National Health Surveillance Agency

QUALITY DATA SUBMISSION MANUAL REGARDING PRODUCTS UNDER INVESTIGATION USED IN CLINICAL TRIALS – SYNTHETIC MEDICINES AND SEMISYNTHETICS

General Medicines Management - GGMED

Coordination of Clinical Research in Medicines and Biological Products – COPEC

2019

QUALITY DATA SUBMISSION MANUAL REGARDING PRODUCTS UNDER INVESTIGATION USED IN CLINICAL TRIALS – SYNTHETIC MEDICINES AND SEMISYNTHETICS

This Manual aims to guide professionals in the field with information on how to apply Resolution RDC/Anvisa nº 09 of February 20, 2015, contributing to the development of safe actions, 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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DDCM; Experimental Medicine Dossier; Synthetics and semi-synthetics; Clinical Trials.

Summary

1. SIGLARY

DCB - Brazilian Common Denomination
DCI - International Common Denomination
DDCM - Clinical Drug Development Dossier
IFA – Active Pharmaceutical Ingredient
ORPC - Clinical Research Representative Organization
RDC – Collegiate Board Resolution

2. INTRODUCTION

The regulation on Clinical Trials with medicines in Brazil makes it mandatory to submit the Experimental Medicine Dossier as part of the Medicines Clinical Development Dossier (DDCM). This manual aims to provide guidance for the sponsor, sponsor-investigator or ORPC to submit quality data relating to synthetic and semi-synthetic medicines under investigation, which must form the Experimental Medicine Dossier (document VII, described in Art. 38 of the RDC No. 09 of February 20, 2015), appropriately.

This is a non-binding regulatory measure, adopted as a complement to health legislation, with the educational purpose of providing guidance on routines and procedures for compliance with legislation, and is not intended to expand or restrict established technical or administrative requirements.

This manual is open to contributions, with a permanent review process. The suggestions received will be evaluated to support its revision and subsequent publication of a new version, with each update.

3. BASE LEGAL

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

4. OBJECTIVE

Without prejudice to the provisions existing in the legal provisions, this manual aims to guide and explain, in a complementary way, the submission of the Dossier of

Experimental Medicine, as part of the Clinical Medicines Development Dossier (DDCM), as described in chapter III of RDC nº 9/2015.

We recommend that data presentation be standardized in terms of order and content to facilitate evaluation.

5. ACTIVE PHARMACEUTICAL INCENTIVE (IFA)

Information regarding the IFA(s) must only be presented for experimental medicines.

5.1 PHYSICAL-CHEMICAL, ORGANOLEPTIC AND BIOLOGICAL CHARACTERISTICS

5.1.1 General information and Characterization of the Active Pharmaceutical Ingredient: The characterization of the active pharmaceutical ingredient must be presented in table form (Annex II), as described below:

a) IFA nomenclature (Brazilian Common Denomination, if any, or International Common Denomination – IUPAC) and synonyms.

b) Company or Laboratory code and Chemical Abstracts Service (CAS);

c) Structural formula, relative and absolute chirality/stereochemistry, formula molecular and molecular mass;

d) General properties, including organoleptic characteristics (description and form physics), particle size distribution, solubility, pH and pKa;

e) Other relevant characteristics of the active substance that may affect the pharmacology or toxicological safety.

5.2 MANUFACTURER'S NAME AND ADDRESS

5.2.1 Manufacturers

The name and address of the manufacturer(s) of the IFA(s) must be presented in the form of a table (Annex III), as described below:

a) Name, address and responsibility of all companies involved in each stage of manufacturing the IFA batches used in the manufacturing of the experimental drug batches to be used in non-clinical trials, and in the different phases of clinical trials, including companies responsible for control quality and carrying out stability studies.

5.3 GENERAL METHOD OF OBTAINMENT

5.3.1 Manufacturing Process and Controls

a) Flowchart of the IFA manufacturing process;

b) Summary information on the critical stages of the manufacturing process and respective process control parameters and specification limits, if applicable;

c) List with description of starting materials, intermediate molecules, their chemical names, reagents and solvents used;

d) List of impurities related to IFA and its manufacturing process, criteria of acceptance and respective justifications, in the form of a table (Annex IV);

e) Critical assessment of the toxicity of impurities, degradation products and residual solvents, arising from the manufacturing process, or starting materials relevant to the IFA, when applicable;

f) Justification for non-compendial specification limits and brief discussion about potential mutagenic impurities, including information about the origin, structure, justification for the established specification limits, in accordance with the ICH M7 Guide;

The absence of routine control for solvents/catalysts used in the process manufacturing, must be justified.

5.4 VALIDATED ANALYTICAL METHODOLOGY AND ACCEPTABLE LIMITS FOR GUARANTEE IDENTITY, QUALITY AND PURITY

5.4.1 Quality control

a) Information about the batches to be used in the production of the medicine experimental non-clinical and clinical trials, including batch number, size, date and place of manufacture and purpose, in the form of a table (Annex V).

b) Description of the quality control tests carried out on the batches to be used in non-clinical and clinical trials, accompanied by the limits of specification with justifications for determining these;

c) Certificate of quality control analysis of the batches to be used in the production of the experimental medicine or, in the absence of this document, technical justification.

