration date through subject code 10823 - CLINICAL TRIALS - Change of Clinical Trial Submission Form.

3. The following do not constitute Modifications to the DDCM:

The. Investigator's Brochure Update. This must be filed as 10821 - CLINICAL TRIALS – Update of Investigator's Brochure, unless it also substantiates a change in the clinical protocol. In this case, the change must be evaluated by the Sponsor and classified as substantial or not, and the respective procedures must be followed.

B. Modifications to the DDCM submission form. These must be petitioned as 10822 - CLINICAL TRIALS - Amendment of the DDCM Petition Form.

6. AMENDMENTS TO THE PROTOCOL

Amendments, in the context of RDC No. 09/2015, are defined as any changes made to the clinical protocol, whether substantial or not.

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

Substantial amendments can be filed at any time after the inclusion of the first clinical protocol in the DDCM, including before Anvisa's final statement.

It is the sponsor's responsibility to assess whether an amendment is considered substantial and its impact on clinical development.

It is essential that amendments clearly identify the part of the protocol to be modified, provide the rationale for each change, and that the clean version and the *track changes* version of the protocol be forwarded. It is important that the Clinical Trial Submission Form is updated in accordance with protocol changes applicable to the fields on this form.

Below are amendments deemed substantial, non-substantial, and amendments that do not constitute an amendment.

1. Substantial Amendments:

Substantial amendments are considered to be changes in the clinical trial protocol that interfere with the safety, physical or mental integrity of the participants or even change the scientific value of the clinical trial protocol, such as:

The. Change in the primary objective of the clinical protocol;

B. Change in primary outcomes;

ç. Use of a new parameter to measure the primary outcome;

d. Removal of the Independent Data Monitoring Committee initially planned for the study;

and. Change in the sample size calculation not foreseen for the study;

f. Reduction in sample size due to the interim analysis provided for in the study;

g. Change from statistical analysis to primary outcomes;

H. Dosage-related changes that are not provided for in the protocol;

i. Extension or continuation of clinical research with removal of the control arm or active arm, crossing between arms *(cross-over),* changing the blinding of the study or inclusion of new participants;

j. Adaptive modifications, such as modification/deletion/addition of treatment arms, alteration of outcomes, modification of dose and/or duration of treatment, or adaptation of randomization schemes;

k Inclusion of a new route of administration;

l. Expansion of use;

m.Others, at the sponsor's discretion (including justification).

2. Insubstantial Amendments:

The. Changing, adding or removing exploratory outcomes;

B. Extension or continuity of the research keeping the participants recruited, without changing the design, methods and primary objectives of the approved project.

ç. Addition of preventive security monitoring, unrelated to any security advisories issued. d. New data or interpretation of pharmacological or toxicological data;

and. Change in the criteria established for the end of the protocol, even if it has already ended;

f. Change in inclusion and exclusion criteria; g.

Minor modifications related to adaptive studies, such as a phase 2/3 study, in which phase 2 is dose choice and phase 3 is a confirmatory study with the dose chosen in phase 2, with no change in the primary outcome or other major changes;

H. Maintenance or increase in the sample size due to the interim analysis foreseen in the study;

i. Unpredicted sample size increase for the study without primary outcome change or other major changes;

j. Change in the number of scheduled visits;

k Change in diagnostic procedures or medical monitoring;

l. Change in secondary or exploratory outcomes;

m.Small clarifications regarding the protocol.

3. The following do not constitute amendments to the protocol:

The. Changes in the clinical protocol submission form. These must be filed as 10823 - CLINICAL TRIALS – Change in Clinical Trial Submission Form.
The applicant must update the Clinical Trial Submission Form whenever there is a change in the data contained therein, as these data reflect the publicity of the trials

clinical trials on Anvisa's website and will be used to guide inspections on Good Clinical Practices. The updating of this form does not depend on the Agency's prior manifestation, except when there is:

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

ii. Inclusion or exclusion of products under investigation to be imported;

iii. Change in storage conditions and shelf life of products under investigations that require prior notice.

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

B. Extension or continuity of clinical research in which a new study design is foreseen, including changes in methods, outcomes or primary objectives. For this type of change, a new clinical protocol must be added to the DDCM.

ç. Deletion, cancellation, suspension or reactivation of a clinical trial protocol.

Substantial amendments must constitute a secondary petition to the primary petition that inserted the clinical protocol into the DDCM of the investigational drug. As a suggestion for greater agility and ease in submitting the amendments for analysis, Annex II of this manual, available in DOC version on Anvisa's website, can be filled out and submitted together with the other documents, optionally. The specific subject of the petition is 10824 - ESSAYS CLINICIANS – Substantial Amendment to Clinical Protocol.

Non-substantial amendments do not have a specific petition subject, and must be integrated into petition 1391 – CLINICAL TRIALS – Clinical Trial Protocol Annual Follow-up Report with the same documents required for substantial amendments.

7. SUSPENSIONS AND CANCELLATIONS

• For DDCM:

A DDCM can be canceled or suspended. These situations have their own petition subjects and should not constitute any of the aforementioned change petitions. After decision of suspension or cancellation, the sponsor must notify Anvisa within a maximum period of 15 calendar days.

In cases of temporary suspension of the DDCM as an immediate security measure, the sponsor must notify Anvisa within 7 (seven) calendar days from the date of suspension, justifying the reasons.

If the cancellation is at the request of the company, including cases of cancellation for security reasons, the petition subject 10826 - CLINICAL TRIALS - must be used.
DDCM cancellation on request;

Cancellations, under the terms of RDC No. 09/2015, are definitive, with no possibility of subsequent reactivation. Thus, once the DDCM is cancelled, no clinical trials related to it can be continued in the country. In the specific case of cancellation of DDCM on request, the requirements that must be submitted for the follow-up plan and for the risk minimization/mitigation measures of the participants of clinical trials already in progress are detailed in the Manual for Notification of Adverse Events and Monitoring Safety in Clinical Trials.

The cancellation of a DDCM can occur at any time, even if it has not yet been evaluated.

For suspensions, the subject to be used is 10828 - CLINICAL TRIALS - Temporary suspension of DDCM. By definition, these have a temporary nature, and can be reversed through petition subject 10829 - CLINICAL TRIALS - Reactivation of suspended DDCM. Reactivation depends on prior approval from Anvisa.

When all activities of a clinical trial in Brazil are closed, it is not necessary the suspension or cancellation of the DDCM. The DDCM will remain active for future protocol additions, and annual updates to the investigational drug development safety update report, investigator brochure update and substantial changes are not mandatory. If a new clinical trial with such a drug is conducted in Brazil, the DDCM must be updated with the documentation of the period in which it was inactive and, for situations in which substantial changes have occurred, these must await a statement from Anvisa.

