National Health Surveillance Agency

# QUALITY DATA SUBMISSION MANUAL REGARDING PRODUCTS UNDER INVESTIGATION USED IN CLINICAL TRIALS - ORGANIC PRODUCTS

General Medicines Management - GGMED

Coordination of Clinical Research in Medicines

and Organic Products - COPEC

2019

# QUALITY DATA SUBMISSION MANUAL
# REGARDING PRODUCTS UNDER INVESTIGATION USED IN CLINICAL TRIALS - ORGANIC PRODUCTS

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

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

**Printing: 3rd edition**

**Organization - Anvisa**
General Medicines Management

**Technical Review - Anvisa**
Adriane Alves de Oliveira
André Luis Carvalho Santos Souza
Bruno de Paula Coutinho
Bruno Zago Franca Diniz
Candida Luci Pessoa e Silva
Carla Abrahao Brichesi Caligaris
Carlos Augusto Martins Netto
Carolina Pingret Cintra
Christiane Santiago Maia
Claudio Nishizawa
Fanny Nascimento Moura Viana
Fernando Casseb Flosi
Flavia Regina Souza Sobral
Gláucia Pacheco Buffon
Kellen do Rocio Malaman
Leonardo Fabio Costa Filho
Miriam Motizuki Onishi
Ricardo Eccard da Silva
Sonia Costa e Silva

**Layout and Review**
Anvisa Publisher

**Graphic project**
Anvisa Publisher

Catalog Sheet:
Manual for Submission of Quality Data Regarding Investigation Products Used
in Clinical Trials – Biological Products / Brasília. Anvisa 2019

66 p.
DDCM; Experimental Drug Dossier; Biological Products; Clinical Trials.

# SUMMARY

## 1. CONFIDENTIAL

DCB - Brazilian Common Denomination
DCI - International Common Denomination
DDCM - Clinical Drug Development Dossier
ORPC - Representative Clinical Research Organization
RDC - Resolution of the Collegiate Board of Directors

## 2. INTRODUCTION

The publication of the regulation on Clinical Trials with drugs in Brazil makes it mandatory to submit the Experimental Drug Dossier as part of the Clinical Drug Development Dossier (DDCM). This manual is intended to provide guidelines for the sponsor, sponsoring investigator or CRO to submit quality data regarding biological products

under investigation, which must compose the Experimental Drug Dossier (document VII, described in Art. 38 of RDC No. 09 of February 20, 2015) in an appropriate manner.

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

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

For the purposes of this manual, biological products are:

I. vaccines;

II. soros hyperimunes;

III. blood products;

IV. biomedicines classified into:

The. medicines obtained from biological fluids or tissues of animal origin; and

B. medicines obtained by biotechnological procedures.

V. monoclonal antibodies;

SAW. medicines containing live, attenuated or dead microorganisms.

## 3. BASE LEGAL

Resolution of the Collegiate Board of Anvisa - RDC No. 9, of February 20, 2015, which provides for the regulation for conducting clinical trials with drugs in Brazil.

## 4. OBJECTIVE

Without prejudice to the existing provisions in the legal provisions, this manual aims to guide and explain in a complementary way, the submission of the Experimental Drug Dossier as part of the Clinical Drug Development Dossier (DDCM), as described in chapter III of RDC No. 09 /2015.

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

## 5. ACTIVE SUBSTANCE

Information concerning active substances must be presented only for the experimental drugs.

### 5.1 PHYSICOCHEMICAL, ORGANOLEPTIC AND BIOLOGICAL CHARACTERISTICS

#### 5.1.1 General information and Characterization of the active substance:

The characterization of the active substance must be presented as described below:

a) Nomenclature of the active substance (Common Brazilian Denomination, if any, or International Common Denomination – IUPAC) and synonyms;

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

c) Primary, secondary, tertiary and quaternary structure and molecular mass relative;

d) Comparison of physical-chemical, structural, biological, immunological characteristics chemical, between the produced molecule and the original molecule, when applicable;

e) Characterization of forms resulting from post-translational modifications;

f) Determination of biological activity;

g) Determination of the degree of purity;

h) Data on aggregates;

i) Determination of physicochemical and immunochemical properties;

j) Determination of organoleptic characteristics, if applicable.

In the case of "non-new" biological medicines that intend to be registered through comparability according to RDC No. 55/2010, the characterization above must be done in a comparative way with the comparator biological product, informing and justifying the number of batches used for each product.

## 5.2 MANUFACTURER'S NAME AND ADDRESS

### 5.2.1 Manufacturers

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

a) Name, address and responsibility of each company involved in the manufacturing stages of the API batches of the active substance used in the manufacture of the experimental drug batches to be used in non-clinical trials and in the different phases of clinical trials, including companies responsible for the control quality and by carrying out stability studies.

## 5.3 GENERAL METHOD OF OBTAINING

### 5.3.1 Manufacturing process and controls

a) Flowchart of the active substance manufacturing process;

b) Brief information on what are the critical steps of the manufacturing process and respective in-process control parameters and specification limits, if applicable.

c) Identification and justification of critical steps in the procurement process, if applicable;

d) Description of the controls in process and justification for determining the specifications, where available;

e) Documentation regarding the control of the transmissibility of Encephalopathies Transmissible Spongiforms (TSEs), referring to starting materials and reagents, according to current health regulations;

f) Viral removal and/or elimination procedures used, when applicable;

g) List of impurities related to the active substance and its process of obtaining, acceptance criteria and respective justifications, in the form of a table (Annex III);

h) Critical assessment of the toxicity of impurities, degradation products and contaminants from the manufacturing process or starting materials relevant to the active substance, where applicable;

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

j) History of the development of the active substance, indicating the size of each batch produced and the purpose of use (stability studies, studies not clinicians and clinicians).

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

## 5.4 VALIDATED ANALYTICAL METHODOLOGY AND ACCEPTABLE LIMITS TO ENSURE IDENTITY, QUALITY AND PURITY

### 5.4.1 Quality control

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

b) Description of the quality control tests performed on the batches to be used in non-clinical and clinical trials, accompanied by the respective specification limits with justification for their determination;

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

### 5.4.2 Validation of Analytical Procedures

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

## 5.5 RESULTS OF STABILITY STUDIES

Stability studies with the active substance should be conducted in order to ensure stability during the intended storage period. Such studies should assess the stability of the active substance under the proposed storage conditions.
Additionally, accelerated stability studies and stress tests can help to understand the degradation profile of the active substance.

In this way, present:

a) Protocol of stability studies

b) Table (Annex VI) with the results of stability studies, 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 the manufacturer of the active substance is located.

c) Table (Annex VI, with the necessary adaptations), containing the 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 active substance.

# 6. EXPERIMENTAL DRUG

The documentation to be presented regarding the investigational drug is listed below:

## 6.1 LIST OF ACTIVE AND INACTIVE COMPONENTS

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

## 6.2 QUANTITATIVE COMPOSITION

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

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

## 6.3 GENERAL DESCRIPTION OF THE MANUFACTURING AND PACKAGING PROCESS

### 6.3.1 General information

a) Name and address of all manufacturers of the intermediate biological product, of the biological product in bulk, of the biological product in its primary packaging, the finished biological product, the diluent and the adjuvant (Annex II);

b) Pharmaceutical form and presentation;

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

### 6.3.2 Manufacturing Process and Controls

a) Flowchart of the manufacturing process, including removal procedures and/or elimination of used virals, when applicable;

b) Summarized information on in-process control tests and respective criteria of acceptance;

c) List of equipment used and respective work capacities;

d) Product development history, indicating the size of each batch produced and the purpose of use (stability study, non-clinical studies and clinical);

e) Description and justifications for changes made in the production process during biological product development, if applicable.