5.4.2 Validation of analytical procedures a) Present, in table form (Annex VI), the parameters, acceptance criteria and validation results of the analytical procedures used, in accordance with current legislation in Brazil or other internationally recognized guidelines , according to the phase of clinical development. Technical justification can be presented for the absence of validation or use of an alternative method validation approach, based on recognized scientific references.

5.5 RESULTS OF STABILITY STUDIES

Stability studies must be conducted to ensure the stability of the API during the intended storage period. Such studies must evaluate the stability of the IFA under the proposed storage conditions. Additionally, accelerated stability studies and stress tests can help understand the API degradation profile.

Therefore, present:

a) Stability study protocol;

b) Table (Annex VII) containing the stability results, according to the legislation in force in the country. The temperature and humidity conditions used in these studies will be determined according to the climatic zone of the region in which IFA manufacturer is;

c) Table (Annex VII, with the necessary adaptations), containing a summary of the results of the photostability study, or technical-scientific justification for its absence;

d) Storage conditions and retest period;

e) Description of primary packaging materials and potential interactions with the IFA.

The description of the IFA (Art. 38, VII "a" of RDC nº 09/2015) is exempt, in the case of APIs already registered in Brazil and/or when described in the pharmacopoeias listed by RDC nº

37, of July 6, 2009, which deals with the admissibility of foreign Pharmacopoeias, except when there is a post-registration change not yet approved by Anvisa.

6. EXPERIMENTAL DRUG

The documentation to be presented regarding the experimental medicine is listed below:

6.1 LIST OF ACTIVE AND INACTIVE COMPONENTS

a) List of all active and inactive components with their respective functions, including those that are not present in the finished product, in table form (Annex VIII).

6.2 QUANTITATIVE COMPOSITION

a) Complete quantitative composition of the formulation, with all its components specified by corresponding technical names and synonyms in accordance with the Brazilian Common Denomination - DCB, if any, or International Common Denomination - DCI or, in its absence, the name Chemical Abstracts Service – CAS, indicating the units of measurement used (Annex VIII);

b) Discussion on the development of the pharmaceutical form, formulation and on compatibility studies with diluents/containers or devices doctors, if applicable.

6.3 GENERAL DESCRIPTION OF THE MANUFACTURING PROCESS AND PACKAGING

6.3.1 General information a)

Name, address and responsibility of all companies involved in each manufacturing stage of batches of experimental medicine to be used in non-clinical trials or in the different phases of clinical trials, including companies responsible for quality control and carrying out studies on stability (Annex III);

b) Pharmaceutical form and presentation;

c) Description of the preparation method for products that must be reconstituted or diluted before use.

6.3.2 Manufacturing Process and Controls

a) Flowchart of the manufacturing process;

b) Summary information on in-process control tests and respective limits specification;

c) List of equipment used and respective work capacities;

d) History of product development, indicating the size of each batch produced and the purpose of use (e.g.: batches for stability studies, non-clinical and clinical);

e) Description and justifications for changes made to the production process during the development of the investigational drug, if applicable.

6.3.3 Packaging

a) Technical specification of the primary packaging;

b) Assessment of the possible interaction between the experimental drug and Primary package.

6.4 ANALYTICAL METHODOLOGY AND ACCEPTABLE LIMITS FOR GUARANTEE IDENTITY

6.4.1 Quality control

a) Information on batches to be used in non-clinical and clinical trials, including batch number, size, date and place of manufacture and purpose, in the table form (Annex X);

b) Description of the quality control tests carried out on the batches to be used in non-clinical and clinical trials, accompanied by the respective specification limits and analytical procedures, in table form (Annex IX);

c) Certificates of quality control analysis of representative batches used in clinical trials.

6.4.2 Validation of Analytical Procedures

a) Table (Annex VI), containing the parameters, acceptance criteria and available results from the validation of the analytical procedures used, in compliance with current legislation in Brazil or other guidelines internationally recognized, according to the stage of development clinical. Technical justification can be presented for the lack of validation or the use of an alternative method validation approach, based on recognized scientific references.

6.4.3 Characterization of impurities

a) Table (Annex XI) containing information on the characterization of impurities, specification limits and respective justifications for choosing these limits;

b) Justification for non-compendial specification limits and brief discussion about potential mutagenic impurities, including information about the origin, structure, justification for established limits, in accordance with the ICH Guide M7;

c) The absence of routine control for solvents/catalysts used in the manufacturing process must be justified.

6.5 RESULTS OF STABILITY STUDIES THAT ENSURE THE USE OF THE EXPERIMENTAL MEDICATION IN PLANNED CLINICAL TRIALS

6.5.1 Summary of stability studies and conclusions

a) Stability study protocol;

b) Table (Annex VII), containing a summary of the stability studies;

c) Brief description of the primary packaging materials, including specifications, size and/or volume used, and potential interactions with the formulation;

Stability studies must be conducted in accordance with the requirements recommended in the specific legislation in force, on representative batches of the experimental medicine.