• **For a Clinical Trial:**

As in the case of DDCM, an individual clinical trial can also be canceled or suspended. These situations have their own petition subjects and should not constitute any of the aforementioned amendment petitions. After a decision to suspend or cancel, the sponsor must notify Anvisa within a maximum period of 15 calendar days, except in cases of temporary suspension as an immediate security measure, when the period is 7 calendar days from the date of suspension. In addition, cancellations, under the terms of RDC No. 09/2015, are definitive, with no possibility of subsequent reactivation.

Cancellation only applies to clinical trial protocols that have already been initiated by the sponsor. If the protocol is provided for in the DDCM, but has not yet been started, the protocol must be deleted, as provided in the previous section.

If the cancellation is at the request of the company, including cases of cancellation for security reasons, the petition subject 10767 – CLINICAL TRIALS – must be used.
Cancellation of Clinical Trial Protocol on request. If the cancellation is due to global transfer of responsibility, the subject of the petition is 10053 - CLINICAL TRIALS -
Global Transfer of Responsibility for Clinical Trial Protocol. In the specific case of cancellation on request, the requirements that must be submitted for the follow-up plan and for the risk minimization/ mitigation measures of the clinical trial participants are detailed in the Manual for Notification of Adverse Events 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 nature, and can be reversed with the subject of petition 10831 - CLINICAL TRIALS - Reactivation of suspended Clinical Trial Protocol. Reactivation depends on prior approval from Anvisa
which will evaluate the company's justification and other criteria such as the potential risk identified, related adverse events, measures already taken (both by the sponsor and by other regulatory authorities, when applicable) and the data of notifications with the drug reported to COPEC, if applicable .

8. GLOSSARY

- Clinical Drug Development Dossier (DDCM) - compiled from documents to be submitted to Anvisa in order to evaluate the steps inherent to the development of an experimental drug in order to obtain information to support the registration or post-registration changes of the aforementioned product;

II - Specific Dossier for each Clinical Trial (DEEC) - compiled from documents to be submitted to Anvisa in order to obtain information regarding clinical trials, to be conducted in Brazil, which are part of the Drug Development Plan
Experimental;

III - Amendment to the clinical trial protocol - any proposal for modification in an original clinical trial protocol, always presented with the justification that motivated it, whether such amendment may be substantial or not;

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

V - Experimental drug - pharmaceutical product under test, object of the DDCM, to be used in the clinical trial, in order to obtain information for its registration or post-registration;

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

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

VIII Research product - experimental drug, placebo, active comparator or any other product to be used in the clinical trial;

IX - 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;

9. BIBLIOGRAPHIC REFERENCES

1. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RDC No. 09, of February 20, 2015, published in the DOU of March 3, 2015. Provides for the regulation for conducting clinical trials with drugs in Brazil. Official Diary of the Union; Executive Branch, of March 3, 2015.

2. EUROPEAN COMISSION. Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of trial (CT-1). Available at: http://ec.europa.eu/health/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf. Accessed on November 20, 2014.

3. FOOD AND DRUG ADMINISTRATION. IND Application Reporting: Protocol Amendments. Available in: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedand Approved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362503.h tm. Accessed on November 19, 2014.

4. HEALTH CANADA. Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications. Available at: https://www.canada.ca/content/dam/hc-sc/migration/hc sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec eng.pdf . Accessed on March 30, 2021.

5. EUROPEAN MEDICINES AGENCY. Guideline on the requirements for quality documentation

concerning biological investigational medicinal products in clinical trials, 2012.

6. EUROPEAN MEDICINES AGENCY. Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials EMA/CHMP/QWP/545525/2017.

10. ANNEXES

The attachments to this manual are also available in DOC format on the Portal Anvisa Electronics > Subjects > Medicines > Clinical Research > Publications > Manuals and Guides.

ANNEX I

PETITION FORM FOR SUBSTANTIAL MODIFICATION OF CLINICAL DRUG DEVELOPMENT DOSSIER (DDCM)

National Health Surveillance Agency
Clinical research
Petition Form for Substantial Modification of the Dossier of Clinical Drug Development (DDCM)

Document Identification
(For use by the receiving body)

1	DDCM Process Number	2	Workday (Day / Month / Year) / /

Company Data

3	Applicant	4	Authorization/Registration Number
5	Maker	6	Authorization/Registration Number

DDCM data

7	**Modification Type:** a) Inclusion of unforeseen clinical trial protocol(s) or different from the one(s) previously established in the initial development plan? b) Exclusion of clinical trial protocol(s)? c) Changes that potentially impact the quality or safety of the product under investigation? The. If yes, see item 8. d) Modification arising from recommendations or alerts issued by health authorities?	a) ( ) Yes ( ) No b) ( ) Yes ( ) No c) ( ) Yes ( ) No d) ( ) Yes ( ) No

8	**Reasons for Substantial Modification:** **a) Modifications related to the Active Pharmaceutical Ingredient - API/Active Substance (biologicals)?** i. Replacement/Inclusion of new manufacturing site or manufacturing steps? ii. Change in the synthesis route (synthetic/semi-synthetic)? iii. Change in the manufacturing process of the active substance of biological products? iii.1 Change in cell banks, involving: iii.1.1 Generation of a new Master Cell Bank (BCM) from the same expression construct with the same cell lineage or highly similar cell lineage? iii. 1.2 Generation of new BCM from a different expression construct with the same coding sequence and the same cell lineage? iii. 1.3 Adaptation of a new BCM in a new culture medium? iii.1.4 Generation of new BCM for a recombinant product or viral vaccine? iii.2 Change in seed banks, involving: iii. 2.1 Establishment of a new Master Seed Bank (BSM)? iii. 2.2 Extension of the number of Work Seed Bank (BST) passes beyond the approved level? iii.3 Changing the cell bank or seed bank manufacturing location? iii.4 Alteration of the fermentation process or viral or cellular propagation, fractionation or extraction: iii.4.1 Critical change (change with high potential impact on the quality of the active substance or finished product, for example, incorporation of disposable bioreactor technology)? iii.4.2 Change with moderate potential to impact the quality of the active substance or finished product (eg extension of in vitro cell age beyond validated parameters)? iii.5 Change in the purification process: iii.5.1 Critical change (change with high potential to impact active substance and finished product quality, eg a change that could potentially impact viral removal/inactivation capacity or active substance impurity profile)? iii.5.2 Change with moderate potential to impact the quality of active substance and finished product (eg change in chemical separation method, such as switching from ion-exchange HPLC to reverse-phase HPLC)? iii.6 Change in the scale of the manufacturing process: iii.6.1 In the stage of fermentation or viral or cellular propagation? iii.6.2 In the purification step?	**a) ( ) Yes ( ) No** i. ( ) Yes No ii. ( ) Yes No iii. ( ) Yes No iii.1.1 ( ) Yes ( ) No iii.1.2 ( ) Yes ( ) No iii.1.3 ( ) Yes ( ) No iii.1.4 ( ) Yes ( ) No iii.2.1 ( ) Yes ( ) No iii.2.2 ( ) Yes ( ) No iii.3 ( ) Yes ( ) No iii.4.1 ( ) Yes ( ) No iii.4.2 ( ) Yes ( ) No iii.5.1( ) Yes ( ) No iii.5.2 ( ) Yes ( ) No iii.6.1 ( ) Yes ( ) No iii.6.2 ( ) Yes ( ) No

