

NATIONAL ADMINISTRATION OF DRUGS, FOODS AND MEDICAL DEVICES  
REGULATION 6677/10

The Regulatory Guideline for Good Clinical Practices in Clinical Pharmacology Studies is hereby approved.

Some A.N.M.A.T. (the agency) regulations are hereby repealed.

Buenos Aires City, November 1, 2010.

Having regard to A.N.M.A.T. Regulation 5330/97, as amended and supplemented by Regulations 3436/98, 3112/00, 690/05, 1067/08 and 6550/08, Dossier Nr 1-47-20664-10-0 of the Registry Office of the National Administration of Drugs, Foods and Medical Devices, and

Whereas,

Clinical Pharmacological Investigation is necessary to obtain strong scientific evidence which enables to improve the public's health care quality.

The development of clinical investigation, in general, should respect basic human rights and freedoms inherent to human nature and enshrined in the National Constitution and Human Rights International Treaties, bearing a constitutional status as incorporated in article 75, sub-title 22 thereof.

In this regard, all clinical investigation should safeguard the dignity of participating subjects, ensuring their personal rights, specially, the respect for their autonomy and physical, psychic and moral integrity.

As stated by Resolution 1490/07 of the Ministry of Health, Good Clinical Practices are worldwide accepted ethical and scientific standards which set out guidelines for the design, conduct, recording and reporting of studies involving the participation of human beings and, when complied with, such standards ensure that the rights, well-being, safety and dignity of the participating subjects are protected and respected.

By means of clinical pharmacological research, a new Active Pharmaceutical Ingredient (API) undergoes the performance of scientifically validated tests to demonstrate its efficacy and safety and thus it provides evidence resulting from the performance of clinical studies.

By means of Regulation 5330/07, A.N.M.A.T. approved the Guideline for Good Research Practices for Clinical Pharmacology Studies, in order to fully guarantee the compliance with the standards set forth, both nation and worldwide, in regard to regulations and ethical and legal values.

The experience acquired in the systematic application of the aforementioned regulation, the progress made in the synthesis and manufacture of new API(s) for human medicine as well as the increasing number of studies submitted for A.N.M.A.T. approval gave rise to the need for a clear definition of this agency's regulation scope and for maximizing the soundness, review and permanent update of its procedural, training, ethical and methodological aspects, from the authorization application stage

and throughout research conduct and, in particular, of the aspects related to the duties of all the players involved in clinical drug research.

A.N.M.A.T.'s duty is to ensure that clinical pharmacology investigations conducted with drugs and medicinal products are compliant with clinical pharmacology standards currently adopted by countries having a strict health vigilance system and with the World Health Organization (WHO) scientific, ethical and legal recommendations.

Ethical principles applicable to the conduct of clinical studies were set forth in Nuremberg (1948) and Helsinki (1964 and updates) declarations of human rights and on ethical principles for medical research involving human subjects, the "Operational guidelines for ethics committees that review biomedical research" (WHO– World Health Organization, 2000) and the "International Ethical Guidelines for Biomedical Research involving Human Subjects" (CIOMS – Council for International Organizations of Medical Sciences, 2002), it becomes appropriate to establish the guidelines to enforce such principles application.

In its decision 306:178, the Argentine Supreme Court of Justice highlighted the legal significance of ethical standards as a set of rules concerning the art of healing professionals, by ruling that: "It is not appropriate to restrict their scope or deprive them from legal relevance; but in turn, they should be ensured substantial respect to avoid the dehumanization of the art of healing, particularly, when from fact confrontation and professional behavior demands, as currently ruled, a judgment of reproach bearing the capacity of affecting the responsibility of the stakeholders may arise" (translation of "... no cabe restringir su alcance ni privarlos de toda relevancia jurídica, sino que se impone garantizarles un respeto para evitar la deshumanización del arte de curar, particularmente cuando de la confrontación de los hechos y de las exigencias de la conducta profesional así reglada, podría eventualmente surgir un juicio de reproche con entidad para comprometer la responsabilidad de los interesados").

The GUIDELINES FOR GOOD CLINICAL PRACTICE IN RESEARCH ON HUMAN SUBJECTS was approved by means of Resolution Nr 1490/07 of the Ministry of Health, with a view to standardizing activities related to clinical research on human subjects and ensuring the respect for ethical values and the rights, safety and integrity of participating subjects.