The definition of the expiration date of the investigational medicinal product must take into account the stability data of both the IFA and the available stability data of the investigational medicinal product. Stability studies can be conducted in parallel with clinical trials. Stability studies carried out using reduced models, such as grouping and matrixing, will be accepted as long as they are conducted in accordance with the Reduced Drug Stability Study Plan, electronic address: http:// www.anvisa.gov.br/medicamentos/ recommends/plano_estudo_2.pdf, and that all expected variations become part of the DDCM. available no

The results of stability studies must guarantee that the experimental medicine will be within quality specifications during the period of use in planned clinical trials.

For clinical trials where medication is dispensed to the research participant for home use, in addition to the stability data already available, the following must be presented:

- **Results of long-term stability study in zone IVb**
  or
- **Accelerated stability study results**
  or
- **Instruction to clinical trial participants reinforcing care for the conservation of the experimental medicine. The model described can be followed no Anexo I.**

In cases of experimental medicines used in multiple doses after reconstitution, dilution or mixing, in-use stability study data must be presented. For experimental medicines diluted or reconstituted immediately before use, there is no need to present an in-use stability study.

7. PLACEBO DESCRIPTION

7.1 COMPOSITION

a) List of all placebo components and their respective functions (Annex VIII).

7.2 ORGANOLEPTIC CHARACTERISTICS a)

Description of the organoleptic characteristics of the placebo and information on how possible differences between placebo and experimental medicine were considered to maintain masking.

7.3 MANUFACTURE PROCESS

a) Flowchart of the manufacturing process;

b) Summary information about the controls in the process and criteria for acceptance.

In cases where the manufacturing and packaging process is the same as that of the experimental medicine, carried out by an identical manufacturer and production line, justification can be sent for the absence of the documents mentioned in this item.

7.4 ANALYTICAL CONTROLS

a) Description of the quality control tests carried out on the placebo batches be used in non-clinical and clinical trials, accompanied by respective specification limits and analytical procedures, in the form of table (Annex IX). Tests that make it possible to differentiate the placebo of their respective experimental medicine;

d) Technical justification for the placebo's expiration date. In cases where there is suspected that changes in physical characteristics or degradation, results of stability studies must be presented, respecting the appropriate particularities of the placebo.

8. MODIFIED COMPARATOR MEDICINE

a) List of all components of the Modified Comparator Medicinal Product, in table form (Annex VIII);

b) Description of the modifications made;

c) Assessment of the impact of modifications on all parameters relevant to the function, stability, efficacy and safety of the medicine. It must be proven that there was no change in these parameters or presented technical justification that supports the proposed changes.

9. CONTROL OF TRANSMISSIBILITY OF ENCEPHALOPATHIES TRANSMISSIBLE SPONGIFORMS (TSE)

a) Documentation regarding the control of transmissibility of Transmissible Spongiform Encephalopathies (TSE), according to current health standards, if applicable.

10. LABEL MODEL(S) OF THE PRODUCT(S) UNDER INVESTIGATION

The following information must be included in label templates, unless their absence can be justified, as, for example, in cases of use of electronic randomization systems:

I. name, address and telephone number of the sponsor, organization of the contract research or investigator (the primary contact for product information, clinical trial and emergencies);

II. presentation, route of administration, dosage and, in the case of trials open, the name/identifier and the concentration/potency;

III. the batch and/or code number to identify the content and operation packaging;

IV. a test reference code that allows identification of the test, of the site, the investigator and the sponsor, if not provided in another place;

V. the subject identification number/treatment number and always where relevant, the visit number;

SAW. the name of the investigator (if not included in the information of sections I or IV);

VII. instructions for use (reference may be made to a leaflet or other explanatory document intended for the trial participant or person who administers the product);

VIII. “for clinical trial use only” or similar wording;

IX. storage conditions;

X. period of use (use limit date, expiration date or re-test date, as applicable), considering, at least, the month/year format, and in a way that avoids any ambiguity; It is

XI. "keep out of the reach of children", except when the product is intended for use in trials in which the product is not taken home by the participant.

The information listed above must appear on the primary packaging and on the Secondary packaging.

The information must be in the language of the country where the clinical trial takes place, however other languages may be included.

The address and telephone number of the primary contact for information about the product, clinical trial and for emergency termination of mischaracterization need not appear on the label when the subject has received a leaflet or card providing these details and has been given instructions to keep this contact in your possession at all times

When the medicinal product is provided to the trial participant or the person administering it within a primary packaging together with the secondary packaging and the secondary packaging contains the data listed above, the following information must be included in the identification of the primary packaging:

I. name of sponsor, organization representing clinical research contractor or investigator;

II. presentation, route of administration, dosage and, in the case of trials open, the name/identifier and concentration/potency;

III. batch and/or code number to identify content and operation packaging;

IV. a trial reference code that allows identification of the study, of the site, the investigator and the sponsor, if not provided in another place; It is

V. the study participant identification number/study number treatment and, where applicable, the visit number.

The description of the route of administration referred to in section II may be excluded for solid oral pharmaceutical forms.