iv. Change, inclusion or exclusion of API/active substance production equipment with different design and operating principle?	iv. ( ) Yes No
v. Changes in the physicochemical properties of the API/Active substance influencing the quality of the investigational drug (eg particle size distribution, polymorphism, etc.)?	v. ( ) Yes No
saw. Modifications related to quality control, such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters such as quantification of content and impurities, provided that the method is not equivalent or superior to the original method ?	saw. ( ) Yes No
b) Modifications related to the Experimental Medication?	**b) ( ) Yes ( ) No**
i. Replacement/Inclusion of new manufacturing site or manufacturing steps, except for immediate/conventional release synthetic and semi-synthetic drugs?	i. ( ) Yes No
ii. Modifications impacting the release of the API or active substance of the investigational drug or critical quality parameters, including stability and impurities, and:	
ii.1 Qualitative changes in composition?	ii.1 ( ) Yes ( ) No
ii.2 Change in the manufacturing process and inclusion or exclusion of equipment with different design and operating principle? ii.3 Increase in lot size above 10 (ten) times the initially approved lot size?	ii.2. ( ) Yes No ii.3. ( ) Yes No
ii.4 Change of primary packaging?	ii4. ( ) Yes No
iii. Modifications related to quality control such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters, provided that the method is not equivalent or superior to the original method?	iii. ( ) Yes No
iv. Extension of the shelf life and/or change in conservation care, provided that there has been a change in the previously established stability assessment criteria, that the values are not within the allowed ranges or that the shelf life is defined based on models reduced stability study plan (grouping and matrixing)? v. Inclusion of a new presentation that will require new stability studies?	iv. ( ) Yes No v. ( ) Yes No
saw. Inclusion of new concentration?	saw. ( ) Yes No
vii. Inclusion of a new pharmaceutical form?	vii. ( ) Yes No
viii. Inclusion of a new route of administration with a change in pharmaceutical form?	viii. ( ) Yes No
c) Modifications related to Placebo or Modified Active Comparator?	**c) ( ) Yes ( ) No**
i. Inclusion of placebo and/or unanticipated modified active comparator previously not DDCM?	i. ( ) Yes No

	d) Others, at the sponsor's discretion (including justifications).	**d) ( ) Yes ( ) No**

ANNEX II

PETITION FORM FOR SUBSTANTIAL AMENDMENT TO PROTOCOL
OF CLINICAL TRIALS

National Health Surveillance Agency
Clinical research
Petition Form for Substantial Amendment to Test Protocol
Clinical

Document Identification
(For use by the receiving agency)

1	Clinical Trial Specific Dossier Process Number	2	Workday (Day / Month / Year) / /

Company Data

3	Applicant	4	Authorization/Registration Number
5	Maker	6	Authorization/Registration Number

Clinical Protocol Data

7 Subject of the Petition (codes and description)		8 Triggering Fact (datavisa)		
9 Title and Code of the Clinical Trial Protocol		10 Protocol No. (Version and date)		
		11 Test Phase	I () II () III () IV ()	

12	**Reasons for Substantial Amendment:** a) Change in the primary objective of the clinical protocol? b) Change in primary outcomes? c) Use of a new parameter to measure the primary outcome? d) Removal of the Independent Data Monitoring Committee originally planned for the study? e) Change in the sample size calculation not foreseen for the study? f) Reduction in sample size due to expected interim analysis in the study? g) Change from statistical analysis to primary outcomes? h) Changes related to dosage, which are not foreseen in the protocol? i) Extension or continuity of clinical research with removal of the control arm or active arm, crossing between arms (cross over), changing the blinding of the study or inclusion of new participants? j) Major modifications related to adaptive studies, such as modification/ deletion/addition of treatment arms, alteration of outcomes, modification of dose and/or duration of treatment, or adaptation of randomization schemes? k) Inclusion of a new route of administration? l) Expansion of use? m) Others, at the sponsor's discretion (including justifications).	a) ( ) Yes ( ) No b) ( ) Yes ( ) No c) ( ) Yes ( ) No d) ( ) Yes ( ) No e) ( ) Yes ( ) No f) ( ) Yes ( ) No g) ( ) Yes ( ) No h) ( ) Yes ( ) No i) ( ) Yes No j) ( ) Yes No k) ( ) Yes ( ) No l) ( ) Yes No m) ( ) Yes ( ) No

ANEXO III

MODELO PARA ENVIO DE INFORMAÇÕES ATUALIZADAS DE ESTABILIDADE

ESTUDO DE ESTABILIDADE DE LONGA DURAÇÃO (30°C ± 2°C / 75 UR ± 5% UR)

Produto:
Princípio ativo:
Nome e Endereço do Fabricante do IFA:
Nome e Endereço do Fabricante do Produto Acabado:
Embalagem primária:
Forma farmacêutica:
Data de Fabricação:
Quantidade de amostras analisadas por período:

Data de Início do Estudo:
Data de Término do Estudo:
Lote:
Lote do IFA:
Tamanho dos lotes (IFA e Produto Acabado):
Dosagem:
Destinação do lote:
Posicão da Embalagem:

Teste	Especificação	Método	Inicial (t0)	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses	36 meses
		*	**	**	**	**	**	**	**	

* Informar também se é farmacopeico ou não

** Devem ser apresentadas justificativas para quaisquer métodos que não serão ou não foram executados em todos os tempos de análise.

11. CHANGE HISTORY

Version	Changes made	Explanation and Justification
1st edition		
2nd Edition	• Inclusion of title **6. History of Changes** • Insertion of a comparative table of essays between versions for a more transparent monitoring of updates performed. *(Page 15)*	
2nd Edition	• Modifications to DDCM o 2. Non-substantial Modifications. ý ~~The. Update of Petition Form for DDCM.~~ *(Page* 4)	• Exclusion of example "a", once that the form update is a secondary petition with the subject itself and should not be integrated into the annual report on the status of non-substantial modification.
2nd Edition	• Modifications to DDCM o 2. Non-substantial Modifications. ý B. Updating the Plan Development do Medicine Experimental. *(Page* 4)	• Inclusion of the "Update of the Drug Development Experimental" as an example of non-substantial modification. THE plan update is only required at the time of application substantial changes, but It should be possible to update it to sponsor's discretion.
2nd Edition	• Modifications to DDCM o 2. Non-substantial Modifications. ý ~~ç. package insert update comparator drug.~~ *(Page* 4)	• Exclusion, for clarity, of the example "c" after receipt of contribution, considering that the drug package insert update comparator is not a covered item by RDC No. 09/2015.
2nd Edition	• Modifications to DDCM o The applicant must update the forms whenever there are change in the data contained therein (~~and not just at the time of~~	• In line with the first amendment, the section that mentioned the possibility of updated form submission modification situation no substantial, as the update of

