5th edition

Brazilian National 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

Brasília, 26/Apr/2021

MANUAL FOR SUBMISSION OF CHANGES, AMENDMENTS, SUSPENSIONS AND CANCELLATIONS

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..

Circulation: 5th edition Organization - Anvisa
General Drug Management

Technical Review - Anvisa
Adriane Alves de Oliveira
André Luís Carvalho Santos Souza
Bruno de Paula Coutinho
Carla Abrahao Brichesi
Carlos Augusto Martins Netto Carolina Pingret Cintra
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Claudiosvam Martins Alves de Sousa
Fanny Nascimento Moura Viana
Fernando Casseb Flosi
Gláucia Pacheco Buffon Kellen do Rocio Malaman
Kellen Christina de Freitas Gissoni
Mariella Zaroni
Miriam Motizuki Onishi
Sônia Costa e Silva

Formatting and Review
Editora Anvisa

Graphic Project
Editora Anvisa

Catalog Card:
Manual for Submission of Changes, Amendments, Suspensions, and Cancellations / Brasília. Anvisa 2021

47 p.
Amendments; Changes; Clinical Trials.

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1. ACRONYM

MCB - Master Cell Bank
COPEC – Clinical Research Coordination for Drug Products and Biological Products
DDCM - Drugs Clinical Development Dossier
DEEC - Specific Clinical Trial Dossier
API - Active Pharmaceutical Ingredient
ORPC – Representative Clinical Trial Organization
RDC – Collegiate Board Resolution

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 CHANGES 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 THE 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.

A clinical trial protocol is considered as foreseen in the plan when all information about the phase, design, objectives, endpoints, comparator, dosage of the experimental drug and comparators, dosage form of the experimental drug, population, hypothesis, sample size and planning statistical data are presented in full in the initial Development Plan or when there is no change in this information. The petition with this development plan must be approved by Anvisa.

The following are the changes considered substantial, non-substantial and changes that do not constitute a change that potentially impact the quality or safety of the experimental drug, modified active comparator or placebo.

Unlisted cases may be discussed with the Agency through the available formal contact channels, if necessary.

1. Substantial changes:

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

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

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

iii. Change of 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 (MCB) from the same expression construct with the same cell line or highly similar cell line; or

iii.1.2 Generation of new MCB from a different expression construct with the same coding sequence and the same cell line;

or

iii.1.3 Adaptation of a new MCB in a new culture medium; or

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

iii.2 Change in seed banks, involving:

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

iii. 2.2 Extension of the number of passes by the Working Seed Bank (WSB) beyond the approved level.

iii.3 Change of the manufacturing site of the cell bank or seed bank;

iii.4 Change of the fermentation or viral or cellular propagation process, fractionation or extraction:

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

iii.4.2 Change with a moderate potential impact on the quality of the active substance or the finished product (for example, *in vitro* extension of cell age beyond validated parameters).

iii.5 Change of the purification process:

iii.5.1 Critical change (change with a high potential impact on the quality of the active substance and the finished

product, for example, a change that can potentially impact the ability to remove/inactivate the virus or impurity profile of the active substance);

Iii.5.2 Change with moderate potential impact on the quality of the active substance and the finished product (for example, change in the method of chemical separation, as a substitution of ion exchange HPLC for 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 stage.

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

v. Changes in the physical-chemical properties of the API/Active substance with influence on the quality of the experimental drug (for example, particle size distribution, polymorphism, etc.);

vi. Changes related to quality control, such as increasing the specification limits, excluding tests and changing the non-compendial analytical method regarding critical quality parameters such as content and impurity quantification, provided that the method is not equivalent or superior to the original method.

b. Changes related to **Experimental Drug**, as described below:

i. Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for synthetic and semi-synthetic drugs for immediate/conventional release;

ii. Changes with an impact on the release of the API or active substance of the experimental drug or critical quality parameters, including stability and impurities, and:

ii.1 Qualitative changes in composition;

ii.2 Change of the manufacturing process and inclusion or exclusion of equipment with different design and operating principle;

ii.3 Batch size increase over 10 (ten) times the batch size initially approved;

ii.4 Change of the primary packaging;

iii. Changes 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. Expansion 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 permitted ranges, or that the shelf life is defined based on reduced models of stability study plan (grouping and matrixing);

v. Inclusion of a new presentation that will require new stability studies;

vi. Inclusion of new concentration;

vii. Inclusion of a new dosage form;

viii. Inclusion of a new route of administration with changes in dosage form;

c. Changes related to **Placebo or Modified Active Comparator**, as described below:

i. Inclusion of placebo and/or modified active comparator not previously provided for in the DDCM.

2. Non-substantial changes:

a. Change of the corporate name of the place of manufacture of the API/active substance or the experimental drug;

b. Exclusion of additional manufacturer of API/active substance or experimental drug for reasons unrelated to safety/quality;

c. Replacement/Inclusion of a new manufacturing site or steps for the manufacture of synthetic and semi-synthetic experimental drugs for immediate/conventional release;

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

e. Replacement/Inclusion of API/active substance or experimental 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 experimental drug;

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

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

i. Quantitative and quality control changes for excipients in the experimental drug;

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

k. Increase in batch size less than 10 (ten) times the batch size initially approved for biological medicines, provided that the conditions below are fully met:

1. The proposed scale uses equipment equivalent to the approved equipment.
2. Changes in the manufacturing process or in-process controls are only those necessary to change the batch size (for example, the same standard formulation, controls and operating procedures are used).
3. The change is not due to recurring events arising during manufacture or stability issues.
4. There is no change in the principle of sterilization procedures for the finished product.
6. The change does not affect the lyophilization step.

l. Change of equipment used in the manufacturing process of API/active substance or experimental drug, keeping the principle of operation unchanged (purpose);
m. Reduced API/active substance or experimental drug shelf life;
n. Extension of the shelf life without any type of change or inclusion of method and/or specification;
o. Substantial change of the registered experimental drug, the change of which has already been approved by the registration area;
p. Update of the DDCM Petition Form;
q. Change of the labeling of the experimental drug;
r. Any changes in placebo previously foreseen in the DDCM;
s. Small clarifications.