If the primary packaging is a blister or small units, such as ampoules, on which the required information cannot be displayed, an outer packaging bearing a label with that information must be provided, however, the primary container must contain the following items:

I. name of sponsor, organization representing clinical research contractor or investigator;

II. route of administration, number of dosage units and, in the case of tests open, the name/identifier and concentration/potency;

III. batch and/or code number to identify the content and operation of packaging;

IV. a trial reference code that allows identification of the study, the location, investigator, and sponsor if not provided elsewhere;

It is

V. the identification number of the person under study/treatment number and, where applicable, the visit number.

The description of the route of administration referred to in item II above may be excluded for oral solid pharmaceutical forms.

Symbols or pictograms may be used to clarify certain labeling information.

Additional information, warnings and/or handling instructions may be displayed.

If it is necessary to change the expiration date, an additional label must be affixed to the investigational medicinal product. The additional label must indicate the new expiration date and repeat the batch number. The additional label can be superimposed on the old expiration date, but cannot be superimposed on the original batch number for quality control reasons. This operation must be carried out at a duly authorized manufacturing site. Exceptionally, as long as it is duly justified, the operation may be carried out in a location authorized by the sponsor of the clinical trial, by a pharmacist or other authorized healthcare professional. The operation must be carried out in accordance with GMP principles, standard and specific operating procedures and under contract, if

applicable, and must be verified by a second person. This additional labeling must be adequately documented in the assay documentation and batch records.

11. GLOSSARY

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

II - Experimental Medicine Dossier – compiled of documents to be submitted to Anvisa as part of the DDCM, which must contain information about the IFA, experimental medicine, placebo, comparator medicine, transmissibility control of transmissible spongiform encephalopathies, label(s) and analysis criticism of non-clinical and clinical studies;

III - Clinical trial - research conducted on human beings with the aim of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of the experimental drug and/or identifying any adverse reaction to the experimental drug and/or studying absorption , distribution, metabolism and excretion of the experimental drug to verify its safety and/ or effectiveness;

IV - Active Pharmaceutical Ingredient (IFA) - any substance introduced into the formulation of a pharmaceutical form that, when administered to a patient, acts as an active ingredient. Such substances may exert pharmacological activity or other direct effects on the diagnosis, cure, treatment or prevention of a disease, and may also affect the structure and functioning of the human body;

V - Investigator-Sponsor - natural person responsible for conducting and coordinating clinical trials, alone or in a group, carried out under their immediate direction independently, developed with the investigator's own financial and material resources, national or international funding entities to research, from private entities and other non-profit entities;

VI - Comparator medicine: medicine or placebo used as a reference in a clinical trial.

VII - Modified comparator medicine: comparator medicine marketed that has undergone any modification, except repackaging with material compatible with that of the original product.

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

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

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

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

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

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13. CHANGE HISTORY

Version	Changes made	Explanation and Justification
1st edition		
2nd Edition	• Title: SUBMISSION MANUAL QUALITY DATA	• New wording for better clarity textual.

	REGARDING THE PRODUCTS UNDER INVESTIGATION USED IN CLINICAL TRIALS SYNTHETIC MEDICINES AND SEMISYNTHETICS	
2nd Edition	• Back cover and title page	• Update layout accordingly with the current model of Manuals and Anvisa Guides.
2nd Edition	• Item 1 – Acronym • Item 2 – Introduction • Item 3 – Base Legal • Item 4 – Objective	• Update layout accordingly with the current model of Manuals and Anvisa guides, including Siglario, Legal Basis and Objective and changing Introduction.
2nd Edition	• Item 5 - Information regarding to the IFA(s) must be presented only to experimental medicines .	• New wording for better clarity textual.
2nd Edition	• Removal of item 5.2.2c	• Size information minimum and maximum of lots regarding IFA was removed due to the reassessment of its relevance.
2nd Edition	• Item 5.3 - METHODOLOGY VALIDATED ANALYTICS AND LIMITS ACCEPTABLE TO GUARANTEE IDENTITY, QUALITY AND PURITY	• Harmonize with what is described in RDC nº 09/2015.
2nd Edition	• Item 5.3b - Table containing the available results from	• Considering that the medicine experimental is still in progress

	validation of analytical methods in compliance with legislation in force in Brazil or other recognized guidelines internationally, according with the stage of development clinical. • For phase I studies, the suitability of methods analytical used must be confirmed. The limits of acceptance and the parameters to be used to validate the analytical methods must be presented in a table. • For phase II and III studies, analytical methods applied to investigational products must have its suitability demonstrated in accordance with the legislation in force, as per applicable for each phase of clinical development, or should justification must be provided technique for using alternative approach, based in scientific references recognized.	development, will also be validation data accepted according to other guidelines internationally recognized.
2nd Edition	• Item 5.4 c - Table with summary the results of the study of photostability or justification	• New wording for better clarity textual.

	technical-scientific for your absence;	
2nd Edition	• Inclusion of item 5.4 d - Assessment of the possible interaction between the IFA and the primary packaging.	• Need to evaluate the possible interaction during the drug development experimental.
2nd Edition	• Item 5.4 - In the case of IFAs already registered in Brazil, may be presented only to documentation relating to "Physicochemical characteristics and organoleptic" and "Information General" of the General Method of Obtaining.	• New writing for better textual clarity.
2nd Edition	• Item 6.2.1 b - Brief description of the formulation development, including justification for the use: • the pharmaceutical form; • excipients used by first time on a medicine or on a new route administration; It is • of excipients not described in the pharmacopoeias recognized by the Anvisa;	• New writing for better textual clarity.
2nd Edition	• Item 6.2.1 c - Description of the preparation method for products that require reconstitution or dilution before use.	• New wording for better clarity textual.
2nd Edition	• Item 6.2.2 a - Flowchart of the manufacturing steps, identifying points of addition of	• New wording for better clarity textual.