The above mentioned rules were incorporated in the Guidelines for Good Clinical Research Practices in Clinical Pharmacology Studies, approved by A.N.M.A.T. Regulation 5330/97.

A.N.M.A.T. Regulation 3436/98 set forth a mechanism to approve the amendments of clinical studies previously authorized by this agency.

A.N.M.A.T. Regulation 3112/00 amended A.N.M.A.T. Regulation 3436/98 in terms of the addition and/or exclusion of authorized health institutions and investigators.

A.N.M.A.T. Regulation 690/05 set forth the Guidelines for Inspections of Clinical Investigators with a view to monitoring that the conduct of clinical studies is compliant with Good Clinical Practice standards and the regulatory requirements in force; and ensuring that the rights and well-being of the subjects participating in the studies are protected and the data obtained are credible.

A.N.M.A.T. Regulation 1067/08 amended A.N.M.A.T. Regulation 5330/97 as to adverse events reporting and A.N.M.A.T. Regulation 2124/05 was repealed.

A.N.M.A.T. Regulation 6550/2008 amended and updated different provisions of A.N.M.A.T. Regulation 5330/97.

In accordance with the aforementioned herein, A.N.M.A.T. deems it necessary to lay down new REGULATORY GUIDELINE FOR GOOD CLINICAL PRACTICE IN CLINICAL PHARMACOLOGY STUDIES.

The Drug Evaluation Office, the National Institute of Drugs and the Legal Affairs Office have been involved to the extent appropriate.

A.N.M.A.T. acts by virtue of the powers granted upon it by Decrees 1490/92 and 425/10.

The Controller of A.N.M.A.T. decrees:

Art. 1 – To approve the REGULATORY GUIDELINE FOR GOOD CLINICAL PRACTICE IN CLINICAL PHARMACOLOGICAL STUDIES hereby included as an Annex and considered a part and parcel hereof.

Art. 2 – To set forth that A.N.M.A.T. shall announce its decision within a ninety working-day period after the procedure initiation date, upon submission of the documentation provided for in Art.1 herein. Such period may be suspended, should any objection arise, until the applicant submits all the pertaining documentation and/or complies with the objections and/or clarifications requested.

Art. 3 - That applicants failing to comply with the policy laid down in Art. 1 herein may be subject to the sanctions under Act 16.463 and Decree 341/92, without prejudice of the adoption of the pertaining preventive measures.

Art. 4 – That A.N.M.A.T. Regulations 5330/97, 3436/98, 3112/00, 690/05, 1067/08 and 6550/08 are hereby repealed.

Art. 5 – That the present Regulation shall come into effect one day after its publication in the Argentine Official Journal.

Art. 6 –The present Regulation shall be registered and conveyed to the Official Registration Office to be published. It shall be communicated to the Secretariat of Policies, Regulations and Institutes under the Ministry of Health, the concerned professional associations and chambers and to A.N.M.A.T. Planning and Institutional Relations Office and Drug Evaluation Office and placed on record. Carlos Chiale.

# ANNEX I: REGULATORY GUIDELINE FOR GOOD CLINICAL PRACTICE IN CLINICAL PHARMACOLOGY STUDIES

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## SECTION A: GENERAL CONSIDERATIONS

### DEFINITIONS

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, recording and reporting of studies involving human subjects. The adoption of this standard provides a public assurance that the participants' rights, safety and well-being are protected, in accordance with the principles of the Declaration of Helsinki and that clinical studies data are reliable.

Clinical pharmacology studies are trials that evaluate the safety and efficacy of a drug intended for a disease prevention, treatment or diagnosis. Broadly considered, research on human health has provided valuable benefits in terms of suffering mitigation and prolongation of human life. However, clinical trials, in particular, involve risks for participating individuals, which gives rise to the need for a governmental regulation and monitoring mechanism ensuring the utmost protection for participants.

### OBJECTIVES

The Regulatory Guideline for Good Clinical Practice in Clinical Pharmacology Studies (GCP-CPS) herein establishes the requirements that sponsors and investigators must comply with within the scope of this agency's authorization granting and monitoring duties.

The Regulatory Guideline for GCP-CPS aims to protect the rights and well-being of human subjects participating in clinical pharmacology studies and to provide an assurance of the quality and integrity of the information produced thereby.