To modify any information contained in the Form, simply submit a new form with updated information and a document describing the rationales for each change.

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.

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

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 and the change that potentially affects the quality or safety of the experimental drug, modified comparator drug and

placebo have their own issues, namely:

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

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

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

It is the sponsor's responsibility to evaluate and classify the changes prior to submission to the Agency, so that a risk/benefit analysis is made and as to the need to present supporting documentation. 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 change in the shelf life of the experimental drug classified as a substantial change according to item 1.b.iv must use the subject code 10849 - CLINICAL TRIALS
– DDCM Change - Change of Shelf Life.

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

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

- Investigate and justify any deviation from the specifications that has been verified, even if it occurred only under the accelerated study conditions;
- Present stability study after dilution or reconstitution, for applicable products;
- Present a photo stability study or rationale 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 should easily allow the identification of the manufacturing plants to which they refer.

The change in the shelf life of the experimental 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 should be integrated into petition 10825 - CLINICAL TRIALS - Update Safety Report of the Investigational Drug Development.

The FAEC must be updated with the new shelf life through subject code 10823 - CLINICAL TRIALS - Change of the Clinical Trial Presentation Form.

3. Do not constitute DDCM Changes:

a. Investigator's Brochure Update. This must be requested as 10821 - CLINICAL TRIALS - Investigator's Brochure Update, unless it also substantiates changes 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. DDCM Changes submission form. These must be requested as 10822 - CLINICAL TRIALS - Change of the DDCM Petition Form.

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 must be filed when they are made and their implementation must await manifestation, while non-substantial amendments must be presented as part of the annual report of the clinical trial. 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 to the DDCM, even before the final manifestation of Anvisa.

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

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

Below are the changes considered substantial, non-substantial and changes that do not constitute an amendment.

1. Substantial Amendments:

Substantial amendments are considered 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:

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;
f. Reduction of the sample size due to the interim analysis provided for in the study;
g. Change of statistical analysis for primary endpoints;
h. Changes related to the dosage, which are not foreseen in the protocol;

i. Extension or continuation of clinical research with removal of the control arm or active arm, crossing between the arms (*cross-over*), change of the blinding of the study or inclusion of new participants;
j. Major changes related to adaptive studies, such as change/exclusion/addition of treatment arms, change of endpoints, change 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 rationale).

2. Non-substantial amendments:

a. Change, addition or removal of exploratory endpoints;
b. Extension or continuity of the research keeping the recruited participants, without changing the design, methods and primary objectives of the approved project.
c. Addition of preventive safety monitoring, unrelated to any safety announcements issued.
d. New data or interpretation of pharmacological or toxicological data;
e. Change in the criteria established for the termination of the protocol, even though it has already ended;
f. Change in the inclusion and exclusion criteria;
g. Minor changes 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, without altering the primary endpoint or other major changes;
h. Maintaining or increasing the sample size due to the interim analysis provided for in the study;
i. Increased sample size not foreseen for the study without altering the primary endpoint 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 endpoints;
m. Small clarifications regarding the protocol.

3. The following are not amendments to the protocol:

a. Changes to the clinical protocol submission form. These must be requested as 10823 -

CLINICAL TRIALS - Change of the Clinical Trial Presentation Form. The applicant must update the Clinical Trial Presentation 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 a prior opinion by the Agency, 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 that require prior manifestation.

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, endpoints or primary objectives. For this type of change, a new clinical protocol must be added to the DDCM.
c. Exclusion, cancellation, suspension or reactivation of clinical trial protocol.

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

Non-substantial amendments do not have a specific petition subject, and must be included in petition 1391 - CLINICAL TRIALS - Annual Clinical Trial Protocol 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 issues and should not constitute any of the change requests mentioned above. After a decision of suspension or cancellation, the sponsor must notify Anvisa within a maximum period of 15 calendar days.

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

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

Cancellations, under the terms of RDC No. 09/2015, are definitive, with no possibility of later reactivation. Thus, once the DDCM is canceled, no clinical trial 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 the clinical trials already underway are detailed in the Manual for Notification of Adverse Events and Safety Monitoring 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 character, and can be reversed through the subject of petition 10829 - CLINICAL TRIALS - Reactivation of suspended DDCM. Reactivation depends on prior approval by Anvisa.

When all activities of a clinical trial in Brazil are closed, there is no need to suspend or cancel DDCM. DDCM will continue to be active for future protocol additions, sending annual updates of the safety update report on the development of the experimental drug, updating the investigator's brochure and substantial changes is 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 manifestation by 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 issues and should not constitute any of the petitions for amendments mentioned above. 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

The 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 excluded, 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 the cancellation is due to a Global Responsibility Transfer, the subject of the petition is 10053 - CLINICAL TRIALS - Global Responsibility Transfer on the Clinical Trial Protocol. In the specific case of cancellation on request, the requirements that must be presented 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 character, and can be reversed with the subject of petition 10831 - CLINICAL TRIALS - Reactivation of the suspended Clinical Trial Protocol. The reactivation depends on prior approval by Anvisa, which will assess the company's rationale and other criteria such as the potential risk identified, related adverse events, measures already taken (both by the sponsor and other regulatory authorities, when applicable) and the notification data with the medicine reported to COPEC, if applicable.