	inputs, critical points, points control and testing intermediaries. For the testing of phases I and II this data can be presented according to availability;	
2nd Edition	• Item 6.2.2 c - Production scale in all stages of development, indicating the minimum and maximum sizes of the batch to be produced.	• Merging item c and d for better textual clarity.
2nd Edition	• Inclusion of item 6.2.4 c - Assessment of possible interaction between the medication experimental and primary packaging.	• Need to evaluate the possible interaction during the drug development period experimental.
2nd Edition	• Item 6.3 a - Presentation of quality control testing carried out on the lots to be used in clinical trials, accompanied by a brief description of the analytical methodology, specifications and their respective justifications;	• New writing for better textual clarity.
2nd Edition	• Item 6.3 - For phase studies II and III must be demonstrated suitability of methods analytics according to the parameters recommended in current national health legislation that provides for the validation of analytical methods or other recognized guidelines internationally. It must be A table with the results is presented, and it is not necessary to present the complete validation report.	• New wording to adapt to possible updates to current legislation.
2nd Edition	• Item 6.4 - Studies of stability must be conducted with representative lots and their	• Inclusion of parameters acceptance in the table to facilitate

	results, together with the acceptance parameters, summarized in a table, accompanied by the technical justification of the proposed validity period for the experimental medicine.	analysis of the results of stability.
2nd Edition	• Item 6.4 – The results of the stability studies should ensure that the experimental medicine will be within quality specifications during the period of use in planned clinical trials.	• Inclusion of a paragraph considering what period of development the studies of stability may be in progress, but it is still necessary to guarantee the quality of the product during use in clinical trials.
2nd Edition	• Item 6.4 - For clinical trials Phase III where medication is dispensed to the research participant for home use, in addition to the stability data already available, should to be presented: • Study results long-term stability in zone IVb • or • Study results accelerated stability • or • Instruction to clinical trial participants reinforcing care for the conservation of the experimental medicine. The attached model can be followed.	• Inclusion of paragraph for guarantee the quality of the product for home use or instruction reinforcing conservation care, considering that during the product development period it is possible that studies in zone IVb are still in progress. trend.
2nd Edition	• Item 7.3 - In cases where the packaging manufacturing process is the same as the medicine It is experimental one, conducted by the manufacturer and production line	• New wording to adapt textual.

	identical production, justification can be sent for the absence of the documents mentioned on this item.	
2nd Edition	• Item 7.4 b - Technical justification of the placebo expiration date. In cases where it is suspected that changes in physical characteristics or degradation, must to be presented results of stability studies, of respecting as due particularities of the placebo.	• New wording for better clarity textual.
2nd Edition	• Item 8.2 a - Name and address of the medicine manufacturer original;	• Inclusion of the manufacturer's address to correct the previous version.
2nd Edition	• Item 8.2 c - Flowchart with the steps of the modification process, identifying input addition points, critical points, control points It is testes intermediaries;	• New writing for better textual clarity and reassessment of the relevance of the information to be presented.
2nd Edition	• Item 8.2 d - Analysis report batch of modified comparator medicine containing the number of the batch, batch size, manufacturing date, analytical control methodologies, acceptable limits and results obtained.	• Inclusion of the analysis report to complement the data that supports the assessment of the quality of the modified product.
2nd Edition	• Item 9 - Labeling model(s) must be presented for primary and secondary packaging(s), if applicable, of the investigational medicinal product. For these	• New wording to adapt textual.

	model(s), we recommend the following fields: •	
2nd Edition	Item 9 h - Following warning phrases, or similar, in Caps Lock:	• New wording to adapt textual.
2nd Edition	• Item 9 - Labeling of the Primary packaging of experimental medicines accompanied by secondary packaging must contain fields for, at least, the following information:	• New writing for better textual clarity.
2nd Edition	• Item 9 – exclusion of item d: ~~Clinical trial participant identification code.~~	• Removed the need for inclusion this information on the primary packaging, as it may appear on the secondary packaging.
2nd Edition	• Item 9 - The address and telephone number of the main contact for obtaining information about the experimental drug, the clinical trial and for breaking the blinding code do not need to appear on the label, as long as the clinical trial participant receives a leaflet or card with such information and be instructed to make contact at in case of doubts or occurrences.	• New writing for better textual clarity.
2nd Edition	• Item 9 - If it is necessary to change the expiration date, additional labeling can be attached to the medicine experimental. This labeling can be superimposed on the previous label to update the expiration date so as not to override the original batch number.	• New wording for better clarity textual.