### 6.3.3 Packaging

a) Technical specification of the primary packaging;

b) Assessment of the possible interaction between the biological product and primary packaging, if applicable.

## 6.4 ANALYTICAL METHODOLOGY AND ACCEPTABLE LIMITS TO ENSURE IDENTITY

### 6.4.1 Quality control

a) Information on the batches to be used in non-clinical and clinical trials, including lot number, size, date and place of manufacture, in the form of table (Annex IX).

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

c) Certificates of analysis of representative batches used in clinical trials

### 6.4.2 Validation of Analytical Procedures

a) Table (Annex V) containing the parameters, acceptance criteria and available results of the validation of the analytical procedures used, in compliance with the legislation in force in Brazil or other guidelines internationally recognized, according to the stage of development clinical. Technical justification may be presented for the absence 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 X) containing information on the characterization of impurities, specification limits;

b) Justification for non-compendial acceptance criteria and brief discussion about potential mutagenic impurities, including information on origin, structure, justification for established limits, according to 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 DRUG IN PLANNED CLINICAL TRIALS

### 6.5.1 Summary of stability studies and conclusions

a) Protocol of stability studies;

b) Table (Annex VI) containing the summary of stability studies;

c) Brief description of the 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 established in the specific legislation in force, in representative batches of the experimental drug.

The definition of the expiry date of the investigational drug must take into account the stability data of both the active substance and the stability data available for the investigational drug. Stability studies can be conducted in parallel with clinical trials. Stability studies carried out using reduced models, such as clustering and matrixing, will be
accepted as long as they are conducted in accordance with the Reduced Stability Study Plan available at: http://www.anvisa.gov.br/medicamentos/recomenda/plano_estudo_2.pdf,

Medicines, and that all expected variations will part of the

The results of stability studies must ensure that the investigational drug will meet quality specifications during the period of use in planned clinical trials.

For clinical trials where the drug 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

  Where

- Accelerated stability study results

  Where

- Instruction to clinical trial participants reinforcing care for the conservation of the investigational drug. The model described in Annex I can be followed.

For cases of experimental drugs for use in multiple doses after reconstitution, dilution or mixing, data from the in-use stability study must be presented. For investigational drugs diluted or reconstituted immediately before use, there is no need to present the in-use stability study.

## 7. PLACEBO DESCRIPTION

### 7.1 COMPOSITION

a) List of all placebo components and their respective functions (Appendix VII).

### 7.2 ORGANOLEPTIC CHARACTERISTICS

a) Description of the organoleptic characteristics of the placebo and information on how possible differences between placebo and experimental drug were balanced to maintain blinding.

### 7.3 MANUFACTURING PROCESS

a) Flowchart of the manufacturing process;

b) Summarized information on what are the controls in process and criteria for acceptance.

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

### 7.4 ANALYTICAL CONTROLS

a) Description of the quality control tests performed on the placebo lots to be used in non-clinical and clinical trials, accompanied by the respective specification limits and analytical procedures, in the form of table (Annex VIII). Tests that make it possible to differentiate the placebo of their respective investigational drug;

b) Technical justification on the validity period of the placebo. In cases where there is suspicion that there may be changes in the physical characteristics or degradation, results of stability studies must be presented, respecting the due particularities of the placebo.

## 8. MODIFIED COMPARATOR MEDICINAL PRODUCT

a) List of all components of the Modified Comparator Drug, in table form (Annex VII);

b) Description of the modifications carried out;

c) Assessment of the impact of changes on all parameters relevant to the function, stability, efficacy and safety of the drug. 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 (TSEs)

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

## 10. TEMPLATE OF LABEL(S) OF THE PRODUCT(S) UNDER INVESTIGATION

The following information should be included in the label templates, unless its absence can be justified, such as the use of an electronic randomization system:

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

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

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

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

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

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

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

VIII. “For Clinical Trial Use Only” or similar text;

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; and

XI. “keep out of reach of children”, except when the product is for use in trials where the product is not taken home by the participant.

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

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 de-characterization does not need to appear on the label when the subject has received a package insert or card providing these details and has been instructed to that you keep this contact in your possession at all times

When the drug is provided to the trial subject or the person administering it in 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 the contracted clinical research or investigator;

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

III. batch and/or code number for content identification and packaging operation;

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

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

The description of the administration route that deals with item II can be excluded for oral solid dosage 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 that bears a label with this information must be provided, however, the primary container must contain the following items:

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

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

III. batch and/or code number for content identification and packaging operation;

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

V. Study person identification number/treatment number and, where applicable, visit number.

The description of the administration route that deals with item II above can be excluded for oral solid dosage 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 should be affixed to the investigational drug. 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 lot number for quality control reasons. This operation must be carried out at a duly authorized manufacturing site. Exceptionally, as long as duly justified, the operation can be performed in a place authorized by the sponsor of the clinical trial, by a pharmacist or other authorized health 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 properly documented in the assay documentation and batch records.

## 11. GLOSSARY

I - Adjuvant: agent that helps or increases the action of the active ingredient (synergism) or that affects its absorption, mechanism of action, metabolism or excretion (pharmacokinetics), in order to improve the effect of the drug;

II - Adventitious agent: microorganisms contaminating the cell culture or starting material, including bacteria, fungus, mycoplasma/spiroplasma, mycobacteria, rickettsiae, protozoa, parasites, transmissible spongiform encephalopathy and viruses that may have accidentally been introduced in the process of production of a biological product;

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

IV - Experimental Drug Dossier - compiled from documents to be submitted to Anvisa as part of the DDCM, which must contain information on the active substance, experimental drug, placebo, comparator drug, transmissible spongiform encephalopathies transmissibility control, label(s) and critical analysis of non-clinical and clinical studies;

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

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

VII - Comparator drug: drug or placebo used as a reference in a clinical trial;

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

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

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

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

XIII - Biological product in bulk: it is the biological product that has completed all the production stages, formulated in its final pharmaceutical form, in bulk, contained in a single, sterile container, if applicable, and released by the manufacturer's quality control;

XIV - Comparator biological product: it is the biological product already registered with Anvisa based on the submission of a complete dossier, and that has already been marketed in the country;

XV - Biological product in its primary packaging: it is the biological product that has completed all stages of production, formulated in its final pharmaceutical form, contained in its final container (primary packaging), sterile, if applicable, not including the labeling process and packaging and released by the manufacturer's quality control;

XVI - Intermediate biological product: it is the pharmaceutical product, of biological origin, partially processed, which will be submitted to subsequent manufacturing steps, before becoming a bulk product;

XVII - Finished biological product: it is the pharmaceutical product, of biological origin, which has completed all stages of production, including the labeling and packaging process;

XVIII - Product under investigation: experimental drug, placebo, active comparator or any other product to be used in the clinical trial;

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

## 12. BIBLIOGRAPHIC REFERENCES

1. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RDC No. 37, of July 6, 2009. Deals with the admissibility of foreign pharmacopoeias. Official Diary of the Union; Executive Branch, of July 8, 2009.
2. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RDC No. 71, of December 22, 2009. Establishes rules for drug labeling.
Official Federal Gazette, December 23, 2009.
3. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RDC No. 55, of December 16, 2010. Provides for the registration of new biological products and biological products and other provisions. Official Gazette of December 17, 2010.

4. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RDC No. 27, of May 17, 2012. Provides for the minimum requirements for the validation of bioanalytical methods used in studies for the purpose of registration and post-registration of medicines. Official Diary of the Union; Executive Branch, of May 22, 2012.
5. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RDC No. 50, of September 20, 2011. Provides for the procedures and conditions for carrying out

of stability studies for registration or post-registration changes of biological products and other provisions. Official Gazette of May 15, 2013.