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 - Representative Clinical Trial Organization (ORPC) - every company regularly installed in national territory contracted by the sponsor or sponsor-investigator, which partially or fully, with Anvisa, assume 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 rationale for the clinical trial;

9. REFERENCES

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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. 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)

	Document Identification
Brazilian National Health Surveillance Agency Clinical Research Petition Form for Substantial Change of the Drugs Clinical Development Dossier (DDCM)	(For use by the receiving agency)

1	DDCM Case Number	2	Hours (Day /Month/Year) //

Company Details

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

DDCM data

7	**Type of Change**: a. Inclusion of clinical trial(s) protocol(s) not foreseen or other than that of the previously established clinical trial(s) in the initial development plan?	a)	( ) Yes	( ) No
	b. Exclusion of clinical trial protocol(s)?	b)	( ) Yes	( ) No
	c. Changes that potentially impact the quality or safety of the investigational product? a. If yes, see item 8.	c)	( ) Yes	( ) No
	d. Change resulting from recommendations or alerts issued by health authorities?	d)	( ) Yes	( ) No

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

	iii.6.1 In the stage of fermentation or viral or cellular propagation?	iii.6.1 ( ) Yes ( ) No
	iii.6.2 In the purification stage?	iii.6.2 ( ) Yes ( ) No
	iv. Change, inclusion or exclusion of API production equipment/active substance with different design and working principle?	iv. ( ) Yes ( ) No
	v. Changes in the physical-chemical properties of the API/Active substance with influence on the quality of the experimental drug (for example, particle size distribution, polymorphism, etc.)?	v. ( ) Yes ( ) No
	vi. Changes related to quality control, such as increasing the specification limits, excluding tests and changing the non-compendial analytical method regarding critical quality parameters such as content and impurity quantification, provided that the method is not equivalent or superior to the original method?	vi. ( ) Yes ( ) No
	b) Changes related to the Experimental Drug?	**b) ( ) Yes ( ) No**
	i. Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for synthetic and semi-synthetic drugs with immediate/conventional release?	i. ( ) Yes ( ) No
	ii. Changes with an impact on the release of the API or active substance of the experimental drug or critical quality parameters, including stability and impurities, and:	
	ii.1 Qualitative changes in composition?	ii.1 ( ) Yes ( ) No
	ii.2 Change of the manufacturing process and inclusion or exclusion of equipment with different design and operating principle?	ii.2. ( ) Yes ( ) No
	ii.3 Increase in batch size over 10 (ten) times the size of the batch initially approved?	ii.3. ( ) Yes ( ) No
	ii.4 Change of primary packaging?	ii.4. ( ) Yes ( ) No
	iii. Changes related to quality control such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method regarding critical quality parameters, provided that the method is not equivalent or superior to the original method?	iii. ( ) Yes ( ) No
	iv. Expansion 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 permitted ranges or that the shelf life is defined based on models reduced from the stability study plan (grouping and matrixing)?	iv. ( ) Yes ( ) No
	v. Inclusion of a new presentation that will require new stability studies?	v. ( ) Yes ( ) No
	vi. Inclusion of new concentration?	vi. ( ) Yes ( ) No
	vii. Inclusion of a new dosage form?	vii. ( ) Yes ( ) No
	viii. Inclusion of a new route of administration with changes in dosage form?	viii. ( ) Yes ( ) No
	c) Changes related to Placebo or Modified Active Comparator?	**c) ( ) Yes ( ) No**
	i. Inclusion of placebo and/or modified active comparator not previously provided for in the DDCM?	i. ( ) Yes ( ) No

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

ATTACHMENT II

APPLICATION FORM FOR SUBSTANTIAL CHANGE TO THE CLINICAL TRIAL PROTOCOL

Brazilian National Health Surveillance Agency Clinical Research Application Form for Substantial Change to the Clinical Trial Protocol	Document Identification (For use of the receiver agency)

1	Case Number of the Specific Clinical Trial Dossier	2	Hours (Day / Month/Year) / /
Company Details			
3	Applicant	4	Authorization/Registration Number
5	Manufacturer	6	Authorization/Registration Number
Clinical Trial Protocol Data			
7	Petition Subject (codes and description)	8	Generator Factor (datavisa)
9	Title and Code of the Clinical Trial Protocol	10	Protocol number (version and date)
		11	Trial Phase I ( ) II ( ) III ( ) IV ( )

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

ATTACHMENT III
TEMPLATE FOR SUBMISSION OF UPDATED STABILITY INFORMATION
LONG-TERM STABILITY STUDY (30ºC ± 2ºC / 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:

Test	Specification	Method	Initial (t0)	3 months	6 months	9 months	12 months	18 months	24 months	36 months
		*	**	**	**	**	**	**	**	

*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

Version	Changes performed	Explanation and Rationale
1st Edition	---	
2nd Edition	• Inclusion of the title **6. History of Changes** (*Page 15*)	• Insertion of a comparative table of essays between versions for a more transparent monitoring of updates made.
2nd Edition	• DDCM Changes ○ 2. Non-substantial changes. ▪ ~~a. Update of DDCM~~ Petition Form. (*Page 4*)	• Exclusion of example "a", since the form update is a secondary petition with its own subject, and should not be integrated into the annual report in the event of a non-substantial change.
2nd Edition	• DDCM Changes ○ Non-substantial changes. ▪ b. Update of the Development Plan for Experimental Drugs. (*Page 4*)	• Inclusion of the Experimental Drug Development Plan Update as an example of a non-substantial change. The update of the plan is only required when petitioning for substantial changes, but it must be possible to update it at the sponsor's discretion.
2nd Edition	• DDCM Changes ○ 2. Non-substantial changes. ▪ ~~c. Label update for comparator medicine~~. (*Page 4*)	• Exclusion, for clarity, of example "c" after receipt of contribution, considering that the update of the comparator package insert is not an item covered by RDC No. 09/2015.
2nd Edition	• DDCM Changes ○ The applicant must update the forms whenever there is a change in the data contained therein ~~(andnot only when submitting the annual reports, for example)~~,	• In line with the first amendment, the excerpt mentioning the possibility of sending an updated form in the case of non-substantial change was removed, since the form update is a secondary petition with its own subject.