	~~submission of annual reports, by example),~~ as these data reflect advertising of clinical trials on the website electronic form of Anvisa and will be used to guide inspections in Good Practices clinics. Updating this form does not depend on prior manifestation of the Agency. *(Page* 5)	form is a secondary petition with its own subject.
2nd Edition	• Amendments to the Protocol o 2. Non-substantial Amendments. ÿ ~~ç. change in documentation used by study team for capture and registration of Dice.~~ *(Page* 9)	• Deletion of example "c" after receipt of contributions reporting that the type of change highlighted is not included in the protocol clinical. For all purposes, any change in documentation or media used during the protocol may be verified at the time of BPC inspection.
2nd Edition	• Amendments to the Protocol o 2. Non-substantial Amendments. ÿ ~~g. update of Presentation Form of the Clinical Trial.~~ *(Page 9)*	• Exclusion of example "g", once that the form update is a secondary petition with the subject itself and should not be integrated into the annual report on amendment status non-substantial.
2nd Edition	• Amendments to the Protocol o The applicant must update the Submission Form Clinical Trial whenever there is change in the data contained therein (~~and~~ **~~not~~** ~~just at the time of submission of annual reports, by example),~~ as these data reflect the publicity of clinical trials in the Anvisa's website and will be used to guide inspections in	• Excluded the passage that mentioned the possibility of submitting form updated on the status of non-substantial modification, as the form update is a secondary petition with subject own. The paragraph in your integrity was moved to constitute subitem of example "c" of item "3. Examples that do not

	Good Clinical Practices. The update of this form does not depend on prior statement by the Agency, **except** when there is: The. Change in title or code of clinical trial protocol; B. Inclusion or exclusion of products under investigation to be imported ç. Change in conditions of storage and shelf life of the products under investigation. For these cases, a new version of the EC will be issued. *(Page 10)*	amendments to the protocol" for better suitability and clarity.
2nd Edition	• Changed the name of the petition subject to: 10827 - CLINICAL TRIALS - Global Transfer of Responsibility about DDCM *(page* 14).	• Changing the subject name of petition.
2nd Edition	• Changed the name of the petition subject to: 10053 - CLINICAL TRIALS - Global Transfer of Responsibility on Clinical Trial Protocol *(page* 15).	• Changing the subject name of petition.
2nd Edition	• Title of item 1 of the Form contained in the annexes I and II • Exclusion of item 7 of the Form contained in annexes I and II	• As the request for the number of process is already done in the header, the field #7 has been removed to avoid redundancies and field title 1 has been clarified for each form
2nd Edition	• Added Annex III, "Template for sending updated stability information" • Modifications to DDCM: o "Changing the expiration date should use subject 10849 – CLINICAL TRIALS - DDCM Modification - Change of Expiry Date. How	• A template for sending stability information in the attempt to harmonize the information received and optimize the analysis by technicians

	ease of analysis of this type of petition, can be completed and submitted together with the others documents, optionally, or Annex III of this manual"	
3rd Edition	• Modifications to DDCM o 1. Substantial Modifications ÿ New item “q”: Inclusion of a placebo not previously provided for in the DDCM;	• A new item referring to exclusively to placebo to be a counterpoint to the new sub-item “c”, item 2. Modifications No substantial. The annexes of the Manual have been updated to reflect this change.
3rd Edition	• Modifications to DDCM o 2. Non-substantial changes ÿ New item “c”: Any changes in placebos previously provided for in the DDCM;	• Based on a risk analysis carried out by COPEC, it was decided to explicitly exemplify that changes related to placebos previously foreseen are no longer considered substantial. One counterpoint was added to item 1 of the same section to except that situation the inclusion of placebos that were not included at the time of the analysis. initial. The annexes to the Manual have been updated to reflect this change.
3rd Edition	• Amendments to the Protocol o Substantial Amendments – transposition of the following examples to now appear as an example of amendments NO substantial: d. New data or interpretation of pharmacological or toxicological data, likely to impact the ~~risk analysis;~~ and. Change in the criteria established for the end of the protocol, even if it has already ended; f. Addition of experimental arms or group placebo; g. Change in inclusion and exclusion criteria; H. Reduction in the number of scheduled visits;	• Based on a risk analysis carried out by COPEC, it was decided to relate these items as examples of NON-substantial amendments to from the 3rd edition. The attachments of Manual have been updated to reflect this change.

	i. Change in diagnostic procedures or medical monitoring; j. Change in the product under investigation; k ~~Change in the dosage of the product under investigation;~~ l. ~~Change in the method of administration of the product under investigation;~~ m. ~~Change in clinical protocol design;~~ no. Change in secondary or exploratory outcomes ~~Presentation Form Update~~ of the Clinical Trial.	
3rd Edition	• Amendments to the Protocol ~~Thus, examples of change of scientific value are the change from a placebo comparator to an active comparator, the insertion or addition of additional arms or changes in the statistical analysis plan.~~	• Considering the new examples of list of substantial changes, the removal of that paragraph was needed to align the text with the list of examples.
Edition	• Cover: inclusion of effective date 4th	• Inclusion is to identify from from what date is the manual in force
4th Edition	• Item 5, sub-item 1. Substantial Modifications: The letters “b, “d” to “i” had the term “investigative product” changed to “experimental drug”	• The change was made to be in according to the terms of the DRC 09/2015.
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 allowed ranges or that the shelf life is defined based on reduced stability study plan models (clustering and matrixing)? Changes related to the shelf life or conservation care of the product under investigation	• Text change was performed to reduce situations in which the change of expiration date must be considered as modification substantial.
4th Edition	• Item 5, sub-item 2: Modifications not d. Update of the Experimental Drug Development Plan, whose change does not impact clinical trials to be conducted in Brazil.	• Phrase included to make it clear that substantial in cases of substantial modification by inclusion of protocol provided for in the plan, a plan of updated development must be provided. For the other cases, the update is considered not substantial.

4th Edition	• Item 5, Sub-item 2: No Modifications • The example has been withdrawn and. Comparator drug package insert update The other items were renumbered from “f” and “g” to “e” and “f”.	• The inclusion was made to reflect the reduction of cases where the change expiration date must be considered as modification substantial.
	• Item 5, sub-item 2: Non-substantial Modifications g. Changes to unforeseen expiration dates 4th Edition in letter k of item 5, sub-item 1 of substantial changes	
4th Edition	• Item 5 – Modifications to the DDCM Substantial modifications must constitute a secondary petition to the primary petition for submission of the DDCM of the investigational drug, with the exception of the modification by inclusion of a clinical trial protocol not provided for in the initial development plan, which is a primary petition.	• The inclusion of the phrase was made to indicate that the modification substantial by protocol inclusion not foreseen in the initial plan of development is a petition primary, as it configures the own Specific Test Dossier Clinic (DEEC), which is a petition primary.
4th Edition	• Item 5, Sub-item 2, Non-substantial Amendments ç. Change in the documentation used by the study team to capture and record data, Subsequent letters were renumbered from “d” to “l” to “c” to “k”.	• The example has been removed to avoid confusion no understanding, according to question 3.2.12 of Q&A document version 2.
4th Edition	• Anexo 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 allowed ranges or that the shelf life is defined based on reduced stability study plan models (clustering and matrixing)? Changes related to the shelf life or conservation care of the product under investigation	• Change made to reflect the manual changes.
4th Edition	• Anexo I, item 8: • a. Exclusion of drug manufacturing site or primary packaging site or secondary packaging site or product manufacturing site?	• Deletion of the item to reflect the criteria established in the manual