6. BRAZIL. ANVISA National Health Surveillance Agency. Study Plan of Stability Reduced from Medicines. Available in: http://www.anvisa.gov.br/medicamentos/recomenda/plano_estudo_2.pdf Accessed: February 20, 2015.

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

8. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RE No. 166, of July 24, 2017. Provides for the validation of analytical methods and other provisions. Official Diary of the Union; Executive Branch, of July 25, 2017.

9. EUROPEAN MEDICINES AGENCY. Committee for Medicinal Products for Human Use (CHMP). Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. CHMP/QWP/185401/2004 final. Available in: http://ec.europa.eu/health/files/eudralex/vol-10/18540104en_en.pdf. Accessed on Sept. 10. 2014.

10. EUROPEAN MEDICINES AGENCY. Committee for Medicinal Products for Human Use (CHMP). Guideline on strategies to identify and mitigate risk for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/07 **Disponível** http:// www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2 **in:**

09/09/WC500002988.pdf Accessed on 03 Sep. 2014.

11. EUROPEAN MEDICINES AGENCY. Committee for Medicinal Products for Human Use (CHMP). Guideline on the requirements for quality documentation concerning biological investigational products trials. medicinal in clinical EMA/CHMP/BWP/534898/2008. Available in: http://ec.europa.eu/health/files/eudralex/vol-10/2012-05_quality_for_biological.pdf.

12. EUROPEAN COMMISSION. The rules governing medicinal products in the European Union. Volume 4 – EU Guidelines to Good Manufacturing Practice. Medicinal products for human and veterinary use. Annex 13 Investigational Medicinal ENTR/F/2/AM/an http:// Products. ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf D(2010)33714 Available in: Acesso em 15 de set. 2014.

13. EUROPEAN COMMISSION. The rules governing medicinal products in the European Union. Volume 10 - Guidance documents applying to clinical trials investigational

medicinal products (IMPs) and 'non investigational medicinal products' (NIMPs). Rev.1, March 2011. SANCO/C/8/SF/cg/a.5.001(2011)332855 Available at: http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011 .pdf Access in 10 of set. 2014.

14. FOOD AND DRUG ADMINISTRATION. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics. Chemistry, Manufacturing, and Controls Disponível em: http://www.fda.gov/downloads/Drugs/Guidances/Documentation ucm070551.pdf Acesso em 15 of set. of 2014.

**15.** FOOD AND DRUG ADMINISTRATION. Center for Drug Evaluation and Research (CDER). Guidance for Industry. INDs for Phase 2 and Phase 3 Studies. Chemistry, Manufacturing, and Controls Information. Sea. 2003. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf Accessed on 15 Sep. 2014.

## 13. CHANGE HISTORY

| Version | Changes made | Explanation and Justification |
|---|---|---|
| 1st edition | | |
| 2nd Edition | • Inclusion of title **11. History of Changes** | • Insertion of comparative table of essays between versions for a more follow-up transparent of updates carried out. |
| 2nd Edition | • New item 5.2.1 | • Merge of sections 2.1.1 and 2.1.2 for simplification, with incorporation of relevant items in the new wording.<br>• Clarification of what are the expected comparisons between the molecule produced and the molecule original. |

| | | |
|---|---|---|
| 2nd Edition | • 5.2.2, item “g” - Critical ~~assessment of toxicity Identific~~ation, qualification and quantification of contaminants, impurities and degradation products from of the manufacturing process of active substance, when applicable<br>• 5.2.2, item “i” - History of the substance development active, pointing out the purpose of use of each batch produced ( stability studies, studies ~~pre~~-clinical and clinical) | • Substitution to clarify the understanding of the area and align with requirements international.<br>• Replacement to suit the terminology. |
| 2nd Edition | • New Item 5.3 - Table containing the available results of validation of analytical methods in compliance with legislation in force in Brazil or other recognized guidelines internationally, according with the stage of development clinical.<br>• For phase I studies, a suitability of methods used analytics should be confirmed. the limits of acceptance and the parameters to be used in the validation of analytical methods must be presented in a table.<br>For phase II and III studies, the analytical methods applied to | • Clarification of which validation results should be presented in accordance with the phase of clinical development. |

| | | |
|---|---|---|
| | products under investigation must have its demonstrated suitability of according to the legislation in force, as applicable for each phase of clinical development, or should be technical justification for the use of an alternative approach, based on scientific references recognized. | |
| 2nd Edition | • 5.4, caput - ~~However~~ Additionally, studies of accelerated stability and stress conditions can help to understand the profile of product degradation.<br>• item "b" - Results of the studies substance stability active, if stored, according to RDC No. 50/2011, ~~justifying their respective peculiarities. At t~~temperature used in these studies will be determined by climate zone in which the manufacturer is located. | • Rewriting the text to correct understanding of the sentence.<br>• To align with requirements of RDC 50/2011. |
| 2nd Edition | • 6.1 - List of all active and inactive components with their respective functions, including those who are not present in the finished product, ~~as buffers and culture media;~~ | • After contributions, the examples were removed not to restrict information requested in the item. |
| 2nd Edition | • 6.3.1, item "d" - History of the product development, | • Replacement to suit the terminology. |

| | | |
|---|---|---|
| | pointing out the purpose of using each batch produced (studies of stability, pre -non-studies~~—~~ clinicians and clinicians) | |
| 2nd Edition | • 6.2.2, item “e” – Valid~~ation report — Tests and~~ acceptance criteria of the critical stages of the manufacturing process, w~~hen — available; —~~<br>• Item “f” - Description of controls in process and justification for determination of specifications, ~~when available; —~~<br>• Item “h” - Identification, qualification and quantification of ~~Critical assessment of the toxicity of —~~ contaminants, impurities and degradation products from of the manufacturing process of experimental drug, if applicable; | • Simplification for alignment to international requirements.<br>• Item information must be always presented, even if are not definitive.<br>• Substitution to clarify the understanding of the area and align with requirements international. |
| 2nd Edition | • 6.3.3, item “c” - Description of possible chemical interactions of excipients with the active substance ~~the active principle~~. | • Terminology correction. |
| 2nd Edition | • Former 6.3.2.1 (now 6.3.3.1) | • Correction of numbering. |
| 2nd Edition | • 6.3.3.1, head out of Item a<br>• For excipients used by the first time on a drug or on a new route administration or excipients not described in pharmacopoeias | • Simplification for the better understanding of the text.<br>• Removal of the requirement to validation of new parameters excipients given the possibility |

| | | |
|---|---|---|
| | listed by RDC No. 37/of ~~06 July~~ 2009~~,~~ which ~~deals with the admissibility of Pharmacopoeias foreigners,~~ ~~in~~ addition to above item information 3.~~3.3,~~ report:<br>• a. Identification tests, tests of purity (including limits for total and individual impurities), content or limit tests and ~~respective table containing the summary of validation tests of parameters~~ ~~and~~ other tests relevant, as well as respective specifications; | of this not be completed during clinical development. |
| 2nd Edition | • Former 6.3.2.2 (now 6.3.3.2) - All excipient~~ materials~~ _ human or animal origin used in the process of manufacturing~~ both of the substance active, as of the drug experimental, or materials that get in touch with these during the manufacturing process,~~ must be identified.<br>• In addition, they must be submitted information about the evaluation of safety of adventitious agents (such as fonts, specifications, and description of the tests performed) and potential viral contamination . | • Correction of numbering.<br>• Simplification of the text by the understanding what it is about just the medicine experimental.<br>• Greater scope of the concept of Contamination. |