	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 a prior opinion by the Agency. (*Page 5*)	
2nd Edition	• Amendments to the Protocol ○ 2. Non-substantial amendments. ▪ ~~c. Change in documentation used by study team for capture and registration ofdata~~. (*Page 9*)	• Exclusion of example "c" after receiving contributions reporting that the type of change highlighted is not 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 ○ 2. Non-substantial amendments. ▪ ~~g. Update of Presentation Form of the Clinical Trial~~ . (*Page 9)*	• Exclusion of example "g", since the update of the form is a secondary petition with its own subject, and should not be integrated into the annual report in the case of a non-substantial amendment.
2nd Edition	• Amendments to the Protocol ○ The applicant must update the Clinical Trial Presentation Form whenever there is a change in the data contained therein ~~(and **not** only 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 Practices.	• The excerpt mentioning the possibility of sending an updated form in the case of a non-substantial change was excluded, since the form update is a secondary petition with its own subject. The paragraph in its entirety was moved to constitute sub-item of example "c" of item 3. Examples that do not constitute amendments to the protocol for better adequacy and clarity.

	The updating of this form does not depend on prior approval by the Agency, **except** when there is: a. Change in the title or code of the clinical trial protocol; b. Inclusion or exclusion of investigational products to be imported c. 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 petition subject to: 10827 - CLINICAL TRIALS - Global Responsibility Transfer on the DDCM (*page 14*).	• Change of the name of the petition subject.
2nd Edition	• Changed the name of the petition subject to: 10053 - CLINICAL TRIALS - Global Responsibility Transfer on Clinical Trial Protocol (*page 15*).	• Change of the name of the petition subject.
2nd Edition	• Title of item 1 of the Form contained in annexes I and II • Exclusion of item 7 of the Form contained in annexes I and II	• As the request for the process number is already made in the header, field 7 has been removed to avoid redundancies and the title of field 1 has been clarified for each form.
2nd Edition	• Added Annex III, "Model for sending updated stability information" • DDCM Changes: ○ "Change of the shelf life must use the subject 10849 - CLINICAL TRIALS - DDCM Change - Change of the Shelf Life.	• A model was created to send stability information, in an attempt to harmonize the information received and optimize the analysis by the technicians

	As a suggestion for greater agility and ease in the analysis of this type of petition, it can be completed and submitted together with the other documents, optionally, Annex III of this manual"	
3rd Edition	• DDCM Changes ○ 1. Substantial Changes ▪ New item "q": Inclusion of placebo not previously provided for in the DDCM;	• A new item referring exclusively to the placebo was inserted to be a counterpoint to the new sub-item "c", item 2. Non-substantial changes. The annexes to the Manual have been updated to reflect this change.
3rd Edition	• DDCM Changes ○ 2. Non-substantial changes ▪ New item "c": Any changes to placebos previously foreseen in the DDCM;	• Based on a risk analysis performed by COPEC, it was decided to explicitly exemplify that changes referring to placebos previously provided for are no longer considered substantial. A counterpoint was added to item 1 of the same section to exclude from this situation the inclusion of placebos that were not included in the initial analysis. The annexes to the Manual have been updated to reflect this change.
3rd Edition	• Amendments to the Protocol ○ Substantial Amendments - transposition of the following examples to now appear as an example of NON-substantial amendments: d. New data or interpretation on pharmacological or toxicological data, likely to have an ~~impact on risk analysis~~; e. Change in the criteria established for the termination of the protocol, even though it has already ended; f. Addition of experimental arms or placebo group;	• Based on a risk analysis performed by COPEC, it was decided to list these items as examples of NON-substantial amendments as of the 3rd edition. The annexes to the Manual have been updated to reflect this change.

	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 product dosage under investigation~~; l. ~~Change in the administration of the investigational product~~; m. ~~Change in the design of the clinical protocol~~; n. Change in secondary or exploratory endpoints ~~Update of Clinical Trial Presentation Form~~.	
3rd Edition	• Amendments to the Protocol ~~Thus, examples of changing the scientific value are the change from a placebo comparator to an active comparator, the insertion of additional experimental arms or changes in the~~ statistical analysis plan.	• Considering the new examples from the list of substantial changes, the removal of this paragraph was necessary to align the text with the list of examples.
4th Edition	• Cover: inclusion of the effective date	• Inclusion is to identify as of which date the manual is in force
4th Edition	• Item 5, sub-item 1. Substantial Changes: 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.
4th Edition	• Item 5, sub-item 1: Substantial Changes k. Changes related to the shelf life since there has been a change in the stability assessment criteria previously established, the values are not within the permitted ranges or the shelf life is defined based on reduced models of the stability study plan (grouping and Matrixing)? ~~Changes related to shelf life or conservation care of the investigational product~~	• The change in the text was made to reduce the situations in which the change in the shelf life should be considered as a substantial change.
4th Edition	• Item 5, sub-item 2: Non-substantial changes d. Update of the Experimental Drug Development Plan, whose change does not impact the clinical trials to be conducted in Brazil.	• Phrase included to make it clear that in cases of substantial change due to the inclusion of a protocol not provided for in the plan, an updated development plan must be provided. For the other cases, the update is considered to be non-substantial.