### APPLICATION AND SCOPE

The Regulatory Guideline herein shall be applied to clinical pharmacology studies with a registry and/or regulatory purpose, nationwide or abroad. Both physical persons and legal entities shall apply for an authorization from the National Administration of Drugs, Foods and Medical Devices (A.N.M.A.T.) prior to running the study and shall comply with the requirements set forth herein. The following studies are within the scope of this Regulatory Guideline:

phase I, phase II and phase III studies;

studies on products already registered at A.N.M.A.T. aiming to evaluate a new indication, a new concentration, if higher than the registered one, a new dosage form or a new pharmaceutical form with a registry purpose;

all pharmacokinetics, bioavailability and bioequivalence studies.

In the framework of its regulation scope, A.N.M.A.T. Office of Drug Evaluation shall have the following duties and powers for the authorization and monitoring of clinical pharmacology studies:

to evaluate the study protocol and information and issue a technical report thereof with the purpose of advising this agency Director upon its authorization, objection or rejection;

to require a protocol amendment before or during the conduct of the study;

to approve, object or reject the investigators and/or the research centers proposed for conducting the study;

to include in this agency's data base the clinical studies submitted as it registers the rate of progress of authorized studies;

before authorizing the conduct of the study, it may perform an inspection of a research center, when deemed appropriate;

through the Department of Foreign Trade under its supervision, the Drug Evaluation Office may intervene in the authorization of country inflow and outflow of material intended for the study, once the study has been approved;

to authorize amendments to the protocol and informed consent document, the addition or change of investigators and/or research centers as well as the import and export of materials intended for the study within A.N.M.A.T. regulation scope;

to evaluate the investigators' progress and final reports;

to analyze the results produced, when deemed appropriate;

to control the compliance of the standards laid down in this Regulatory Guideline by means of summoning the investigator or sponsor and/or inspecting the contract research organization (CRO) of a clinical pharmacology study;

to summon, examine and/or question the participants included in the study as part of the study routine evaluation, whenever there is information indicating a hazard to their health, if there are doubts as to the compliance with regulations in force or whenever the regulatory authority deems it relevant and opportune;

to suspend the study in a research center due to noncompliance with the regulations herein or for participants' safety reasons.

#### GENERAL PRINCIPLES

The interests and well-being of every participant of the study shall prevail over the interests of science and society in all clinical pharmacology studies.

Clinical pharmacology studies must respect accepted ethical and scientific principles, the investigation participants' physical and mental integrity as well as their privacy and personal data protection, pursuant to Act 25.326 or any law replacing it.

According to the type of active pharmaceutical ingredient (API) under study, clinical pharmacology studies shall be conducted after running pre-clinical studies which prove that the investigational product has a potential therapeutic advantage and that the risks participants are exposed to are justified by the benefits expected.

Pre-clinical studies shall be conducted in accordance to Good Laboratory Practice (GLP) standards and investigational products shall be manufactured, handled and stored under the Good Manufacturing Practice (GMP) standards. In studies of undefined or not GLP or GMP governed products, for instance, biological products, the sponsor shall set the guidelines for development, control and usage procedures, which shall require A.N.M.A.T. approval.

The sponsor and investigators of clinical pharmacology studies within the scope of this Regulatory Guideline shall fulfill the obligations established herein.

Clinical pharmacology studies shall be described in a clear and detailed protocol and require a Research Ethics Committee assessment and approval as well as an A.N.M.A.T. authorization prior to the enrollment of participants in a research center.

Clinical pharmacology studies shall be conducted by investigators holding credited qualification and training to perform them, as set forth in 2.2. (c) and 2.2. (d) of SECTION B.

Investigators shall obtain a free and voluntary informed consent from the prospective participants or their legal representatives before entering the study.

Treatments and procedures related to the study shall be free of charge for all participants.

The transport of the biological samples obtained in the studies shall comply with applicable international and domestic regulations.

#### NONCOMPLIANCE

Investigators and sponsors failing to comply with the Regulatory Guideline herein shall be subject to the sanctions and preventive measures provided for in Act 16.463 and Decree 341/92 or the regulations replacing them, without prejudice of the criminal actions which may take place and/or the relevant report to the authorities governing the pertaining professional practice.