| | | |
|---|---|---|
| 2nd Edition | • Item 6.4, item “e” - Table containing the results available from the validation of analytical methods in compliance with legislation in force in Brazil or other recognized guidelines internationally, according with the stage of development clinical.<br>• For phase I studies, a suitability of methods used analytics should be confirmed. the limits of acceptance and the parameters to be used in the validation of analytical methods must be presented in a table.<br>• For phase II and III studies, the analytical methods applied to products under investigation should have its suitability demonstrated according to legislation in force, as applicable for each stage of clinical development, or should justification be presented technique for using alternative approach, based in scientific references recognized. | • Clarification of which validation results should be presented in accordance with the phase of clinical development. |

| | | |
|---|---|---|
| 2nd Edition | • Item 6.5 - Studies of stability must be conducted with batches representatives and their results summarized in a table accompanied by the justification expiration date technique proposed for the drug experimental. **only for medicines experimental of temperature storage environment:** For Phase III clinical trials where there is a dispensation of medication for the participant research for home use, in addition to data from stability already available, should be presented:<br>• Study results of long-term stability in zone IVb<br>Where<br>• Study results of accelerated stability<br>Where<br>• Instruction to participants of the clinical trial reinforcing the conservation care of | • Inclusion of paragraph for ensure product quality in home use or instruction reinforcing the care of conservation, considering that development period of product it is possible that the studies in zone IVb are still in progress. |

| | | |
|---|---|---|
| | experimental drug. He can follow the attached model. | |
| 2nd Edition | • 7.2 - Description of how the possible differences ~~organoleptics~~ between placebo and experimental drug were masquerades. | • Rewriting the text for greater scope of possible differences. |
| 2nd Edition | • 7.4 Item “b” - Technical justification the expiration date of the placebo., - ~~except~~ Us in ~~cas~~es where there is suspicion that there may be changes in characteristics physical or degradation. In ~~that case,~~ must be presented study results of placebo stability . - ~~respecting the due placebo features.~~ | • Numbering correction<br>• New wording for better clarity textual. |
| 3rd Edition | Front cover<br>• Change from 2nd ~~E~~dition 20~~17 to~~ 3rd Edition 2019. | • Edition update. |
| 3rd Edition | against layer<br>• Change of “Copy~~right©2017”~~ for “Copyright©2019”.<br>• Change of “Print r~~un: 2nd edition”~~ for “Printing: 3rd edition”.<br>• Updating the names of the Anvisa team members who participated in the technical review of the manual. | • Edition update. |

| | | |
|---|---|---|
| | • Update of the Catalog Sheet from ~~24p~~ to 66p. | |
| 3rd Edition | • 5.1.1 - The characterization of the active substance must be presented in ~~accordance with the DRC No. 55/2010,~~ as described below:<br><br>• 5.1.1 item “a” - Nomenclature of the active substance (Name Brazilian Common, if any, or Common Denomination International – IUPAC) and synonyms<br><br>• 5.1.1 item “b” - Company code or Laboratory and Chemical Abstracts Service (CAS), if applicable;<br><br>• 5.1.1 item “c” - Primary, secondary, tertiary and quaternary structure and relative molecular mass;<br><br>• 5.1.1 item “g” - ~~Description and justification for modifications carried out in the post molecule cultivation, when applicable;~~ | • Removal of the term “according to with RDC 55/2010” not to leave the manual linked to a another RDC from Anvisa.<br>• Added more detail about how it should be presented the nomenclature of the substance active.<br>• Inclusion of new item for better characterization of active substance.<br>• Combination of items “b”, “c” and “d” of the 2nd edition in a single item “c” in 3rd edition.<br>• Removal of the need to present information about the post modification sites you translated<br>• Excluding the need to present information about changes in the post molecule crop. |
| 3rd Edition | • ~~5.2 GENERAL METHOD OF OBTAINING~~ | • Changing the item title and reformulation of information requested. |

| | | |
|---|---|---|
| | ~~The manufacturing process, described as a general method of obtaining of the active substance, is according to RDC No. 55/2010, as described below:~~<br>~~• 5.2.1 General Information~~<br>~~a) Name and address of the manufacturer of the active substance used in the manufacture of batches of experimental drug;~~<br>• 5.2 NAME AND ADDRESS OF MAKER<br>The name and address of the active substance manufacturer(s) must be presented in the form table (Annex II), as Described below:<br>a) Name, address and responsibility of each company involved in the stages of manufacturing batches of substance active used in the manufacture of drug lots experimental to be used in non-clinical trials and different stages of testing clinicians, including companies responsible for control quality and carrying out stability studies. | • Updating of information that are asked about the active substance manufacturers. |

| | | |
|---|---|---|
| 3rd Edition | • 5.3 ANALYTICAL METHODOLOGY VALIDATED AND ACCEPTABLE LIMITS<br><br>5.3 GENERAL METHOD OF OBTAINING<br><br>5.3.1 Manufacturing process and controls | • Changing the item title and reformulation of information requested.<br><br>• Clarification that the process of manufacturing must be presented in the form of flowchart. |
| | • 5.3.1 - Item "a" - a) Flowchart of the API manufacturing process active substance; | • Removal of the need to present this information. |
| | • 5.3.1 - Item "b" - b) Lista dos main equipment used in manufacturing; | • Removal of the need to present this information. |
| | • 5.3.1 - Item "c" - c) Description of the manufacturing steps of active substance; | • Inclusion of the need to present information about the critical steps of the process manufacturing and its controls in process. |
| | • 5.3.1 item "b"- b) Information summary of the critical steps in the manufacturing process and their in-process control parameters and specification limits, if applicable. | • Addition of the term, as it is understood that eventually the process may not have steps critics. |
| | • 5.3.1 item "c" - Identification and justification of critical steps in the procurement process, if applicable; | • Inclusion of this item because it understands whether the TSE control is a control stage in the manufacture of the active substance. |
| | • 5.3.1 item "e" – e) Documentation related to the control of transmissibility of Spongiform Encephalopathies Transmissible (EET), referring to | • The text has been rewritten to describe more clearly what is the information requested about impurities generated in the manufacturing process of the active substance. |

| | | |
|---|---|---|
| | starting materials and reagents, according to current health regulations; | • The text has been rewritten to describe more clearly what is the information requested about impurities generated in the manufacturing process of the active substance. |
| | • 5.3.1 item "g"- g) Identification, qualification and quantification of contaminants, impurities and degradation products arising from the manufacturing process of the active substance, when applicable; | • Removal of the need to present this information. |
| | • 5.3.1 item "g"- g) List of impurities related to the active substance and its process of obtaining, acceptance criteria and respective justifications, in the form of a table (Annex III); | • The text has been rewritten to describe more clearly what is the information requested about impurities generated in the manufacturing process of the active substance. |
| | • 5.3.1 item "h" - h) Size minimum and maximum of lots produced; | • The text has been rewritten to describe more clearly what is the information requested about impurities generated in the manufacturing process of the active substance. |
| | • 5.3.1 item "h" - h) Critical assessment of the toxicity of impurities, degradation products and contaminants, arising from the manufacturing process or starting materials relevant to the IFA, when applicable; | |
| | • 5.3.1 item "i" – i) Justification for non-compendial specification limits and brief discussion of potential mutagenic impurities, including information on origin, structure, justification for specification limits | |