4th Edition	• Item 5, sub-item 2: Non-substantial changes ~~e. Update of package insert of comparator medicine~~ The remaining items were renumbered from "f" and "g" to "e" and "f".	• The example was removed to avoid confusion in understanding, as per question 3.2.8 of the document Questions and Answers version 2.
4th Edition	• Item 5, sub-item 2: Non-substantial changes g. Changes in shelf lives not provided for in letter k of item 5, sub-item 1 of substantial changes	• The inclusion was made to reflect the reduction of cases in which the change in the shelf life should be considered as a substantial change.
4th Edition	• Item 5 - DDCM Changes Substantial changes must constitute a petition secondary to the primary petition for submission of the DDCM of the experimental drug, with the exception of the change by including a clinical trial protocol not provided for in the initial development plan, which is a primary petition.	• The inclusion of the sentence was made to indicate that the substantial change due to the inclusion of a protocol not provided for in the initial development plan is a primary petition, as it configures the Specific Clinical Trial Dossier (DEEC) itself, which is a primary petition.
4th Edition	• Item 5, sub-item 2, Non-substantial amendments ~~c. Change in the documentation used by the study team to capture and record the data;~~ Subsequent letters were renumbered from "d" to "l" to "c" to "k".	• The example was removed to avoid confusion in understanding, as per question 3.2.12 of the document Questions and Answers version 2.
4th Edition	• 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 models of the stability study plan (grouping and Matrixing)? ~~Changes related to shelf life or conservation care of the investigational product~~	• Change made to reflect changes to the manual.
4th Edition	• Annex I, item 8: • ~~r. Exclusion of drug manufacturing site or primary packaging site or secondary packaging or manufacturing site of the product?~~	• Exclusion of the item to reflect the criteria established in the manual

4th Edition	• Annex I, item 8: • ~~t. Other changes?~~ ~~o If yes, please specify:~~	• Exclusion of the item to reflect the criteria set out in the manual as substantial change
4th Edition	• Annex II, item 12: exclusion of the item The subsequent item was renumbered "13" to "12".	• Exclusion of the item, as the criteria established to be considered a substantial amendment is already in the subsequent question.
4th Edition	• Annex II, item 13: ~~f) Other changes?~~ ~~o If yes, please specify:~~	• Exclusion of the item to reflect the criteria set out in the manual as a substantial amendment
5th Edition	• Cover: inclusion of the effective date	• Inclusion is to identify as of which date the manual is in force
5th Edition	• Acronym: MCB - Master Cell Bank COPEC – Clinical Research Coordination for Drug Products and Biological Products DEEC - Specific Clinical Trial Dossier	• Update of the acronym with new acronyms inserted in the document.
5th Edition	• Item 5 - DDCM Changes • A clinical trial protocol is considered as foreseen in the plan when all information about the phase, design, objectives, endpoints, comparator, dosage of the experimental drug and comparators, dosage form of the experimental drug, population, hypothesis, sample size and planning statistical data are presented in full in the initial Development Plan or when there is no change in this information. The petition with this development plan must be approved by Anvisa. • ~~It is the sponsor's responsibility to assess whether a change 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 in the examples below.~~ • Below are ~~examples of~~ changes considered substances, non-substantial and changes that do not constitute a change that potentially have an impact ~~related to~~ in the quality or safety of the experimental drug, modified active comparator or placebo. ~~investigational~~	• Insertion of what is considered as a clinical trial protocol provided for in the Development Plan. • Exclusion of the item added to a greater detail of the lists of substantial and non-substantial changes in order to reduce subjectivity. Rewritten text for clarification. Taken from the last sentence as a more detailed list of examples of substantial and non-substantial

	~~product~~. ~~We emphasize that the lists below are illustrative only, not exhausting all possibilities.~~	changes has been inserted, however, cases not listed can still be discussed with the Agency in accordance with the next paragraph.
5th Edition	• Unlisted cases may be discussed with the Agency through the available formal contact channels, if necessary. • Item 5.1 - Changes related to the Active Pharmaceutical Ingredient - API/Active Substance (biological products), as described below: • i. Replacement/Inclusion of a new manufacturing site or manufacturing stages; • ii. Change of the synthesis route (synthetic/semi-synthetic); • iii. Change of 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 (MCB) from the same expression construct with the same cell line or highly similar cell line; or • iii. 1.2 Generation of new MCB from a different expression construct with the same coding sequence and the same cell line; or • iii. 1.3 Adaptation of a new MCB in a new culture medium; • iii.1.4 Generation of new MCB for a recombinant product or viral vaccine • iii.2 Change in seed banks, involving: • iii2.1 Establishment of a new Master Seed Bank (MSB); or • iii.2.2 Extension of the number of passes from the Working Seed Bank (WSB) beyond the approved level • iii.3 Change of the manufacturing site of the cell bank or seed bank; • iii.4 Change of the fermentation or viral or cellular propagation process, fractionation or extraction: • iii.4.1 Critical change (change with a 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 impact on the quality of the active substance or finished product (eg extension of cell age	• Inclusion of the possibility of discussing other items not listed. • Inclusion of examples of changes related to the API/Active Substance to reflect the main objective of this review: to detail the changes considered as substantial and non-substantial.

	in vitro beyond validated parameters) • iii.5 Change of the purification process • iii.5.1 Critical change (change with a high potential impact on the quality of the active substance and the finished product, for example, a change that can potentially impact the ability to remove/inactivate the virus or impurity profile of the active substance); • iii.5.2 Change with moderate potential impact on the quality of the active substance and the finished product (for example, change in the chemical separation method, as a substitution of ion exchange HPLC for 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 stage • iv. Change, inclusion or exclusion of API production equipment/active substance with different design and working principle. • v. Changes in the physical-chemical properties of the API/Active substance with influence on the quality of the experimental drug (eg, particle size distribution, polymorphism, etc.) • vi. Changes related to quality control, such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method regarding critical quality parameters such as content and impurity quantification, provided that the method is not equivalent or superior to the original method	
5th Edition	• Item 5.1 - Changes related to the Experimental Drug, as described below: • i. Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for synthetic and semi-synthetic drugs for immediate/conventional release; • ii. Changes with an impact on the release of the API or active substance of the experimental drug or critical quality parameters, including stability and impurities, and: • ii.1 Qualitative changes in the composition;	• Inclusion of examples of changes related to the Experimental Drug to reflect the main objective of this review: to detail the changes considered as substantial and non-substantial.