4th Edition	• Anexo I, item 8: ~~• t. Other modifications?~~ ~~o If yes, specify:~~	• Deletion of the item to reflect the criteria established in the manual as a substantial modification
4th Edition	• Annex II, item 12: item exclusion The subsequent item was renumbered from “13” to “12”.	• Exclusion of the item, as the criteria established to be considered substantial amendment is already in subsequent question.
4th Edition	• Annex II, item 13: ~~f) Other modifications?~~ ~~o If yes, specify:~~	• Deletion of the item to reflect the criteria established in the manual as a substantial amendment
5th Edition	• Cover: inclusion of effective date	• Inclusion is to identify from from what date is the manual in force
5th Edition	• Sign: BCM - Master Cell Bank COPEC - Coordination of Clinical Research in Medicines and Biological Products DEEC - Specific Clinical Trial Dossier	• Update of the seglary with new abbreviations inserted in the document.
5th Edition	• Item 5 – Modifications to the DDCM • A clinical trial protocol is considered as provided for in the plan when all information about the phase, design, objectives, outcomes, comparator, dosage of the investigational drug of the comparators, pharmaceutical form of the investigational drug, ~~population, hypothesis, sample~~ and planning statistics are fully presented in the initial Development Plan or when there is no change in this information. The petition with this development plan must be granted by Anvisa.	• Insertion of what is considered to be planned clinical trial protocol in the Development Plan.
	~~• It is the sponsor's responsibility to assess whether a modification is considered substantial or not its impact on clinical development. This assessment should always be done on a case-by-case basis, based on the above criteria and the examples below.~~ • Below are examples ~~of changes~~ considered substantial , non-substantial, and • Rewriting of the text for clarification. changes that do not constitute a modification that potentially generate an impact related to the quality or safety of the investigational drug, modified active comparator or placebo. ~~product under investigation. We emphasize that the lists below are illustrative only, not exhausting all possibilities.~~	• Deletion of the item added to a more detailed lists of substantial changes and not substances in order to reduce subjectivity. Removal of the last sentence as it was a more detailed list of examples from modifications substantial and non-substantial,

	• Cases not listed may be discussed with the Agency through the formal contact channels available, if necessary.	but cases not listed yet can be discussed with the Agency according to the next paragraph. • Inclusion of the possibility of discussion of other items not listings.
5th Edition	• Item 5.1 - Modifications related to the Active Pharmaceutical Ingredient - API/Active Substance (biological products), as described below: • i. Replacement/Inclusion of a new manufacturing site or manufacturing steps; ii.. Alteration of the • synthesis route (synthetic/semi-synthetic); • iii. Change in the manufacturing process of the active substance of biological products: • iii.1 Change in cell banks, involving: • iii.1.1 Generation of a new Master Cell Bank (BCM) from the same expression construct with the same cell lineage or highly similar cell lineage; or iii. 1.2 Generation of new BCM from • a different expression construct with the same coding sequence and the same cell lineage; or iii. 1.3 Adaptation of a new BCM in a new culture • medium; • iii.1.4 Generation of a new BCM for a recombinant product or viral vaccine • iii.2 Change in seed banks, involving: • iii2.1 Establishment of a new Master Seed Bank (BSM); or iii.2.2 Extension of the number of tickets • of the Working Seed Bank (BST) beyond the approved level • iii.3 Change of place of fabrication of the cell bank or seed bank; iii.4 Alteration of the fermentation process or viral or • cellular propagation, fractionation or extraction: • iii.4.1 Critical change (change with high potential to impact the quality of the active substance or finished product, for example, incorporation of disposable bioreactor technology) • iii.4.2 Change with moderate potential to impact the quality of the	• Inclusion from examples from modifications related to API/Active Substance to reflect the main objective of this review: detail the changes considered as substantial And no substantial.

	active substance or finished product (e.g. extension of in vitro cell age beyond validated parameters) • iii.5 Changing the process of purification • iii.5.1 Critical change (change with high potential to impact the quality of the active substance and the finished product, for example, a change that could potentially impact the viral removal/inactivation capacity or impurity profile of the active substance); • iii.5.2 Change with moderate potential to impact the quality of the active substance and the finished product (for example, change in chemical separation method, such as substitution of ion exchange HPLC for reverse phase HPLC) • iii.6 Change in the scale of the manufacturing process • iii.6.1 In the fermentation or viral or cellular propagation step iii.6.2 In the • purification step • iv. Change, inclusion or exclusion of API/ substance production equipment active with different design and operating principle. v. Modifications in the physicochemical • properties of the API/Active substance influencing the quality of the experimental drug (eg particle size distribution, polymorphism, etc.) • saw. Modifications related to quality control, such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters such as quantification of content and impurities, provided that the method is not equivalent or superior to the original method	
5th Edition	• Item 5.1 - Modifications related to the Experimental Drug, as described below: i. • Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for immediate/conventional release synthetic and semi-synthetic drugs; ii. • Modifications impacting the release of the API or active substance of the investigational drug or critical quality parameters, including stability and impurities, and: • ii.1 Qualitative changes in the	• Inclusion from examples from modifications related to Experimental drug for reflect the main objective of this review: detail the changes considered substantial and not substantial.

	composition; • ii.2 Change in the manufacturing process and inclusion or exclusion of equipment with different design and operating principle; ii.3 Increase in the lot size above 10 (ten) times the initially approved • lot size; • ii.4 • ii.5 Change of primary packaging; • iii. Modifications related to quality control such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters, provided that the method is not equivalent or superior to the original method; iv. Extension of the shelf life and/or change in conservation care, provided that there has been a change in the • previously established stability assessment criteria, that the values are not within the allowed ranges or that the shelf life is defined based on models reduced stability study plans (grouping and matrixing); • v. Inclusion of a new presentation that it will demand new stability studies; saw. Inclusion • of a new concentration; vii. Inclusion of a new • pharmaceutical form; viii. Inclusion of a new route • of administration with a change in pharmaceutical form; •	
5th Edition	• Item 5.1 - Modifications related to the Placebo or Modified Active Comparator as described below: • i. Inclusion of a previously unanticipated modified placebo and/or active comparator in the DDCM.	• Inclusion from examples from modifications related to Placebo or Active Comparator for reflect the main objective of this review: detail the changes considered substantial and not substantial.
5th Edition	• Item 5.2 - Non-substantial Modifications: • ~~d. Update of the Experimental Drug Development Plan, whose change does not impact clinical trials to be conducted in Brazil;~~ • ~~and. Spell correction in documents;~~ • The. Modification of the corporate name of the place of manufacture of the API/active substance or of the	• Exclusion of “Plan Update of Development”, because it is not need to submit annually this update with the report annual security. the plan of