| | | |
|---|---|---|
| | established, in accordance with the Guia I M7; | |
| 3rd Edition | • ~~5.3 ANALYTICAL METHODOLOGY~~ VALIDATED AND ACCEPTABLE LIMITS<br>5.4 ANALYTICAL METHODOLOGY VALIDATED AND ACCEPTABLE LIMITS TO GUARANTEE IDENTITY, QUALITY AND PURITY<br><br>• 5.4.1 Quality Control<br><br>• 5.3 item "a" – a) Brief description of control tests ~~quality carried out in the batches of active substance, accompanied of the respective specifications with justification for the determination of these;~~<br><br>• 5.4.1 item "a" – a) Information of the lots to be used in the production of the investigational drug from non-clinical and clinical trials, including batch number, size, date and place of manufacture and purpose, in the form of a table (Annex IV).<br><br>• 5.3 item "b"- b) ~~Description of reference standards used;~~<br><br>• 5.3 item "c" – c) Brief description ~~of the evaluations of the profiles of impurity and contaminants;~~ | • Changing the item title and reformulation of information requested.<br><br>• Inclusion of this sub-item for better separation of requested information.<br><br>• The text has been rewritten to describe more clearly what is the information requested about the controls quality performed in the process of manufacturing the active substance.<br><br>• The text has been rewritten to describe more clearly what is the information requested about the controls quality performed in the process of manufacturing the active substance.<br><br>• Removal of the need to present this information.<br><br>• All information related to impurities were grouped in item 5.3.1 of the manual 3rd edition.<br><br>• The text has been rewritten to describe more clearly what information is requested about the controls of quality performed in the manufacturing process of the active substance. |

| | | |
|---|---|---|
| | • 5.4.1 item "b" – b) Description of quality control tests carried out in the lots to be used in non-clinical trials and clinical, accompanied by the respective specification limits with justification for their determination;<br><br>• 5.3 item "e"- e) Table ~~containing the available results of validation of analytical methods in compliance with legislation in force in Brazil or other recognized guidelines internationally, according with the stage of development clinical~~<br>~~- For phase I studies, a suitability of methods used analytics should be confirmed, the limits of acceptance and the parameters to be used in the validation of analytical methods must be presented in a table.~~<br>~~- For phase II and III studies, the analytical methods applied to products under investigation should have its suitability demonstrated according to legislation in force, as applicable for each stage of clinical development, or should justification be presented~~ | • The text has been rewritten to describe more clearly what information is requested on the validation of the analytical procedures carried out in the manufacturing process of the active substance.<br><br>• The text has been rewritten to describe more clearly what information is requested on the validation of the analytical procedures carried out in the manufacturing process of the active substance. |

| | | |
|---|---|---|
| | ~~technique for using~~ ~~alternative approach, based~~ ~~in scientific references~~ ~~recognized.~~<br>• 5.4.2 Validation of Procedures Analytics<br>• Present, in the form of table (Annex V), the parameters, the criteria for acceptance and the results of validation of procedures analytics used in compliance with the legislation in force in Brazil or other recognized guidelines internationally, from according to the stage of clinical development. He can justification be presented technique for the absence of validation or use of alternative approach to method validation, based in scientific references recognized. | |
| 3rd Edition | • 5.4 ~~5.5~~ STUDY RESULTS OF STABILITY<br>The stability studies with the active substance must be conducted in order to ensure the stability during the | • Changing the item numbering.<br>• Terminology correction.<br>• The text has been rewritten to describe more clearly what is the information requested about studies of stability performed with the active substance. |

| | | |
|---|---|---|
| | intended storage. Such studies should evaluate the active substance stability under storage conditions proposals. Additionally, the accelerated stability studies and under stressful conditions can help to understand the product degradation profile of the active substance.<br><br>• 5.4 items “a” to “d” - a) Description and specification of materials packaging;<br>b) Results of studies of stability of the active substance, if stored, in accordance as RDC Nº 50/2011. A temperature used in these studies will be determined by climate zone in which the manufacturer meets.<br>c) Table with the summary of the results of the study of photostability or justification technical-scientific for your absence;<br>d) Assessment of possible interaction between the active substance and the Primary package.<br>• 5.5 items “a” to “e”: a) Protocol of stability studies | • The text has been rewritten to describe more clearly what information is requested about studies of stability performed with the active substance. |

| | | |
|---|---|---|
| | • Table (Annex VI) with the results of studies of stability, according to legislation in force in the country. At temperature conditions and moisture used in these studies will be determined according to the zone climate of the region in which the active substance manufacturer meets.<br>• Table (Annex VI, with the necessary adaptations), containing the summary of results of the study of photostability or technical-scientific justification for your absence;<br>• Storage conditions and retest period;<br>• Description of materials primary packaging and potential interactions with the active substance. | |
| 3rd Edition | • 6.1 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 VII). | • Inclusion of table model present in Annex VII listing the active and inactive components for harmonization of understandings. |

| | | |
|---|---|---|
| 3rd Edition | • 6.2 Quantitative composition complete formulation, with all its components specified by names corresponding technicians and synonyms according to Name Ordinary Brazilian - DCB, if any, or Name Ordinary International - DCI or, in your absence, the denomination Chemical Abstracts Service – CAS, indicating the units of measures used (Annex VII); | • Table model indication present in Annex VII for harmonization of understandings. |
| 3rd Edition | • 6.2 b) Discussion about the shape development pharmaceutical, formulation and about studies from compatibility with diluents/containers Where medical devices, I know applicable. | • Insertion of snippet about to better clarity about what the Anvisa expects to receive in this document. This snippet is a merging of items “c” and “d” of section 6.3.1 of the 2nd Edition. |
| 3rd Edition | • 6.3.1 General information d) Name and address of all product manufacturers intermediate biological bulk organic product biological product in your | • Inclusion of Annex III indication with a table model for harmonization of understandings. |

| | | |
|---|---|---|
| | primary packaging,<br>finished biological product,<br>diluent and adjuvant<br>(Annex II); | |
| 3rd Edition | • 6.3.1 General information<br>Allocation of items “c” and “d”<br>to section 6.2 | • Allocation for clarity. |
| 3rd Edition | • 6.3.2 Manufacturing Process and controls<br>a) Protocol ~~summarized~~<br>Process flowchart of manufacturing, including removal procedures and/or elimination viral used, when applicable; | • Insertion of item “g” of section 6.3.2 in this item for better clarity. |
| 3rd Edition | • 6.3.2 Manufacturing Process and Controls<br>b) Summarized information of the tests of in-process control and related acceptance criteria; | • Insertion of this item at the beginning by closer to the current item “a”. |
| 3rd Edition | • 6.3.2 Manufacturing Process and controls<br>Ready from equipment used And respective work capabilities; | • Clarity about the expectation of the Anvisa in relation to this item. |

| | | |
|---|---|---|
| 3rd Edition | • 6.3.2 Manufacturing Process and Controls<br>~~d) Identification and justification of the critical stages of the manufacturing process;~~<br>~~e) Tests and acceptance criteria of the critical stages of the manufacturing process;~~<br>~~f) Description of the controls in process and justification for determining the specifications;~~<br>~~g) Viral removal and/or elimination procedures used, when applicable;~~<br>~~h) Identification, qualification and quantification of contaminants, impurities and degradation products arising from the manufacturing process of the experimental drug, when applicable;~~<br>~~i) Production scale at all stages of development, indicating the minimum and maximum sizes of the batch to be produced;~~ | • Deleting these items with your insertion into other sections. |