	The labeling of other products under investigation must follow the same model as the medicine experimental. When any field(s) are not applicable, provide justification.	
2nd Edition	• Item 10 – Glossary	• Inclusion of glossary for adaptation to the new model of Anvisa manuals and guides.
2nd Edition	• Title 12 - History of Changes • Insertion of comparative table of editorials between versions to monitor updates.	
3rd Edition	• General • In general, changes carried out in this 3rd Edition of the Manual of Quality, aimed to update and clarify the guidance, particularly on way of presenting data and quality information, which now may be presented in tables.	• International guides were used (Health Canada, FDA and EMA) to support changes to improve formatting and make the description of the evidence to be presented, according to recommended by RDC nº 09/2015 (Bibliographic references).
3rd Edition	• Layer Change from ~~2nd~~ Edition ~~2017~~ to 3rd 2019 Edition	• Edition update.
3rd Edition	• Change of ~~"Copyright©2017"~~ to "Copyright©2019". • Change of ~~"Printing: 2nd edition"~~ for "Printing: 3rd edition". • Update member names of the Anvisa team who participated in the technical review of the manual. Update of the Catalog Sheet ~~24p~~ for 43p.	• Edition update.

3rd Edition	• Item 5. PHARMACEUTICAL SUPPLY ACTIVE (IFA) • Item 5.1 - ...AND BIOLOGICAL (Included) • Item 5.1.1 - General information and Characterization of the input active pharmacist (Edited); ...>Information must be presented in table – Annex II (Included) b)>c) ...+ molecular mass; (Edited/ Included) ...>b) Company code or Laboratory and Chemical Abstracts Service (CAS) (Included) c)>d) ... + size distribution of particle, solubility, pH, pKa (Edited/Added) • d)>e) ... (Edited)	• New wording to improve clarity textual. • Inclusion of Annex, with model of Table for presenting the information about IFA.
3rd Edition	• 5.2 GENERAL METHOD OF OBTAINMENT (Edited/Repositioned) ...>5.2 Name and Address of Manufacturer ... reference RDC nº 60/2014 (Deleted) • 5.2.1 General Information (Edited/Repositioned) ...>5.2.1 Manufacturers ...>Information must be presented in table – Annex III (Included) • 5.2.2 Manufacturing Process (Edited) ...>5.3 GENERAL METHOD OF OBTAINMENT	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the information about the manufacturers of the IFA.

	...>5.3.1 Manufacturing Process and Controls • a) .... + critical steps of the process (Edited/Added) • b) ... (Edited/Repositioned) ...>e) Mutagenic impurities – Guide ICH M7; (Edited/Added)	
3rd Edition	• 5.3 ANALYTICAL METHODOLOGY VALIDATED AND ACCEPTABLE LIMITS TO GUARANTEE IDENTITY, QUALITY AND PURITY ...5.4 (Repositioned) ...5.4.1 Quality Control (Repositioned) • a) ...+ lot number, size, location, purpose (Edited/Added) ...>Information must be presented in table – Annex V (Included) ... >b) Description of QC tests[...] (Repositioned) • b) Table containing the results available from validation[...]; • Validation according to the development phase development (Edited/Deleted) ...<phase criteria (Excluded) ...>5.4.2 Validation of procedures analytics (Repositioned) ...>Information must be presented in table – Annex VI (Included) • c)... (repositioned) ...>c) COA	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the information about Methodology Analytics, control parameters and IFA specification limits.

3rd Edition	• 5.4 RESULTS OF STUDY STABILITY (Edited/Repositioned) • ...> 5.5 RESULTS OF STUDY STABILITY • ...<for phase I or II studies [...] (Deleted) • a) Packaging material description [...] (Edited/Repositioned) • ...>a) Study protocol stability (Included) • b) Stability of the IFA and justifications (Edited/Included) • ...>b) Table (Annex VII) + conditions stability according to the conditions/area of the region • c) Photostability [...] (Edited) • ...c) Table (Annex VII) (Included) • d) Packaging and IFA interaction (Edited/Repositioned) • ...>e) Packaging and interaction with IFA	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the results of stability studies and photostability of IFA.
3rd Edition	• 6. EXPERIMENTAL DRUG • 6.1 LIST OF ALL COMPONENTS AND COMPOSITION QUANTITATIVE • a) Table with all components [...](Edited/Repositioned)	• New writing and formatting for improve clarity
	• 6.2 GENERAL DESCRIPTION OF THE PROCESS MANUFACTURE AND PACKAGING • 6.2.1 General information (Edited/Change order) • ...>6.1 LIST TWO COMPONENTS ACTIVE AND INACTIVE	

3rd Edition	...>a)....+ Information must be presented in table – Annex VIII (Included) • ...>6.2 QUANTITATIVE COMPOSITION • ...>a)...+ Information must be presented in table – Annex VIII (Included) • 6.2.2 Information about the steps of manufacturing (Edited/Repositioned) • ...>6.3 GENERAL DESCRIPTION OF THE MANUFACTURING PROCESS AND PACKAGING • ...>6.3.1 General information • 6.2.3 Information about excipients • 6.2.3.1 Excipients described in pharmacopoeias [...] 6.2.3.2 Excipients used for the first time time[...] (Deleted) a) Specification of the excipient [...] (Deleted) b) manufacturing process data d excipient[...] (Deleted) 6.2.4 Packaging (Edited/Repositioned) b) Inviolability[...] 6.3.3 Packaging • ... >Inviolability: considered as specification	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the composition do Medicine Experimental.
	• 6.3 THE ANALYTICAL METHODOLOGY AND THE ACCEPTABLE LIMITS • a) Presentation of QC tests (Repositioned) • b) Assessment of the profiles of impurities [...] (Repositioned>6.4.3)	