	experimental drug; • B. Exclusion of an additional manufacturer of the API/active substance or investigational drug for reasons not related to safety/quality; • ç. Replacement/Inclusion of a new manufacturing site or manufacturing steps of an immediate/ conventional synthetic and semi-synthetic experimental drug; • d. Changes related to the secondary and tertiary packaging of the API/active substance or investigational drug; • and. Replacement/Inclusion of API/active substance or investigational drug quality control site; • f. Inclusion of an additional analytical test to evaluate the same process control parameter, quality control and stability of API/active substance or investigational drug; • g. Narrowing of limits of specification of in-process control tests, quality control and stability of the API/active substance or investigational drug; • H. Alteration, inclusions or exclusions of the analytical method for purposes of adaptation to an official compendium recognized by Anvisa regarding in-process control, quality control and stability of the API/active substance or experimental drug; • i. Quantitative and quality control changes of excipients of the investigational drug; • j. Increase in batch size of less than ten (10) times the batch size initially approved for synthetic or semi-synthetic drugs; • k Increase in batch size of less than 10 (ten) times the batch size initially approved for biological drugs, provided that the conditions below are fully met: • 1. The proposed scale uses equipment(s) equivalent to the approved equipment(s). • 2. Changes to the manufacturing process or in-process controls are only those necessary for the change in lot size (eg the same formulation, controls and standard operating procedures are used). • 3. The change is not due to events	updated development should only be submitted to ANVISA with a new proposed clinical protocol. • Removed “spelling corrections” because these are usually made as an administrative letter or in the next amendment to the protocol and not necessarily as a non-substantial modification. • Inclusion from examples from non-substantial changes to reflect the main objective of this review: detail the changes considered substantial and not substantial.

	recurring issues arising during manufacturing or stability issues. • 4. There is no change in the principle of the sterilization procedures of the finished product. • 6. The change does not affect the lyophilization step. • l. Alteration of equipment used in the manufacturing process of API/active substance or experimental drug, keeping the operating principle (purpose) unchanged; • m. Reduction of the validity period of the API/active substance or investigational drug; • no. Extension of the validity period without any type of change or inclusion of method and/or specification; • The. Substantial modification to the registered investigational drug, the modification of which has already been approved by the registration area; •	
5th Edition	• Item 5.2 - Non-substantial Modifications: • Substantial modifications must constitute a secondary petition to the primary petition for submission of the DDCM of the investigational drug, with the exception of the modification by inclusion of a clinical trial protocol not provided for in the initial development plan, which is a primary petition. The inclusion and exclusion of clinical trials and the change that potentially impacts the quality or safety of the investigational drug, modified comparator drug and placebo have their own issues, namely: • 10818 - CLINICAL TRIALS - Modification of DDCM - Inclusion of clinical trial protocol not provided for in the initial development plan • ~~The inclusion of clinical trial protocols that were already foreseen in the initial development plan must be done using a specific subject, according to Manual for Clinical Development Dossier Submission Medicines (DDCM) and Specific Clinical Trial Dossier.~~ • 10819 - CLINICAL TRIALS - Modification of DDCM - Exclusion of Clinical Trial Protocol • 10820 - CLINICAL TRIALS - Modification of DDCM - Alteration that potentially generates an impact on the quality or safety of the product under investigation	• Inclusion of the Quality change to comply with the Affairs lists to follow. • Text removed for next paragraph in order to leave in that item just the name of the Subjects. • Inclusion of quality change because it is one of the classified subjects as “DDCM Modification”.

	• Item 5.2 - Non-substantial Modifications: • For cases of Changes that potentially generate an impact on the quality or safety of the experimental drug, active comparator or placebo, according to the examples above, must use the subject of petition 10820 - CLINICAL TRIALS - Modification of DDCM – Change that potentially impacts the quality or safety of the product under investigation. He must A comparative (comparative) documentation table between the current approved initial situation and the proposed change must be presented , together with the respective technical justification documents addressing that the change will not impact the clinical development of the product. • The change in the validity period classified as a substantial modification according to item 1.b.iv must use subject 10849 - CLINICAL TRIALS – Modification of DDCM – Change of Expiration Date. • The change in the expiration date of the investigational drug classified as non-substantial according to item 2.m and 2.n, as well as all others . Experimental Drug Development Safety Update Report. • The FAEC must be updated with the new expiration date through subject code 10823 - CLINICAL TRIALS - Change of Clinical Trial Submission Form.	• Restructuring do paragraph removing the petition subject 10820 for the items listed above. • Phrase included to make it clear that type of term change validity must be submitted using subject 10849 and which must be submitted using the subject 10825. • Inclusion of information about FAEC update with new expiry dates for all situations mentioned in paragraph previous.
5th Edition	• Item 5.3 - Modifications to the DDCM do not: a. Investigator's Brochure Update. This • must be filed as 10821 - CLINICAL TRIALS - Investigator's Brochure Update, unless it also substantiates a change in the clinical protocol. In this case, the change must be evaluated by the Sponsor and classified as substantial or not, and the respective procedures must be followed. B. Modifications to the DDCM submission form. These must be •	• Inclusion of examples that are not classified as modifications to DDCM to reflect the main objective of this review: to detail the changes considered as substantial and non-substantial.

	petitioned as 10822 - CLINICAL TRIALS - Amendment of the DDCM Petition Form.	
5th Edition	• Item 6 – Amendments to the protocol: ~~Substantial changes are those where one or more of the following criteria are met:~~ ~~• Change in the clinical trial protocol that interferes with the safety or physical or mental integrity of individuals;~~ ~~• Change in the scientific value of the clinical trial protocol;~~ ~~Conceptually, a clinical trial has scientific value if:~~ ~~The. Evaluate a therapeutic or diagnostic intervention that may lead to improvements in health or quality of life; or~~ ~~B. Is a preliminary etiological, pathophysiological or epidemiological study to develop such an intervention; or~~ ~~ç. Test a hypothesis that can generate important knowledge about the structure or functioning of human biological systems, even if this knowledge has no immediate practical ramifications.~~	• Removed to section 6.1 – Substantial amendments. • Excluding the concept of value scientific and left only the lists of amendments considered as substantial and non-substantial, because this concept presents language wide, which may generate doubts and the consequent submission from modifications that are not considered to be substantial.
5th Edition	• Item 6 – Amendments to the protocol: • It is the sponsor's responsibility to assess whether an amendment is considered substantial or not ~~and~~ its impact on clinical development. This ~~assessment should always be done on a case-by-case basis, based on the above criteria.~~	• Removed the last sentence as the above criteria were excluded.
5th Edition	• Item 6 – Amendments to the protocol: • It is essential that amendments clearly identify the part of the protocol to be modified, provide the rationale for each change, and that the clean version and the track changes version of the protocol be forwarded. It is important that the Clinical Trial Submission Form is updated in accordance with protocol changes applicable to the fields on this form.	• Included in the text in order to facilitate the conference of proposed changes by amendment with the protocol previously approved.
5th Edition	• Item 6 – Amendments to the protocol: ~~• Below are some examples for each category of amendments, including examples of situations that do not constitute an amendment. We emphasize that the list below is for illustrative purposes only, not exhausting all possibilities.~~ • Below are amendments deemed substantial, non-substantial, and changes that do not constitute an amendment.	• Rewriting the text for clarification.