#### SECTION B: DOCUMENTS REQUIREMENTS FOR A CLINICAL PHARMACOLOGY STUDY AUTHORIZATION APPLICATION

##### OBJECTIVE

This section sets out and describes all the documents required by A.N.M.A.T. for the baseline and continuous review of a clinical pharmacology study.

The sponsor of a clinical pharmacology study is responsible for submitting all the documents set forth herein.

##### GENERAL DOCUMENTS

Study authorization application: in order to request authorization, the sponsor of the study shall submit to A.N.M.A.T. the following documents in the order set below:

an EFCA1 form completed and signed by the sponsor (Section F);

a receipt of the fee payment;

the composition of the Independent Data Monitoring Board (IDMB), if appropriate;

a proof of the sponsor's delegation of functions to his or her legal representative certified by an Apostille of the Hague and its corresponding sworn translation, if appropriate;

a sponsor's original sworn statement asserting that the investigational product complies with GMP standards. In the case of products not fully governed by GMP standards, the manufacturing conditions not meant to comply with such norms shall be identified;

the study protocol;

a general version of the informed consent;

an investigational product monograph;

an application for the import or export of study materials or samples. In the case of drugs, details as to the name, pharmaceutical form, strength and quantity shall be

furnished. In the case of biological samples, the type and purpose shall be detailed; whereas for other materials, the description and quantity shall be informed;

for the import of narcotic drugs, a sworn statement by the importing company technical director rendering the lot numbers of the products to be used and the list of investigators authorized to receive them shall be submitted;

a copy in Spanish of the investigational product label.

Application for authorization of the investigator and the research center: for authorizing each principal investigator and research center, the sponsor shall submit the following documents:

an EFCA2 form completed and signed (Section F);

a copy of the authorization to conduct the clinical pharmacology study;

the investigator's abridged Curriculum Vitae which shall be signed and dated by him or her;

a certified copy of the investigator's degree certification and professional license awarded by the sanitary authority of the jurisdiction where the study shall be conducted. Likewise, a certified copy of his or her proofs of training and/or experience in clinical research shall be required;

for Phase II and Phase III studies, a certified copy of the certificate of specialist or the certificate of residency completion or the certificate of graduate specialization in the disease under study;

an original letter stating the commitment to comply with the study protocol (indicating its title), the Declaration of Helsinki and A.N.M.A.T. Regulatory Guideline for GMP-CFS;

a certified copy of the study approval by a Research Ethics Committee (REC), with a detail of the documents reviewed, for example, protocol, informed consent, and investigational product monograph. Only one approval by a REC shall be accepted per each research center;

a dated list of the members of each REC, including name, birth date, gender, profession and occupation, position in the committee and relationship with the institution;

a certified copy of the study authorization issued by the highest authority of the host institution. Should the jurisdiction health authority require the registration of health research studies, a certified copy of the proof of the study registration in the jurisdiction shall be submitted;

a certified copy of the authorization by the institution authority for the study review by an external REC, if appropriate;

a certified proof of the research center operating license in force;

an informed consent document specific for the research center, if appropriate;

General documents shall be submitted in the above mentioned order.

All the documents submitted to the agency shall be in Spanish, except for the investigational product monograph since it shall be used only as study background information. The protocol, informed consent and EFCA forms shall be submitted both in print and digital format (the latter shall be enclosed.)

In the event that an amendment to any of the documents, including the protocol, informed consent and investigational product monograph already submitted is needed, the original document with the document amended and a letter explaining the mistake and identifying the original submission file number shall be submitted.

The following documents shall not be submitted to the agency but they shall be requested should an inspection of the research center be conducted:

clinical data forms (CDF);

participants' enrolment forms and clinical follow-up diaries, excluding questionnaires of the study primary objectives assessment;

material to be used in informative meetings with potential participants;

a monitoring plan.

## INVESTIGATIONAL PRODUCT MONOGRAPH

### Introduction

The investigational product monograph is a collection of the clinical and non-clinical data of the product with the purpose of providing the necessary information for the investigational product correct clinical use and appropriate evaluation. This Regulatory Guideline sets out the investigational product monograph information and structure requirements.

An investigational product monograph containing the corresponding clinical and pre-clinical information shall be submitted for Phase I, Phase II and Phase III clinical pharmacology studies.