3rd Edition	• c) QC report (Repositioned>c) • d) Table with validation results [...] (Repositioned>6.4.2) • 6.4 ANALYTICAL METHODOLOGY AND OS ACCEPTABLE LIMITS TO GUARANTEE THE IDENTITY • 6.4.1 Quality Control • ...>a) Lots to be used – table (Appendix X) • ...b) Description of QC tests – table (Annex IX) • ...>c) COA • 6.4.2 Validation of Procedures Analytics • ...>Table (Annex VI) • 6.4.3 Characterization of impurities • ...a) Table (Annex XI) • ...b) Justification for limits of impurities (ICH M7 Guide) • ...>c) Justification for absence of QC of solvents	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the information about Methodology Analytics, control parameters and Limits of specification of Experimental Medicine.
3rd Edition	• 6.4 RESULTS OF STUDY STABILITY • Reference to RDC 1/2005 (Edited) to “Current legislation” • ...>6.5 RESULTS OF STUDY OF STABILITY THAT ENSURE THE USE OF THE MEDICATION EXPERIMENTAL IN TESTS PLANNED CLINICS • ...> 6.5.1 Summary of studies stability and conclusions • ...a) Protocol [...] • ...b) Table (Annex VII)	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the results of stability studies of the Experimental Medicine.

	• ...>c) Packaging materials • Defining the expiration date [...] (Edited) • Stability studies must be carried out in representative batches [...] (Deleted) • For phase III clinical trials where medication is dispensed to the research participant to home use, in addition to stability data already available, must be presented:	• Need to present documents listed in this item for all clinical trials where there are dispensing for home use and not only for phase III studies.
3rd Edition	• 7. PLACEBO • 7.1 COMPOSITION • a) Table with the formula [...] (Edited) • ...>a) List two components[...] (Annex VIII)	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the Placebo composition.
3rd Edition	• 7.2 FEATURES ORGANOLEPTICS • A) Description of how the differences[...] (Edited) • ...>a) Description of characteristics organoleptic	• New writing and formatting for improve clarity.
3rd Edition	• 7.3 MANUFACTURE PROCESS • a) Name and addresses[...] (Deleted) • c) Control of critical steps (Edited) • ...>b) Summary information of which in-process controls[...]	• New writing and formatting for improve clarity.
3rd Edition	• 7.4 ANALYTICAL CONTROL • a) Brief description specifications, methods[...] (Edited)	

	• b) Justification for the deadline validity of placebo (Edited)	• New writing and formatting for improve clarity.
3rd Edition	• 8 COMPARATOR MEDICATION MODIFIED • 8.1 DESCRIPTION • a) Table with formula[...] • ...> List of all components – Table (Annex VIII)	• New writing and formatting for improve clarity. • Inclusion of Annex, with model of Table for presenting the composition do Medicine Modified Comparator.
3rd Edition	• 9 SIGN MODEL • (Edited) • ...>10 SIGN MODEL TWO PRODUCTS UNDER INVESTIGATION	• Inclusion of the Instruction text Good practice regulations Manufacturing of Medicines experimental (IN nº 45/2019).
3rd Edition	• 12. BIBLIOGRAPHICAL REFERENCES • -RE No. 899/2003 (Updated) • ...>-RE nº 166/2017. • ...> EMA Guide: Requirements for quality documentation • ...> Health Canada Guide: Documentation requirements Of Quality • ...> IN nº 45/2019: Good practices in Manufacturing for Medicines Experimental.	• New writing and formatting for improve clarity
3rd Edition	• 14. Attachments • Annex II - Physical characteristics- chemical, organoleptic and biological • Annex III - Name and address of manufacturer. • Annex IV - Impurities related to the active substance.	• These attachments have been included to facilitate organization, visualization and receipt of information.

	• Annex V - Batches of the substance active to be used in medicine production experimental. • Annex VI - Validation of analytical procedures. • Annex VII - Results of stability studies. • Annex VIII - List of components active and inactive. • Annex IX - Quality control. • Annex X - Lots of medicine experimental to be used in non-clinical trials and clinicians. • Annex XI - Characterization of impurities.	

14. ATTACHMENTS

ANNEX I

Protocol XYZ001 – Clarification Document for Participants about the Study Medication

Medicine XYZ – Enter the presentation of the medicine

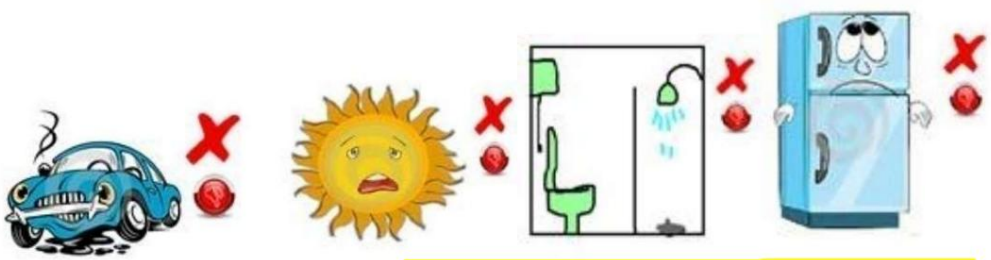
General information: •

Participants in study XYZ001 will receive medication XYZ every X days. Please follow the instructions below to take your medication at home. • Don't forget to return empty and/or unused packaging at the next study visit. • Do not use the medication if it is damaged or appears to be spoiled.