	• ii.2 Change of the manufacturing process and inclusion or exclusion of equipment with different design and operating principle; • ii.3 Increase in batch size over 10 (ten) times the size of the batch initially approved; • ii.4 • ii.5 Change of the primary packaging; • iii. Changes 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. Expansion 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 permitted 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; • vi. Inclusion of new concentration; • vii. Inclusion of a new dosage form; • viii. Inclusion of a new route of administration with changes in dosage form; •	
5th Edition	• Item 5.1 - Changes related to the Placebo or Modified Active Comparator, as described below: • i. Inclusion of placebo and/or modified active comparator not previously provided for in the DDCM.	• Inclusion of examples of changes related to Placebo or Active Comparator to reflect the main objective of this review: to detail the changes considered as substantial and non-substantial.
5th Edition	• Item 5.2 - Non-substantial changes: • ~~d. Update of the Development Plan of the Experimental Drug, whose change does not impact the clinical trials to be conducted in Brazil;~~ • ~~e. Spell check in documents;~~ a. Change of the corporate name of the place of manufacture of the API/active substance or the experimental drug;	• Exclusion of the “Development Plan Update”, as it is not necessary to submit this update annually to the annual safety report.

	• b. Exclusion of additional manufacturer of API/active substance or experimental drug for reasons unrelated to safety/quality; • c. Replacement/Inclusion of a new manufacturing site or steps for the manufacture of synthetic and semi-synthetic experimental drugs for immediate/conventional release; • d. Changes related to the secondary and tertiary packaging of the API/active substance or experimental drug; • e. Replacement/Inclusion of API/active substance or experimental 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 experimental drug; • g. Narrowing of specification limits for in-process control tests, quality control and stability of the API/active substance or experimental drug; • h. Change, inclusions or exclusions of analytical method for purposes of adaptation to official compendium recognized by Anvisa regarding process control, quality control and stability of the API/active substance or experimental drug; • i. Quantitative and quality control changes for excipients in the experimental drug; • j. Batch size increase less than 10 (ten) times the batch size initially approved for synthetic or semi-synthetic drugs; • k. Batch size increase less than 10 (ten) times the batch size initially approved for biological medicines, provided that the conditions below are fully met: • 1. The proposed scale uses equipment equivalent to the approved equipment. • 2. Changes in the manufacturing process or in-process controls are only those necessary to change the batch size (for example, the same standard formulation, controls and operating procedures are used). • 3. The change is not due to recurring events arising during manufacture or stability issues.	The updated development plan should only be submitted to ANVISA with a new proposed clinical protocol. • "Spelling corrections" removed as these are usually made as an administrative letter or in the next amendment to the protocol and not necessarily as a non-substantial change. • Inclusion of examples of non-substantial changes to reflect the main objective of this review: to detail the changes considered to be substantial and non-substantial.

	• 4. There is no change in the principle of sterilization procedures for the finished product. • 6. The change does not affect the lyophilization step. • l. Change of equipment used in the manufacturing process of API/active substance or experimental drug, keeping the principle of operation unchanged (purpose); • m. Reduced API/active substance or experimental drug shelf life; • n. Extension of the shelf life without any type of change or inclusion of method and/or specification; • o. Substantial change of the registered experimental drug, the change of which has already been approved by the registration area; •	
5th Edition	• Item 5.2 - Non-substantial changes: • Substantial changes must constitute a petition secondary to the primary petition for submission of the DDCM of the experimental drug, with the exception of the change by including 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 experimental drug, modified comparator drug and placebo have their own issues, namely: • 10818 - CLINICAL TRIALS - DDCM Change - Inclusion of a 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 specific subject, according to the Manual for Submission of Drugs Clinical Development Dossier (DDCM) and Specific Clinical Trial Dossier.~~ • 10819 - CLINICAL TRIALS - DDCM Change - Exclusion of clinical trial protocol • 10820 - CLINICAL TRIALS - DDCM Change - Change that potentially impacts the quality or safety of the investigational product.	• Inclusion of the Quality change to be in accordance with the Subjects listed below. • Text removed for next paragraph in order to leave in that item only the name of the Subjects. • Inclusion of quality change because it is one of the classified subjects as “DDCM Change”.

	• Item 5.2 - Non-substantial changes: • For cases of changes that potentially impact the quality or safety of the experimental drug, active comparator or placebo, you should ~~according to examples above, should use the subject of petition 10820 – CLINICAL TRIALS – Change DDCM – Change that potentially impacts the quality or safety of the investigational product. A~~ comparative table documentation ~~(comparative) of the between~~ the situation ~~initial~~ current approved and of the proposal for amendment accompanied ~~by~~ respective technical rationales and any additional documents needed to prove that the change will not impact the clinical development of the product. • The change in shelf life classified as a substantial change according to item 1.b.iv must use the subject 10849 - CLINICAL TRIALS - DDCM Change - Change of Shelf Life. • The change in the shelf life of the experimental drug classified as non-substantial according to item 2.me and 2.n, as well as all other non-substantial changes do not have a specific petition subject, and should be integrated with petition 10825 - CLINICAL TESTS - safety Update Report on Experimental Drug Development. • The FAEC must be updated with the new shelf life through subject code 10823 - CLINICAL TRIALS - Change of the Clinical Trial Presentation Form.	• Restructuring of the paragraph by removing the subject of petition 10820 for the items listed above. • Phrase included to make it clear what kind of expiration change should be submitted using subject 10849 and which should be submitted using subject 10825. • Inclusion of information on updating the FAEC with new shelf lives for all situations mentioned in the previous paragraph.
5th Edition	• Item 5.3 - Do not constitute DDCM Changes: • a. Investigator's Brochure Update. This must be requested as 10821 - CLINICAL TRIALS - Investigator's Brochure Update, unless it also substantiates changes 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 in the DDCM submission form .	• Inclusion of examples that are not classified as changes to the DDCM to reflect the main objective of this review: to detail the changes considered to be substantial and non-substantial.