A patient's information leaflet shall be accepted as an investigational product monograph for studies conducted with API(s) already registered at A.N.M.A.T.

### General information

General information shall include:

sponsor's name

investigational product monograph number and edition date;

generic name(s) as per the International Non-proprietary Name (INN) or similar code or investigational product code, if no generic name is available yet;

ATC (Anatomical Therapeutic Chemical) classification, if appropriate;

CAS (Chemical Abstract Service) classification;

physical-chemical properties;

qualitative and quantitative formula;

pharmaceutical form to be studied, including excipients;

investigational product pharmacologic properties, therapeutic potential and its qualitative and quantitative relation with the study therapeutic indication;

pharmacokinetic characteristics;

the safety margin and envisaged adverse effects in the doses proposed.

### Pre-clinical information

Pre-clinical information shall account for the nature, scale and duration of the trial. The description of each pre-clinical study shall be submitted with the following sections:

Materials and methods which shall include:

a detailed and justified plan indicating the GLP it is governed by;

the product used and information concerning its origin, composition, lot number, quality control protocol number and expiry date;

the animals or substitutive models used and information indicating their number, species, strain, gender, age and weight;

the experimental conditions and information about dose, frequency, route of administration, duration, type of feeding and environmental conditions.

A summary of the results produced, including nature, time of appearance, frequency, intensity, duration and reversibility of the pharmacologic and toxic effects and dose response, as well as the statistical analysis of such results.

Discussion of the most significant findings and conclusions, including the dose response of the effects observed, the relevance for human beings and any other aspect intended to be studied in human beings. The findings of the effective and non toxic doses (therapeutic index) in the same animal species and their ratio for the human dose proposed shall be compared, if appropriate.

Preclinical pharmacology

Pharmacodynamics: the potential therapeutic activity shall be demonstrated and the product and/or its metabolites possible mechanisms of action shall be described, including the evaluation of pharmacologic actions other than the therapeutic effects intended.

Special pharmacodynamics: pharmacodynamic effects as per the indications proposed, dose-effect and time-effect curves.

General pharmacodynamics: studies on the cardiovascular system, respiratory system, central nervous system, autonomic nervous system, neuromuscular system, urinary system, endocrine system, digestive system, etc.

Pharmacodynamic interactions: studies determining these types of relations.

Mechanisms of action: a description of the mechanisms observed.

Pharmacokinetics: determination of the speed and magnitude of absorption, distribution model, biotransformation, speed and paths of elimination and the API location in the tissues. Studies shall include single dose and repeated dose pharmacokinetics, distribution in non-pregnant and pregnant animals, biotransformation, excretion and kinetic interactions.

General pre-clinical toxicology

Acute toxicity studies should have been conducted on three species, of which one should not be rodents. Likewise, at least two routes of administration should have been tried; one should be related to the way proposed for human use while the other one should ensure drug absorption. For single dose use in humans, the product should have been used for at least two weeks in the pre-clinical trial. The report shall include:

toxic effects appearance time and duration, dose-effect ratio and reversibility as well as the differences in routes of administration (proposed therapeutic use and absorption test);

toxicity symptoms and cause of death;

biochemical and hematologic parameters;

clinical and anatomical and pathological observations;

estimated toxic dose.

Repeated dose sub-acute toxicity studies shall be conducted on at least two species, of which one should not be rodents, for at least 12 to 24 weeks for a proposed human use of up to 4 weeks, according to the product type, its proposed therapeutic use and the animal species used. The route of administration should be the same as the one proposed for clinical use. At least, three doses shall be used, of which the highest one should produce demonstrable toxic effects and the lowest one should be equivalent to the proposed therapeutic dose, according to the sensitiveness of the species used. These studies shall include:

toxic effects appearance time and duration, dose-effect ratio and reversibility as well as gender and species related differences;

morbidity and mortality data;

biochemical, hematologic and nutritional parameters;

clinical and anatomical and pathological observations;

no effect dose and toxic dose;

target organs.

Repeated dose chronic toxicity studies shall be performed on two species, of which one should not be rodents, for over 24 weeks according to the type of product, the proposed therapeutic use and the animal species used. The route of administration shall be the same as the one proposed for clinical use. At least, three doses shall be used, of which the highest one should produce demonstrable toxic effects and the lowest one should be equivalent to the proposed therapeutic dose for human use, according to the sensitiveness of the species used. The concerning report shall contain the same requirements applicable to sub-acute toxicity.