Medication storage instructions:

• Describe medication storage precautions for the patient, adding examples of inappropriate storage.

Ex.: The medication must be stored at room temperature (15ºC - 25ºC) and away from light. Do not leave medication stored in the car or exposed to the sun. Do not store medication in the bathroom. Do not store the medicine in the refrigerator or freeze it.



Center Contact Information: Enter the person responsible and telephone contact.

Instructions for using the medication at home: Ex.:

You will take X doses of XYZ at the same time every day, in the morning and in the evening, approximately 12 hours apart, with a glass of water. It's okay to take it before or after eating. The tablet must be swallowed whole, it must not be chewed, crushed, dissolved or divided.

If you vomit shortly after swallowing the tablets, you should only repeat the dose if all the tablets can be seen, counted and are intact. If you miss a scheduled dose for any reason (for example, if you forget or if you vomit), you can take the dose again no later than 2 hours after the correct time. If more than 2 hours have passed, the forgotten/missed dose should not be taken and you should wait for the next dose at the next scheduled time (12 hours).

Contact the study team if you have any questions about storing or taking your study medication!

ANNEX II

PHYSICAL-CHEMICAL, ORGANOLEPTIC AND BIOLOGICAL CHARACTERISTICS

Nomenclature

1.Brazilian Common Denomination (DCB)	
2.International Common Denomination (INN)	
3.Chemical name	
4. Company or Laboratory code	
5. Chemical Abstracts Service (CAS)	

Structure

1.Structural formula, including relative and absolute chirality/stereochemistry	
2.Molecular Formula	
3.Relative Molecular Mass	

General Properties

1.Physical description (e.g. appearance, color, physical state)	
2. Physical form (e.g. preferred polymorphic form, solvate, hydrate) and particle size distribution	
3. Solubility (e.g.: aqueous/non-aqueous mg/mL)	
4. pH by pKa	
5.Other relevant information	

ANNEX III

MANUFACTURER'S NAME AND ADDRESS

Name	Address	Responsibility	Clinical trial phase

ANNEX IV

IMPURITIES RELATED TO IFA

Impurities related to API (e.g. starting materials, by-products, intermediates, chiral impurities, degradation products, metabolites)	Criterion of acceptance	Justification of the acceptance criteria

Impurities related to the manufacturing process (e.g. residual solvents, reagents, catalysts)	Criterion of acceptance	Results (Non-clinical or clinical batches)		
		Batch	Batch	Batch

ANNEX V

BATCHES OF ACTIVE SUBSTANCE TO BE USED IN THE PRODUCTION OF THE EXPERIMENTAL DRUG

Lot Number* Lot Size		Date and place of Manufacturing	Purpose (e.g. Phase 3 clinical trial)

(*) Attach copies of Analysis certificates

ANNEX VI

VALIDATION OF ANALYTICAL PROCEDURES

Validation parameters*	Acceptance criteria (where applicable)	Results or values found
Specificity		
Linearity		
Working range		
Precision		
Accuracy		
Detection limit		
Limit of quantification		
Conclusion:		

* The parameters listed are examples, and other applicable parameters may be presented.

ANNEX VII

RESULTS OF STABILITY STUDIES

Name of the Medicine: Batch: Manufacturer Manufacturing date: Lot size: Storage conditions:	Stability Protocol: Start date: Study duration: Packing size: Kind of packing Proposed expiration date:
	Test intervals

Specifications			Data (initial)	Data (1m)	Data (3m)	Data (6m)	Data (12m)
Test	Method	Limits of specification					

ANNEX VIII

LIST OF ACTIVE AND INACTIVE COMPONENTS

Components (IFA, excipients, dyes, coatings, diluents)	Function	Pharmaceutical Form: (e.g. modified-release coated tablet)			
		Concentration 1		Concentration 2, 3...(if applicable)	
		Quantity/unit	%	Quantity/unit	%

ANNEXURE IX

QUALITY CONTROL

Tests (e.g. identity, content, impurities, degradation products)	Specification limits (*)	Analytical procedure (Reference)

(*) Follow pharmacopoeial specification limits or justify the use of another reference

ANNEX

LOTS OF EXPERIMENTAL MEDICATION TO BE USED IN NON-CLINICAL AND CLINICAL TRIALS

Lot Number* Lot Size		Date and place of Manufacturing	Purpose (e.g. Phase 3 clinical trial)

(*) Attach copies of Analysis certificates

ANNEX XI

CHARACTERIZATION OF IMPURITIES

Impurities and Products Degradation, metabolites	Limits of specification	Specification limit justification