5th Edition	• Item 6.1 - Substantial Amendments: • Substantial amendments are considered to be changes in the clinical trial protocol that interfere with the safety, physical or mental integrity of the participants or even change the scientific value of the clinical trial protocol, such as:	• Item removed from section 6.
5th Edition	• Item 6.1 - Substantial Amendments: • and. Change in sample size calculation not foreseen for the study. • f. Reduction in sample size due to the interim analysis provided for in the study; • g. Change from statistical analysis to primary outcomes; • H. Dosage-related changes that are not provided for in the protocol; i. Extension or continuation of clinical • research with removal of the control arm or active arm, crossing between arms (cross-over), changing the blinding of the study or inclusion of new participants; • j. Major modifications related to adaptive studies, such as modification/deletion/addition of treatment arms, alteration of outcomes, modification of dose and/or duration of treatment, or adaptation of randomization schemes; • k Inclusion of a new route of administration; l. • Expansion of use; • m. Others, at the sponsor's discretion (including justification).	• Inclusion of more examples of substantial amendments to reflect the main objective of this review: detail the changes considered as substantial and non-substantial.
5th Edition	• Item 6.2 - Non-substantial Amendments: • B. Proposal pExtending or continuing the research with the same recruited participants, without changing the design, methods and primary objectives of the original project okay. If there are any of these • Replacement of the word "original" modifications, another research protocol must be submitted, not an amendment;	• Item rewriting to clarify and include the word "primary" in goals to align with the criteria for substantial amendments. to "approved", because at the moment of a possible extension of the study, the original project may have already passed through a series of changes previous. • Deleted the last sentence, as the extension of a search can undergo some types of changes and be

40

		classified as an amendment substantial.
5th Edition	• Item 6.2 - Non-substantial Amendments: • g. Minor modifications related to adaptive studies, such as a phase 2/3 study, in which phase 2 is dose choice and phase 3 is a confirmatory study with the dose chosen in phase 2, with no change in the primary outcome or other major changes; • H. Maintenance or increase in the sample size due to the interim analysis foreseen in the study; • i. Maintenance or increase in the sample size due to the interim analysis foreseen in the study; • j. Reduction ~~Change~~ in the number of scheduled visits;	• Inclusion of examples that are classified as Amendments not substantial to reflect the main objective of this review: to detail the changes considered as substantial and non-substantial.
5th Edition	• Item 6.2 - Non-substantial Amendments: ~~• The applicant must update the Clinical Trial Submission Form whenever there is a change in the data contained therein (and not just at the time of submission of annual reports, for example), as these data reflect the advertising of clinical trials on Anvisa's website and will be used to guide inspections in Good Clinical Practice. The updating of this form does not depend on the Agency's prior expression, except when there is: • Change in the title or code of the clinical trial protocol;~~ ~~•~~ ~~• Inclusion or exclusion of products under investigation to be imported~~ ~~• Change in storage conditions and shelf life of products under investigation.~~ ~~• For these cases, a new version of the CE will be issued.~~	• Paragraphs removed for the section 6.3.a
5th Edition	• Item 6.3 - Examples ~~that do not constitute~~ • Items removed for section 5.3 - Protocol amendments: ~~• a) Investigator Brochure Update. This should be requested as 10821 - CLINICAL TRIALS – Update of Investigator's Brochure, unless it also substantiates a change in the clinical protocol. In this case, the change must be evaluated by the Sponsor and classified as substantial or not, and the respective procedures must be followed.~~ ~~• b) Changes to the DDCM submission form or attached documents. These must be filed as 10822 -~~	"They do not constitute Modifications to the DDCM", as they are more applicable to DDCM modifications than to amendments to the protocol.

	~~CLINICAL TRIALS – Amendment of the DDCM Petition Form.~~	
5th Edition	• Item 6.3 - They do not constitute amendments to the protocol: • b) a) ~~C~~hanges in the clinical protocol submission form. These must be filed as 10823 -– CLINICAL TRIALS – Change in Clinical Trial Submission Form. • The applicant must update the Clinical Trial Submission Form whenever there is a change in the data contained therein, as these data reflect the advertising of clinical trials on Anvisa's website and will be used to guide inspections in Good Clinical Practices. The updating of this form does not depend on the Agency's prior manifestation, except when there is: i. Change in the title or code of the clinical trial protocol; • • ii. Inclusion or exclusion of products under investigation to be imported; • iii. Change in storage conditions and shelf life of products under investigation. • For these cases, a new version of the CE will be issued.	• Information removed from section 6.2.
5th Edition	• Item 6.3 - They do not constitute amendments to the protocol: • b) ~~Proposal to extend the clinical protocol~~ Extension or continuity of clinical research in which a new study ~~d~~design is foreseen , change in ~~n~~ design, including changing methods, outcomes or primary objectives . For this type of change, a new clinical protocol must be added to the DDCM, with no amendment to the protocol ~~already submitted, as explained in the examples of non-substantial amendments.~~	• Rewriting the text to align with the three submission possibilities from an extension study: 1. Substantial amendment 2. Non-substantial amendment 3. New protocol, depending on the proposed changes.
5th Edition	• Item 7 – Suspensions and Cancellations: • In cases of temporary suspension of the DDCM as an immediate security measure, the sponsor must notify Anvisa within 7 (seven) calendar days from the date of suspension, justifying the reasons.	• Inclusion of information about the DDCM suspension period as security measure in order to be in line with Art. 52 of the DRC 09/2015.
5th Edition	• Item 7 – Suspensions and Cancellations: • If the cancellation is made at the request of the company, including cases of cancellation for security reasons, the petition subject 10826 - TESTS must be used CLINICS – Cancellation of DDCM on request; if the cancellation happens by	• Item withdrawn, as the transfer global responsibility takes place without canceling the DDCM.