	These must be requested as 10822 - CLINICAL TRIALS - Change of the DDCM Petition Form.	
5th Edition	• Item 6 - Amendments to the protocol: ~~Substantial changes are those where one or more than 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:~~ ~~a. It evaluates a therapeutic intervention or diagnosis that can lead to improvements in health or quality of life; or~~ ~~b. It is an etiological, pathophysiological or preliminary epidemiological study to develop such an intervention; or~~ ~~c. It tests a hypothesis that can generate important knowledge about the structure or about the functioning of human biological systems, even if that knowledge does not have immediate practical ramifications.~~	• Removed to section 6.1 - Substantial amendments. • Excluding the concept of scientific value and leaving only the lists of amendments considered as substantial and non-substantial, as this concept has a broad language, which may generate doubts and the consequent submission of changes 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 because the above criteria were excluded.
5th Edition	• Item 6 - Amendments to the protocol: • It is essential that the amendments clearly identify the part of the protocol to be modified, present the rationale for each change and that the clean version and the version with the marked changes (track changes) of the protocol be sent. It is important that the Clinical Trial Submission Form is updated in accordance with the protocol changes applicable to the fields on this form.	• Included in the text in order to facilitate the checking of the amendments proposed by the amendment with the previously approved protocol.
5th Edition	• Item 6 - Amendments to the protocol: • ~~Here 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 only illustrative, not exhausting all possibilities.~~ • Below are the changes considered substantial, non-substantial and changes that do not constitute an amendment.	• Rewritten text for clarification.

5th Edition	• Item 6.1 - Substantial Amendments: • Substantial amendments are considered changes to the clinical trial protocol that interfere with the safety, physical or mental integrity of the participants or even alter the scientific value of the clinical trial protocol, such as:	• Item removed from section 6.
5th Edition	• Item 6.1 - Substantial Amendments: • e. Change in the calculation of the sample size not foreseen for the study. • f. Reduction of the sample size due to the interim analysis provided for in the study; • g. Change of statistical analysis for primary endpoints; • h. Changes related to the dosage, which are not foreseen in the protocol; • i. Extension or continuation of clinical research with removal of the control arm or active arm, crossing between the arms (cross-over), change of the blinding of the study or inclusion of new participants; • j. Major changes related to adaptive studies, such as change/exclusion/addition of treatment arms, change of endpoints, change 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 rationale).	• Inclusion of more examples of substantial amendments to reflect the main objective of this review: to detail the changes considered to be substantial and non-substantial.
5th Edition	• Item 6.2 - Non-substantial amendments: • b. ~~Proposal for~~ Extension or continuity of the research ~~with the~~ keeping the same recruited participants, without changing the design, methods and primary objectives of the original project approved. ~~If there are any of these changes, another research protocol must be submitted, not an amendment;~~	• Rewritten item to clarify and include the word “primary” in objectives to be in line with the criteria for substantial amendments. • Replacement of the word "original" for "approved", because at the time of a possible extension of the study, the original project may have already undergone a series of previous changes. • The last sentence is excluded, as the extension of a search may suffer some types of changes and be classified as a

		substantial amendment.
5th Edition	• Item 6.2 - Non-substantial amendments: • g. Minor changes related to adaptive studies, such as 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, without altering the primary endpoint or other major changes; • h. Maintaining or increasing the sample size due to the interim analysis provided for in the study; • i. Maintaining or increasing the sample size due to the interim analysis provided for in the study; • j. ~~Reduction~~ Change in the number of scheduled visits;	• Inclusion of examples that are classified as Insubstantial Amendments 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 Presentation Form whenever there is a change in the data contained therein (and not only at the time of submission of the annual reports, for example), as these data reflect advertising of clinical trials on the Anvisa website and will be used to guide inspections in Good Clinical Practices. The update of this form does not depend on a prior opinion by the Agency, 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 the conditions of storage and shelf life of investigational products.~~ • ~~For these cases, a new version of the CE will be issued.~~	• Paragraphs removed for section 6.3.a
5th Edition	• Item 6.3 - ~~Examples that~~ Do not constitute amendments to the protocol: • a) Update of the Researcher's Brochure. ~~This must be requested as 10821 - CLINICAL TRIALS - Update of Investigator's Brochure, unless also substantiates changes in the clinical protocol. In this case, the change must be assessed 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 requested as 10822 - CLINICAL TRIALS Amendment of DDCM Petition Form.~~	• Items removed for section 5.3 - "Do not constitute DDCM Changes", as they are more applicable to DDCM changes than to amendments to the protocol.