| | | |
|---|---|---|
| 3rd Edition | ~~• 6.3.3.1 New excipients~~<br>~~For excipients used for the first time in a drug or in a new route of administration or excipients not described in the pharmacopoeias listed by RDC 37/2009, in addition to the information in item 3.3.3, inform: a) Identification tests, purity tests (including~~ total and individual ~~impurity limits), content or limit tests and other tests for~~<br>~~relevant, as well as the respective specifications;~~<br>~~b) Data from the manufacturing process and characterization of controls that are relevant to the safety of the excipient.~~<br>~~When the aforementioned data is not available above, the applicant must provide a technical justification for his absence.~~<br>~~6.3.3.2 Excipients of human or animal origin~~<br>~~All source excipients human or animal used in manufacturing process must be identified~~<br>~~In addition, information on the safety assessment of adventitious agents (such as sources, specifications and description of tests performed)~~ and ~~potential contamination must be submitted.~~<br>~~6.3.4 Adjuvant~~<br>~~When applicable, submit the following information regarding the adjuvants:~~<br>~~a) Physicochemical characterization;~~<br>~~b) Mechanism of action;~~ | • Excluding the need to present information about new excipients, adjuvants and thinners.<br>• Excluding the item “Excipients of human or animal origin” and inserted in section 9. |

| | | |
|---|---|---|
| | ~~c) adsorptive properties;~~<br><br>~~d) Purity.~~<br><br>~~6.3.5 Thinner~~<br><br>~~When applicable, submit the following information regarding the diluents:~~<br><br>~~a) Composition;~~<br><br>~~b) Physicochemical characterization;~~<br><br>~~c) Purity.~~ | |
| 3rd Edition | • 6.3.~~5~~ ~~6.3.~~3 Packaging<br><br>a) Technical specification of the primary packaging ~~and, if any, of the packaging secondary~~<br><br>b) Assessment of the possible interaction between ~~the active substance, th~~e biological product and primary packaging, if applicable. c) Description of how the inviolability of the ~~packaging will be guaranteed until the experimental drug is used.~~ | • Improved clarity on the understandings of Anvisa. |

| | | |
|---|---|---|
| 3rd Edition | • 6.4 ANALYTICAL METHODOLOGY AND ACCEPTABLE LIMITS FOR GUARANTEE IDENTITY<br>~~a) Brief description of the quality control tests performed on the batches to be used in the tests~~ clinical trials, accompanied by the respective specifications and justifications. b) Description ~~of the reference standards used; c) Brief description o~~f the evaluations of the impurity ~~and contaminant profiles; d) Certificate of analysis of representative batches of the~~ investigational drug containing the name and address of the place of manufacture, batch number, batch size, date of manufacture, analytical control methodologies, ~~boundaries~~ acceptable and results obtained.<br>~~e) Table containing the available results of the validation of the analytical methods in~~ accordance with the ~~legislation in force in Brazil or other recognized guidelines internationally, according to the stage of~~ clinical development.<br>~~For phase I studies, the suitability of analytical methods~~ used must be confirmed. You ~~acceptance limits and parameters to be used in the validation of analytical methods must be~~ presented in a table.<br>~~For phase II and III studies, the analytical methods applied to the products under investigation must have their suitability demonstrated in accordance with the legislation in force, as applicable for each phase of clinical development, or must be~~ | • Deletion of old and new text structuring to ensure greater clarity.<br>• Presentation of models of attached tables to be filled with the information that Anvisa considers essential, for greater clarity for the sector regulated and harmonization of procedures.<br>• Inclusion of the Guide reference ICH M7 for impurities mutagens. |

| | | |
|---|---|---|
| | ~~technical justification was presented for the use of an alternative approach, based on scientific references recognized.~~<br><br>6.4.2 Quality control<br>d) Information on the lots to be used in the tests do not clinicians and clinicians, including lot number, size, date and place of manufacture, in the table form (Annex IX).<br>e) Description of the tests of control from quality carried out in the lots to be used in the tests do not clinical And clinical, accompanied by the respective specification limits and analytical procedures, in table form (Annex VIII);<br>f) Batch analysis certificates representatives used in clinical trials<br><br>6.4.2 Validation of Analytical Procedures<br><br>b) Table (Annex V) containing the parameters, the criteria for acceptance and results available from the validation of procedures analytical used, in accordance with the legislation in force in the Brazil or other guidelines | |

| | | |
|---|---|---|
| | recognized internationally, according with a phase do clinical development. He can justification be presented technique for absence of validation or the use of alternative approach to method validation, based in scientific references recognized.<br><br>6.4.3 Characterization of impurities<br>d) Table (Annex X) containing information on a characterization of impurities, specification limits;<br>e) Justification for the criteria for non-compendial acceptance and brief discussion on potentials impurities mutagens, including information about origin, structure, justification for the boundaries established, from according to the ICH Guide M7;<br>f) The absence of control of routine for solvents/catalysts used in the process of manufacture must be justified. | |

| | | |
|---|---|---|
| 3rd Edition | • **6.5 RESULTS TWO STABILITY STUDIES** WHAT ENSURE A USE DO MEDICINE EXPERIMENTAL IN TESTS PLANNED CLINICS<br><br>6.5.1 Summary of studies of stability and conclusions<br>a) Protocol of the studies of stability;<br><br>b) Table (Annex VI) containing the summary of studies from stability;<br><br>c) Brief description of the packaging materials, including specifications, size and/or volume used, and potential interactions with the formulation; | • Improved clarity on the Anvisa's expectations. Recommendation of table attached to filling with data from stability. |
| 3rd Edition 6.5 | Stability studies should be conducted in accordance with the requirements recommended in the specific legislation in force ~~described in RDC No. 50/2011,~~ in representative batches of the investigational drug. respective ~~justifying your particularities.~~<br>~~The results of studies of stability must guarantee that the investigational drug will be within the quality specifications during the period of~~ | • Adequacy of the text for better clarity. |

| | | |
|---|---|---|
| | ~~use in planned clinical trials.~~<br><br>~~The protocol of such studies should take into account the profile of stability of the active substance and the expiry date justified based on available results that ensure adequate administration to~~ clinical ~~trial participants.~~<br><br>The definition of the expiration date of the investigational drug must take into account the stability data of both the API and the<br><br>available stability data of the investigational drug.<br><br>Stability studies can be conducted in parallel with clinical trials. stability studies<br><br>made using models<br><br>reduced, such as matrixing or grouping, may be accepted~~ as long as t~~hey are conducted in a<br>according to the Study Plan of Reduced Stability of<br>Medicaments, available at: http://<br>www.anvisa.gov.br/medicamen<br><br>tos/recomenda/plano_estudo_2.pdf, and that all predicted variations become part of the DDCM.<br><br>~~Stability studies should be conducted with representative lots and their results summarized in a table accompanied by the technical justification of the proposed shelf life for the investigational drug.~~<br><br>The results of studies of<br>stability must guarantee that the investigational drug will be | |

| | | |
|---|---|---|
| | within quality specifications during the period of use in planned clinical trials.<br><br>Room for medicines temperature storage experimental only.<br><br>For Phase III clinical trials where if medication is dispensed to the research participant for home use, in addition to the stability data already available, the following must be presented:<br><br>• Stability study results long-term in zone IVb or<br><br>• Stability study results accelerated or<br><br>• Instruction to clinical trial participants reinforcing care for the conservation of the investigational drug. The model described in Appendix I can be followed.<br><br>For drug cases for multiple use or requiring multiple doses after reconstitution, dilution or mixing, data on stability study in use. For diluted experimental drugs or reconstituted immediately before use there is no need to presentation of the stability in use study. In that case shows compatibility between the product and the diluent. | • Need to present the documents listed in this item for all clinical trials where there is dispensation for use home and not just for phase III studies. |