Special pre-clinical toxicity

The effects on fertility shall be determined before initiating Phase III.

Embryo-toxicity, teratogenicity and prenatal and postnatal toxicity studies shall be performed on not less than two species, of which one shall not be rodents, with at least three doses, of which the higher one should be sub-toxic.

In vivo and in vitro mutagenic activity with or without metabolic activation. In vitro trials results shall be available before the first exposure of human subjects. The standard battery of tests shall be available before Phase II studies.

In vivo and in vitro carcinogenicity data.

According to the type of product, the results of studies on animal local irritation or sensitization, among others, shall be submitted upon request.

## Biological products

Biological products include vaccines, blood and blood products, allergens, gene therapies, recombinant proteins and other animal or cellular products with a specific therapeutic activity. As these products are more difficult to characterize than the synthetic ones, a more detailed description of their structure and manufacturing or obtaining process is required to demonstrate their safety, quality and efficacy.

As a general rule, biological products toxicity studies should be performed on two animal species appropriate for the type of product, unless:

the study to be conducted is a long term study or there is only one appropriate species, in which case one species shall be accepted;

there is no appropriate species, in which case the use of transgenic animals expressing the human receptor or the use of homologous proteins shall be considered;

if neither of the above mentioned is the case, a repeated dose study on a single species for a period appropriate to the investigational product shall be conducted. Said study should evaluate the specific functions and morphology, for example, the cardiovascular and respiratory ones.

In addition to the requirements outlined for synthesis products, pre-clinical information of biotechnological products shall include:

toxicological evaluation of contaminants and impurities;

anti-genicity reactions, for instance, of anti-product antibodies;

immune-toxicity reactions, for example, for immune-modulators, if appropriate.

## Clinical information

a detailed discussion of the known effects of the investigational product on humans, including information about pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities shall be submitted.

The following information about pharmacokinetics shall be included:

regarding pharmacokinetics: absorption, protein binding, metabolism, distribution and elimination;

absolute and/or relative bioavailability using a reference dosage form;

regarding bioequivalence: whenever appropriate, for example, in case the product is manufactured with a technology different from the one used to demonstrate its efficacy and safety;

population sub-groups as to gender, age, impaired organic function;

interactions with another drug and foods;

other pharmacokinetics-related data.

A summary of information shall be provided about the safety, pharmacodynamics, efficacy and the dose response of the product and its metabolites, if appropriate, produced from studies in healthy and ill volunteers. The implications of said information shall be discussed.

Complete information about adverse drug reactions shall be submitted in tables. Based on the experience with the product and related products, the incidence patterns across indication or sub-group shall be discussed.

If the product is marketed abroad, a summary of the relevant information stemming from its use. If the product was not approved or was suspended or recalled from the market of other country(s), which countries and the rationale for such measures shall be explained.

#### Excipients

In the case of excipients without a history of use in human beings, all the studies supporting the safety of their use shall be submitted.

### PROTOCOL

#### General

This Regulatory Guideline sets out the information and structure required for the clinical pharmacological studies protocol.

#### General information

the study complete title, including the clinical development phase;

the version number and date;

the sponsor's name;

a protocol summary

a visits and procedures schedule.

#### Background and justification

a description of the problem to be investigated and the current knowledge about it;

information about the investigational product, including a summary of the efficacy, pharmacokinetics, tolerance and toxicity data obtained from the pre-clinical and clinical studies;

the purpose and relevance of the research proposed;

the fundamentals for the development phase proposed for the study. A relevant methodological justification should a phase overlapping occur.

#### Objectives

a description of the primary and secondary objectives.

#### Design of the study

the study design and justification of its choice;

method for random assignment, if appropriate;

other bias reducing methods.

#### Population under study

envisaged number of participants, including the calculation of potency and its justification;

criteria for inclusion and exclusion of participants including diagnose based criteria;

criteria for participant withdrawal.

#### Statistical analysis

a study hypothesis with a specification of the null and alternative hypothesis;

specification of descriptive methods and statistical tests for variables;

criteria for managing missing, excluded and false data;

criteria for inclusion or exclusion of participants in the analysis;

information technology tools to be used;

criteria for processing safety information;

interim analysis schedule, if appropriate.