42

	~~global transfer of responsibility, the subject of the petition is 10827 – CLINICAL TRIALS - Global Transfer of Responsibility on DDCM.~~ • Item 7 – ~~Suspensions and Cancellations:~~	
5th Edition	• For DDCM: • When all activities of a clinical trial in Brazil are closed, it is not necessary to suspend or cancel the DDCM. The DDCM will remain active for future protocol additions, and annual updates to the investigational drug development safety update report, investigator brochure update and substantial changes are not mandatory. If a new clinical trial with such a drug is conducted in Brazil, the DDCM must be updated in which it was inactive and, for situations in which substantial changes have occurred, these must await a statement from Anvisa.	• Item included to clarify that DDCM remains active, even after all activities are closed of a clinical trial in Brazil. In that case, it is not necessary to send update reports from security, as long as you don't have a active study in the country.
5th Edition	• Item 7 – Suspensions and Cancellations: • For a Clinical Trial: • For suspensions, the subject to be used is 10830 - CLINICAL TRIALS - Temporary suspension of Clinical Trial Protocol. By definition, these have a temporary nature, and can be reversed with the subject of petition 10831 - CLINICAL TRIALS - Reactivation of suspended Clinical Trial Protocol. Reactivation depends on prior approval from Anvisa, which will evaluate the company's justification and other criteria such as the potential risk identified, related adverse events, measures already adopted (both by the sponsor and by other regulatory authorities, when applicable) and the data of notifications with the drug reported to COPEC, if applicable.	• Inclusion of risk analysis by Anvisa for reactivation of the study.
5th Edition	• Item 9 - Bibliographic References • 5. EUROPEAN MEDICINES AGENCY. Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, 2012. • 6. EUROPEAN MEDICINES AGENCY. Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials EMA/CHMP/QWP/545525/2017.	• Inclusion of bibliographic references used for document review.

5th Edition	• Item 10 - Attachments • The attachments of this manual are also available in DOC format on Anvisa's Electronic Portal > Subjects > Medicines > Clinical Research > > Publications > Manuals and Guides.Forms.	• Update of the location where attachments are available on the website of Anvisa due to migration to gov.br domain.
5th Edition	• Annex I • Item 8. Reasons for Substantial Modification: • 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 excipient quality control? • d) Changes in the description and composition of the investigational drug? • e) Changes related to the place of manufacture of the investigational drug? • f) Changes related to the production process of the investigational drug? • g) Changes related to the investigational drug production equipment? • h) Changes related to drug lot size? experimental • i) Changes related to the packaging of the investigational drug? • j) Inclusion of a new presentation? • k) Changes related to the term of validity provided that there has been a change in the previously established stability assessment criteria, that the values are not within the allowed ranges or that the validity period is defined based on reduced stability study plan models (grouping and matrix)? • l) Inclusion of a new concentration? • m) Inclusion of a new pharmaceutical form? • n) Dosage-related changes? • o) Expansion of use? • p) Inclusion of a new route of administration? • q) Inclusion of a new therapeutic indication? • r) Inclusion of a placebo not previously provided for in the DDCM • a) Modifications related to Active Pharmaceutical Ingredient – API/Active Substance (biological products)? • i. Replacement/Inclusion of new manufacturing site or manufacturing steps? ii. Change in the • synthesis route (synthetic/semi-synthetic)?	• Update of Annex I to reflect the changes proposed by the new manual text in Items 5.1 and 5.2.

	• iii. Change in the manufacturing process of the active substance of biological products? • iii.1 Change in cell banks, involving: • iii.1.1 Generation of a new Master Cell Bank (BCM) from the same expression construct with the same cell lineage or highly similar cell lineage? iii. 1.2 Generation of new BCM from a • different expression construct with the same coding sequence and the same cell lineage? • iii. 1.3 Adaptation of a new BCM in a new culture medium? • iii.1.4 Generation of new BCM for a recombinant product or viral vaccine? • iii.2 Change in seed banks, involving: • iii. 2.1 Establishment of a new Master Seed Bank (BSM)? • iii. 2.2 Extension of the number of Work Seed Bank (BST) passes beyond the approved level? • iii.3 Changing the cell bank or seed bank manufacturing location? iii.4 Alteration of the fermentation process or viral or cellular • propagation, fractionation or extraction: • iii.4.1 Critical change (change with high potential to impact the quality of the active substance or finished product, e.g. incorporation of disposable bioreactor technology)? • iii.4.2 Change with moderate potential to impact the quality of the active substance or finished product (eg extension of cell age in vitro beyond validated parameters)? • iii.5 Change in the purification process: • iii.5.1 Critical change (change with high potential to impact active substance and finished product quality, eg a change that could potentially impact viral removal/inactivation capacity or active substance impurity profile)? • iii.5.2 Change with moderate potential to impact the quality of active substance and finished product (eg change in chemical separation method, such as switching from ion-exchange HPLC to reverse-phase HPLC)? • iii.6 Change in the scale of the process of	

	manufacturing: • iii.6.1 In the stage of fermentation or viral or cellular propagation? • iii.6.2 In the purification step? • iv. Change, inclusion or exclusion of API/active substance production equipment with different design and operating principle? • v. Changes in the physicochemical properties of the API/ Active substance influencing the quality of the investigational drug (eg particle size distribution, polymorphism, etc.)? • saw. Modifications related to quality control, such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters such as quantification of content and impurities, provided that the method is not equivalent or superior to the original method ? • b) Modifications related to the Experimental Medication? • i. Replacement/Inclusion of new manufacturing site or manufacturing steps, except for immediate/conventional release synthetic and semi-synthetic drugs? • ii. Modifications impacting the release of the API or active substance of the investigational drug or critical quality parameters, including stability and impurities, and: • ii.1 Qualitative changes in composition? • ii.2 Change in the manufacturing process and inclusion or exclusion of equipment with different design and operating principle? ii.3 Increase in lot size above 10 (ten) times the initially approved lot size? • ii.4 Change of primary packaging? • iii. Modifications related to quality control such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method referring to critical quality parameters, provided that the method is not equivalent or superior to the original method? • iv. Extension of the shelf life and/or change in conservation care, provided that there has been a change in the	

46

	previously established stability evaluation criteria, that the values are not within the allowed ranges or that the validity period is defined based on reduced models of stability study plan (grouping and matrixing)? • v. Inclusion of a new presentation that will require further stability studies? saw. • Inclusion of new concentration? vii. • Inclusion of a new pharmaceutical form? • viii. Inclusion of a new route of administration with a change in pharmaceutical form? • c) Modifications related to Placebo or Modified Active Comparator? • i. Inclusion of previously unanticipated modified placebo and/or active comparator in the DDCM? • d) Others, at the sponsor's discretion (including justifications)	
	• Annex II • Item 12. Reasons for Substantial Amendment: • f) Reduction of the sample size due to the interim analysis foreseen in the study? • g) Change from the statistical analysis to the primary outcomes? • h) Dosage-related changes that are not provided for in the protocol? • i) Extension or continuity of clinical research with removal of the control arm or active arm, crossing between arms (cross-over), changing the blinding of the study or inclusion of new participants? • j) Major modifications related to adaptive studies, such as modification/deletion/ addition of treatment arms, alteration of outcomes, modification of dose and/or duration of treatment, or adaptation of randomization schemes? • k) Inclusion of a new route of administration? • l) Expansion of use? • m) Others, at the sponsor's discretion (including justifications)	• Update of Annex II to reflect the changes proposed by the new manual text in Items 6.1 and 6.2.