| | | |
|---|---|---|
| 3rd Edition 7. PLACEBO<br>7.1 COMPOSITION | ~~a) Table with the formula containing the description and concentration of each component per unit.~~<br>a) List of all placebo components and their respective functions (Appendix VII). | • Creation of a specific model of table containing list of placebo components. |
| 3rd Edition 7.2 FEATURES ORGANOLEPTIC | ~~a) Description of how possible differences between placebo and experimental drug were masked.~~<br>a) Description of the organoleptic characteristics of the placebo and information on how possible differences between placebo and experimental drug were considered to maintain the masking. | • Greater clarity on the reason for the request to send this information. |
| 3rd Edition 7.3 MANUFACTURING PROCESS | ~~a) Name and address of all manufacturers involved in the production of the placebo;~~<br>~~b) Summary production protocol in the form of a flowchart, with identification of the controls in process;~~<br>~~c) Control of critical and intermediate steps, in the case of products sterile.~~<br>~~d) Description of the primary packaging and, if relevant to the quality of the placebo, the secondary packaging~~<br>a) Flowchart of the process of manufacturing; | • Change for clarity about Anvisa's expectations in regarding that topic. |

| | | |
|---|---|---|
| | b) Summary information of which are the in-process controls and acceptance criteria.<br><br>In cases where the manufacturing and packaging process is the same as the experimental drug, conducted by an identical manufacturer and production line, justification can be sent for the absence of the documents mentioned ~~in item 7.3~~ in this item. | |
| 3rd Edition | 7.4 ANALYTICAL CONTROLS<br><br>a) ~~Brief description of the specifications, analytical methods and criteria of acceptance~~ Description of the quality control tests performed on the placebo batches to be used in non-clinical and clinical trials, accompanied by the respective specification limits and analytical procedures, in the form of a table (Annex VIII). Must be included Specifications must include tests that ~~make it possible to differentiate~~ placebo from its respective investigational drug.<br><br>b) Technical justification regard~~ing~~ the validity period of the placebo. In cases where there is suspicion that changes in the physical or degradation characteristics may occur, results of a stability study must be presented, respecting the due particularities of the placebo. | • Clarity about understandings from Anvisa. Model indication of table to fill in item “a” |

| | | |
|---|---|---|
| 3rd Edition | **8. MEDICATION MODIFIED COMPARATOR**<br>a) List of all you components do Comparator Drug Modified, in the form of table (Annex VII);<br>b) Description of the modifications carried out;<br>c) Assessment of the impact of modifications in all relevant parameters for the function, stability, effectiveness and safety of medicine. It must be proved that there was no alteration of those parameters or presented technical justification that subsidize the modifications proposals. | • Insertion of a section about comparator drug modified for harmonization with the Quality Manual of synthetic and semi synthetics. |

| | | |
|---|---|---|
| 3rd Edition | **9. CONTROL FROM TRANSMISSIBILITY FROM ENCEPHALOPATHIES SPONGIFORM TRANSMISSIBLE (EET)**<br><br>a) Documentation related to control of transmissibility from Transmissible Spongiform Encephalopathies (TSEs), according to current health regulations, if applicable. | • Insertion of ETT section for alignment with the Manual quality of medicines synthetic and semi-synthetic |
| 3rd Edition | ~~8. LABEL TEMPLATE~~<br><br>~~All labeling text must be written in Portuguese.~~<br><br>~~Model(s) of labeling for primary and secondary packaging(s), if applicable~~, of ~~the investigational drug must be presented. For this model(s), we recommend the following fields:~~<br><br>~~a) Name of sponsor, pharmaceutical form, route of administration, number~~ of pharmacotechnical units ~~and, in the case of an open study, the name and concentration of the drug~~;<br><br>~~b) Batch number or product identification code;~~<br><br>~~c) Clinical trial reference code;~~ | • Insertion of the Instruction text Regulation of Good Practices for Medicines Manufacturing experimental. |

| | | |
|---|---|---|
| | d) Identification code of the clinical trial participant; and<br><br>) Instruction for use (reference may be made to an explanatory pamphlet or other document that guides the clinical trial participants or person administering the drug);<br><br>f) Storage conditions;<br><br>g) Expiry date;<br><br>h) following warning phrases, or similar, in capital letters:<br><br>"EXCLUSIVE USE IN TESTS CLINICS"<br><br>"EVERY MEDICINE MUST BE KEPT OUT OF REACH OF CHILDREN".<br><br>The labeling of the primary packaging of investigational drugs accompanied by secondary packaging must contain fields for, at least, the following information:<br><br>a) Name of the sponsor, route of administration, and in the case of an open study, the name and concentration of the drug;<br><br>b) Batch number or product identification code;<br><br>c) Clinical trial reference code;<br><br>Other labeling information may appear on the secondary packaging. | |

| | | |
|---|---|---|
| | ~~Symbols, pictograms and warnings can be included on both the primary packa~~ging and ~~the~~ secondary.<br><br>~~The address and telephone number of the main contact for obtaining information abo~~ut ~~the investigational drug, the clinical trial an~~d ~~for breaking the blinding code do not need to appear on the label, provided that the clinical trial participant receives a leaflet or card with such information.~~<br><br>~~information and be instructed to make contac~~t ~~in case of questions or~~ occurrences.<br><br>~~If it is necessary to change the expiry date, an additional labeling can be attached to the investigational drug. This labeling can be superimposed on the previous label to update the shelf life so that it does not overlap wit~~h the ~~original lot number.~~<br><br>~~The labeling of other investigational products must follow the same model as the drug experimental. When some field(s) are not applicable, provide justification.~~<br><br>## 10. LABEL MODEL<br><br>The following information should be included on labels unless its absence can be justified, such as the use of an electronic randomization system:<br><br>I. name, address and telephone number of sponsor, organization | |

| | | |
|---|---|---|
| | the research contractor or investigator (the primary contact for information about the product, clinical trial, and emergencies);<br><br>II. presentation, route of administration, posology and, in the case of open trials, name/identifier and concentration/potency;<br><br>III. the batch and/or code number to identify the contents and the packaging operation;<br><br>IV. a test reference code that allows identification of the trial, site, investigator, and sponsor, if not provided elsewhere;<br><br>V. the subject identification number/ treatment number and, where relevant, the visit number;<br><br>WE. the name of the investigator (if not included in the information in items I or IV);<br><br>instructions for use (can be reference is made to a bull or other explanatory document intended for the trial participant or the person administering the product);<br><br>VIII. “For Clinical Trial Use Only” or similar text;<br><br>IX. storage conditions;<br><br>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; and<br><br>XI. "keep out of reach of children", except when the product is for use in trials where the product is not taken home by the participant.<br><br>The information listed above must appear on the primary and secondary packaging.<br><br>Information must be in the language of the country where the clinical trial takes place, however other languages may be included.<br><br>The address and telephone number of the primary contact for information about the product, clinical trial, and for emergency de-characterization does not need to appear on the label when the subject has received a package insert or card that<br><br>provides these details and was instruction has been passed to keep this contact in your possession at all times<br><br>When the drug is given to the trial participant or the person administering it within a primary packaging together with the secondary packaging and, if the secondary packaging contains the data listed above, the following information must be included in the identification of the primary packaging:<br><br>I. name of sponsor, organization representing the | |

| | | |
|---|---|---|
| | clinical research contracted or investigator;<br><br>II. presentation, route of administration, posology and, in the case of open trials, name/identifier and concentration/potency;<br><br>III. batch and/or code number for content identification and packaging operation;<br><br>IV. a trial reference code that allows identification of the study, site, investigator, and sponsor, if not provided elsewhere; and<br><br>V. the study participant identification number/treatment number and, where applicable, the visit number.<br><br>The description of the administration route that deals with item II can be excluded for oral solid dosage forms.<br><br>If the primary packaging is a blister or small units, such as ampoules, on which the required information cannot be displayed, an outer packaging that bears a label with this information must be provided, however, the primary container must contain the following items:<br><br>I. sponsor name, representative organization of contracted clinical research or investigator;<br><br>II. route of administration, number of dosage units | |