#### Efficacy evaluation

efficacy parameters to be assessed, including measurement instruments and methods;

efficacy criteria.

#### Investigational products

a description of the investigational products indicating API, formulation, dose, route of administration and treatment and follow-up frequency and duration;

In the case of biological products trials, a detail of the identification and assessment methodology ensuring the preparation uniformity or the consistency of the lots under study;

allowed and un-allowed drugs;

criteria for treatment discontinuation;

foreseen rescue treatment and follow up in case of failure or adverse events.

#### Adverse events

adverse events recording and reporting procedures;

emergency blind breaking procedure, if appropriate;

#### Ethical aspect

specific mention that the investigation shall be reviewed by a REC;

informed consent obtainment procedures;

protection of participants' information and identity confidentially;

details of participants' coverage and compensation for injuries;

justification for available payments or compensation for expenses for participants;

access for participants to the intervention identified as beneficial in the trial or to an appropriate alternative or benefit upon completion of the trial;

justification for using a placebo, if appropriate

justification for conducting the research in a vulnerable group, if appropriate;

possible conflicts of interest.

#### Administrative and other aspects

investigational products maintenance and storage procedures;  
clinical data record keeping and reports;  
trial documents handling;  
monitoring and audit procedures;  
criteria for trial discontinuation;  
results publication plan.

#### INFORMED CONSENT

The information document used to obtain the consent of a potential participant or of his or her legal representative, pursuant to legal provisions, shall include the following:

research title, objective or purpose;  
sponsor's data in the country: name or denomination and company name and address;  
approximate number of participants intended for the study;  
study experimental aspects;  
study treatments, assignment method and probability for each treatment;  
all the procedures to which the participant shall be submitted, the visits schedule they are expected to fulfill and their envisaged participation duration;  
a statement that all the investigational products and procedures will be free-of-charge for the participants;  
the reasonably expected benefits from participants' involvement in the study. A clear remark must be made if the participant is not intended to obtain any clinical benefit from the study;  
the risks and discomforts foreseen for the participants and; in case of pregnancy and breastfeeding, for the embryo, fetus or infant;  
a description of pregnancy prevention and protection methods;  
study alternative procedures or treatments and their potential benefits;  
the commitments undertaken by the participants should they accept to participate in the study;  
the intended use of all the samples obtained, if appropriate;  
the available compensation for participants for the expenses arising from their participation. In case a compensation for participating in the study were allowed, its amount and payment form;  
medical assistance and coverage for the participants which shall be afforded by the sponsor in case of damage, injury or adverse event related to the study as well as contact information for such cases;  
the proof of an insurance policy or any other form of guarantee in Argentina for the coverage of the risks or potential damages that may arise from participating in the study;  
the following phrase shall be included: "By signing this informed consent you do not waiver your rights pursuant to the Argentine Civil Code and laws concerning civil

liability for damages” (translation of: “Con la firma de este consentimiento informado Usted no renuncia a los derechos que posee de acuerdo con el Código Civil y las leyes argentinas en materia de responsabilidad civil por daños”).

special mention shall be made as to the fact that the sponsor finances the investigators’ fees and the study procedures costs through an agreement with the investigator and/or the institution;

the possible conflict of interest and the investigator’s institutional membership;

an assurance that the participant’s involvement in the investigation is voluntary and that the candidate may refuse to participate or may abandon the study at any time with no need to explain his or her reason to do so and with no loss of the benefits he or she is entitled to;

an assurance that the participant’s personal data shall remain confidential, even when the investigation results are published, pursuant to Law 25.326;

the commitment to provide timely answers to questions, clarifications or doubts about the procedures, risks and benefits concerning the investigation;

the commitment to timely communicate to the participant or his or her legal representative all the new information that might change his or her decision to continue participating in the study;

the envisaged situations by which the investigation or a person’s participation could be prematurely discontinued;

a description of the rights a person is entitled to as a participant of a research study, including the access to his or her study-related information and his or her right to have it available;

the permission the participant shall give to the sponsor’s representative, REC and the Regulatory Authority to access his or her medical records, which shall contain its scope and a special mention to the fact that such authorization is granted by signing the informed consent form;

contact information of the investigator and the REC that approved the study;

the following phrase shall be included: “This clinical pharmacology study was authorized by A.N.M.A.T. Should you have any doubt about the investigation treatment, call toll free A.N.M.A.T. Responde at 0800-333-1234.” [translation of: “Este estudio de farmacología clínica ha sido autorizado por A.N.M.A.T. Si usted tuviera alguna duda sobre el tratamiento de la investigación, puede consultar a A.N.M.A.T. responde al 0800-333-1234 (línea gratuita)”].

a signature page, with a space for the date, signature and print name of the participant, legal representative and witness, if appropriate, and of the investigator who led the process.