5th Edition	• Item 6.3 - The following are not amendments to the protocol: • ~~b)~~ a) Changes to the clinical protocol submission form. These must be requested as 10823 –– CLINICAL TRIALS - Change of Clinical Trial Presentation Form. • The applicant must update the Clinical Trial Presentation 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 a prior opinion by the Agency, 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 storage conditions and shelf life of the investigational products. • For these cases, a new version of the CE will be issued.	• Information removed from section 6.2.
5th Edition	• Item 6.3 - The following are not amendments to the protocol: • b) ~~Proposal for the extension of the clinical protocol –~~ Extension or continuity of clinical research which is expected to the new study design, including change of methods, endpoints 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 possibilities of submitting 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 DDCM as an immediate safety measure, the sponsor must notify Anvisa within 7 (seven) consecutive days from the date of suspension, justifying the reasons.	• Inclusion of information on the DDCM suspension term as a safety measure in order to be in line with Art. 52 of the RDC 09/2015.
5th Edition	• Item 7 - Suspensions and Cancellations: • If the cancellation occurs at the request of the company, including cases of cancellation for safety reasons, the subject of petition 10826 - CLINICAL TRIALS - Cancellation of DDCM on request must be used;	• Item withdrawn, as the Global Responsibility Transfer occurs without the cancellation of the DDCM.

	~~if the cancellation is due to a Global Responsibility Transfer, the petition subject is 10827 – CLINICAL TRIALS - Global Responsibility Transfer over DDCM.~~	
5th Edition	• Item 7 - Suspensions and Cancellations: • For DDCM: • When all activities of a clinical trial in Brazil are closed, there is no need to suspend or cancel DDCM. DDCM will continue to be active for future protocol additions, sending annual updates of the safety update report on the development of the experimental drug, updating the investigator's brochure and substantial changes is 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 manifestation by Anvisa.	• Item included in order to clarify that DDCM remains active, even after all activities of a clinical trial in Brazil are closed. In this case, it is not necessary to send safety update reports until you have an 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 character, and can be reversed with the subject of petition 10831 - CLINICAL TRIALS - Reactivation of the suspended Clinical Trial Protocol. The reactivation depends on prior approval by Anvisa which will assess the company's rationale and other criteria such as the identified potential risk, related adverse events, measures already taken (both by the sponsor and other regulatory authorities, when applicable) and the notification data with the medicine reported to COPEC, if applicable.	• Inclusion of risk analysis by Anvisa to reactivate the study.
5th Edition	• Item 9 - 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 to revise the document.

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

	• ii. Change of the synthesis route (synthetic/semi-synthetic)? • iii. Change in the manufacturing process of the active substance in biological products? • iii.1 Change in cell banks, involving: • iii.1.1 Generation of a new Master Cell Bank (MCB) from the same expression construct with the same cell line or highly similar cell line? • iii. 1.2 Generation of new MCB from a different expression construct with the same coding sequence and the same cell line? • iii. 1.3 Adaptation of a new MCB to a new culture medium? • iii.1.4 Generation of new MCB for a recombinant product or viral vaccine? • iii.2 Change in seed banks, involving: • iii. 2.1 Establishment of a new Master Seed Bank (MSB)? • iii. 2.2 Extension of the number of passes from the Working Seed Bank (WSB) beyond the approved level? • iii.3 Change of the manufacturing site of the cell bank or seed bank? • iii.4 Change of the fermentation or viral or cellular propagation process, fractionation or extraction: • iii.4.1 Critical change (change with a 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 impact on the quality of the active substance or the finished product (for example, extension of cell age in vitro beyond validated parameters)? • iii.5 Change of the purification process: • iii.5.1 Critical change (change with a high potential impact on the quality of the active substance and the finished product, for example, a change that can potentially impact the ability to remove/inactivate the virus or impurity profile of the active substance)? • iii.5.2 Change with moderate potential impact on the quality of the active substance and the finished product (for example, change in the method of chemical separation, as a substitution of ion exchange HPLC for	

	reverse phase HPLC)? • iii.6 Change in the scale of the manufacturing: • iii.6.1 In the stage of fermentation or viral or cellular propagation? • iii.6.2 In the purification stage? • iv. Change, inclusion or exclusion of API production equipment/active substance with different design and working principle? • v. Changes in the physical-chemical properties of the API/Active substance with influence on the quality of the experimental drug (for example, particle size distribution, polymorphism, etc.)? • vi. Changes related to quality control, such as increasing the specification limits, excluding tests and changing the non-compendial analytical method regarding critical quality parameters such as content and impurity quantification, provided that the method is not equivalent or superior to the original method? • b) Changes related to the Experimental Drug? • i. Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for synthetic and semi-synthetic drugs with immediate/conventional release? • ii. Changes with an impact on the release of the API or active substance of the experimental drug or critical quality parameters, including stability and impurities, and: • ii.1 Qualitative changes in composition? • ii.2 Change of the manufacturing process and inclusion or exclusion of equipment with different design and operating principle? • ii.3 Increase in batch size over 10 (ten) times the size of the batch initially approved? • ii.4 Change of the primary packaging? • iii. Changes related to quality control such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method regarding critical quality parameters, provided that the method is not equivalent or superior to the original method? • iv. Expansion 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 permitted ranges or that the shelf life is defined based on models reduced from the stability study plan (grouping and matrixing)? • v. Inclusion of a new presentation that will require new stability studies? • vi. Inclusion of new concentration? • vii. Inclusion of a new dosage form? • viii. Inclusion of a new route of administration with changes in dosage form? • c) Changes related to Placebo or Modified Active Comparator? • i. Inclusion of placebo and/or modified active comparator not previously provided for in the DDCM? • d) Others, at the sponsor's discretion (including rationales)	
	• Attachment II • Item 12. Reasons for Substantial Amendment: • f) Reduction of the sample size due to the interim analysis foreseen in the study? • g) Change of the statistical analysis for primary endpoints? • h) Changes related to the 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), change in the blinding of the study or inclusion of new participants? • j) Major changes related to adaptive studies, such as change/exclusion/addition of treatment arms, change of endpoints, change 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 rationales)	• Update of Annex II to reflect the changes proposed by the new text of the manual in Items 6.1 and 6.2.