| | | |
|---|---|---|
| | and, in the case of open assays, the name/identifier and concentration/ potency;<br><br>III. batch and/or code number for content identification and packaging operation;<br><br>IV. a trial reference code that allows identification of the study, site, investigator, and sponsor, if not provided elsewhere; and<br><br>v. the study person identification number/treatment number and, where applicable, the visit number.<br><br>The description of the administration route that deals with item II above can be excluded for oral solid dosage forms.<br><br>Symbols or pictograms may be used to clarify certain labeling information.<br><br>Additional information, warnings and/or handling instructions may be displayed.<br><br>If it is necessary to change the date of validity, a label must be affixed additional to the drug experimental. The additional label must indicate the new expiration date and repeat the batch number. the label additional can be superimposed on the old expiration date, but cannot be superimposed on the original lot number for quality control reasons.<br>This operation must be carried out at a properly | |

| | | |
|---|---|---|
| | authorized. Exceptionally, from that duly justified, the operation can be performed in a place authorized by the sponsor of the clinical trial, by a pharmacist or other authorized health 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 documented<br><br>properly in the test documentation and batch records. | |
| 3rd Edition | • 12. Bibliographic References<br><br>~~• 1. BRAZIL. ANVISA Agency National Surveillance sanitary. RE Resolution No. 899, of May 29, 2003. Determines the publication of "Guide to Validation of analytical methods and bioanalytical" BRASIL. Diary Union officer; Power Executive, of June 2, 2009.~~<br><br>• 8. BRAZIL. ANVISA Agency National Surveillance sanitary. RE Resolution No. 166, of July 24, 2017. Provides for the validation of analytical methods and gives other measures. Official Gazette of | • The change was due to text adequacy. |

| | | |
|---|---|---|
| | Unity; Executive Power, of 25 of July 2017. | |
| 3rd Edition | • 14. Attachments<br>• Annex II - Name and address from the manufacturer.<br>• Annex III - Impurities substance related active.<br>• Annex IV - Substance batches active to be used in drug production experimental.<br>• Annex V - Validation of analytical procedures.<br>• Annex VI - Results of stability studies.<br>• Annex VII - List of active components and inactive.<br>• Annex VIII - Control of quality.<br>• Annex IX - Lots of experimental drug to be used in tests non-clinical and clinical.<br>• Annex X - Characterization of impurities. | • These attachments have been included for facilitate organization, viewing and receiving information. |

## 14. ANNEXES

### ANNEX I

**Protocol XYZ001 - Document of Clarification to Participants on the**

**Study Drug**

**XYZ Drug – Insert drug presentation**

**General information:**

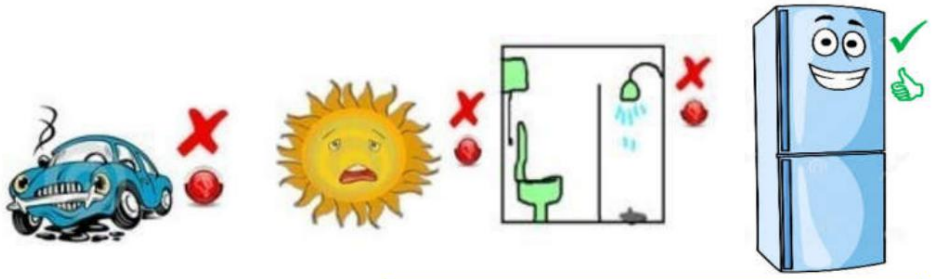
• Participants in study XYZ001 will receive XYZ medication every X days.
Please follow the instructions below to take the medication at home.
• Do not forget to return empty and/or unused containers at the next study visit.

• Do not use the medication if it is damaged or appears to be spoiled.

**Medication storage instructions:**

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

Eg: *The medication should be stored in a refrigerator (from 2 to 8°C) and away from light. Do not leave the medication stored in the car or exposed to the sun. Do not store medication in the bathroom. Do not freeze the medicine.*



**Center Contact Information:** Insert the person in charge and telephone contact.

**Instructions for using the medication at home:**
Ex.: *You will take X doses of XYZ at the same time each day, morning and evening, approximately 12 hours apart. The injection should be given in the places taught by the doctor, each time in one place.*
*If you miss a scheduled dose for any reason (for example, if you forget), you can take the dose again up to a maximum of 2 hours after the correct time. If more than 2 hours have passed, the missed/ 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 study medication!

## ANNEX II

### MANUFACTURER'S NAME AND ADDRESS

| Name | Address | Responsibility | Clinical trial phase |
|---|---|---|---|
| | | | |

## ANNEX III

### IMPURITIES RELATED TO ACTIVE SUBSTANCE

| Impurities related to API (eg starting materials, by-products, intermediates, degradation products, contaminants, metabolites) | Criterion of acceptance | Justification of the acceptance criteria |
|---|---|---|
| | | |

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

## ANNEX IV

### LOTS OF ACTIVE SUBSTANCE TO BE USED IN THE PRODUCTION OF EXPERIMENTAL DRUG

| Lot Number* Lot Size | | Date and place of manufacturing | Purpose (eg clinical trial Phase 3) |
|---|---|---|---|
| | | | |

(*) Attach copies of Certificates of Analysis

## ANNEX V

### VALIDATION OF ANALYTICAL PROCEDURES

| Validation parameters* | Acceptance criteria (when applicable) | Results or values found |
|---|---|---|
| specificity | | |
| linearity | | |
| working range | | |
| Precision | | |
| Accuracy | | |
| Detection limit | | |
| Limit of quantification | | |
| Conclusion: | | |

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

## ANNEX VI

### RESULTS OF STABILITY STUDIES

| | |
|---|---|
| Drug Name:<br>Batch:<br>Maker<br>Manufacturing date:<br>Lot size:<br>Storage conditions: | Stability Protocol:<br>Start date:<br>Study duration:<br>Packing Size:<br>Kind of packing<br>Proposed shelf life: |
| | test intervals |

| Specifications | | | Data (initial) | Data (1m) | Data (3m) | Data (6m) | Data (12m) |
|---|---|---|---|---|---|---|---|
| Test | Method | Criterion from acceptance | | | | | |
| | | | | | | | |

## ANNEX VII

### LIST OF ACTIVE AND INACTIVE COMPONENTS

| Components (IFA, excipients, diluents) | Occupation | Pharmaceutical Form: (eg: solution for injection, lyophilic powder, etc.) | | | |
|---|---|---|---|---|---|
| | | Concentration 1 | | Concentration 2.3... (if applicable) | |
| | | Qty/unit | % | Qty/unit | % |
| | | | | | |

## ANNEX VIII

### QUALITY CONTROL

| Tests (eg identity, content, impurities) | Specification limits (*) | Analytical procedure (Reference) |
|---|---|---|
| | | |

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

## ANNEX IX

### LOTS OF EXPERIMENTAL DRUG TO BE USED IN TRIALS NOT CLINICIANS AND CLINICS

| Lot Number* Lot Size | | Date and place of manufacturing | Purpose (eg clinical trial Phase 3) |
|---|---|---|---|
| | | | |

(*) Attach copies of Certificates of Analysis

## ANNEX X

### CHARACTERIZATION OF IMPURITIES

| Impurities and Products of Degradation, metabolites, etc. | Limits of specification | Specification limit justification |
|---|---|---|
| | | |