## AMENDMENTS TO THE PROTOCOL, INFORMED CONSENT AND INVESTIGATIONAL PRODUCT MONOGRAPH

Amendments to the protocol and informed consent

The objections to the protocol made by the agency in the baseline evaluation shall be changed and submitted as an amendment before its final authorization.

Amendments to the protocol and informed consent require an approval by the REC and the authorization by A.N.M.A.T. before their implementation; unless it is necessary to implement them immediately to protect participants' safety. Administrative amendments shall be enclosed to the next progress report.

The amendment shall make reference to the version number and edition date. In case of amendments to the informed consent, it is recommended that only the modifications and their contexts be documented, with no need to repeat unchanged information.

An EFCA3 form (Section F) completed and signed by the sponsor's legal representative shall be submitted with the protocol and/or informed consent amendment.

Should there be informed consent versions specific for a research center the different versions highlighting the changes shall be submitted.

Investigational product monograph update

The investigational product monograph shall be updated whenever new results of the investigational product study are obtained.

The new version of the investigational product monograph shall be submitted to A.N.M.A.T. as soon as available. One updated investigational product monograph for all the studies of the same product shall be accepted.

The following shall be submitted with the investigational product monograph new version:

an EFCA4 form (Section F) completed and signed by the sponsor's legal representative;

a summary of the changes made and the relevance of the new information regarding the risks and benefits expected from the study.

#### SERIOUS AND UNEXPECTED ADVERSE DRUG REACTIONS

The sponsor shall inform A.N.M.A.T. of any serious and unexpected adverse drug reaction concerning the investigational product within a ten working-day period after the moment he or she learnt about it. The serious and unexpected adverse drug reactions produced by a comparator product already registered at A.N.M.A.T. to be marketed nationwide or those related to a placebo shall be reported only to A.N.M.A.T. Pharmacovigilance System.

In blinded studies, whenever the sponsor receives a report of a serious adverse event (SAE), he or she shall verify the treatment provided to the participant in order to find out whether it is the case of an unexpected and serious adverse drug reaction (ADR) as defined in 7.1., but he or she shall not unmask the treatment to the investigator or persons in charge of the data analysis and discussion.

The unexpected and serious ADR report shall include the following information:

the denomination of the adverse reaction;

investigational product code, INN and trade mark;

type of report: baseline, update (update number) or final;

sponsor's name;

the research center and investigator's name;

A.N.M.A.T. regulation authorizing the study conduct;  
the name or title of the study;  
participant's code, age and sex;  
the date of the unexpected and serious ADR appearance, the date of investigator's report and the date the sponsor received it;  
unexpected and serious ADR seriousness criteria;  
unexpected and serious ADR brief description;  
investigational product information: daily dose, route of administration, start and suspension date, therapy duration and indication;  
inform if the reaction disappeared after treatment suspension;  
inform if the reaction reappeared with treatment re-introduction;  
concomitant drugs: dosage form and start and termination date;  
participant's history significant for the unexpected and serious ADR.

Every six months, after the date the agency authorized the first study on the investigational product, the sponsor shall submit a single summary per investigational product, of all the unexpected and serious ADR occurred in any of the research centers for the pertaining period, which shall include the following information:

A.N.M.A.T. dossier or regulation number concerning the investigational product;  
a list of unexpected and serious ADR classified by organ system and reaction type, including the participant code, denomination of the adverse reaction, date of appearance and country of occurrence.

the investigational product overall risk-benefit assessment and a particular assessment per type of reaction, including all the cases in which the same reaction occurred.

The agency shall be informed of any risk increase over benefits in any of the studies on an investigational product within a ten day-period after the finding occurred.

#### STUDY PROGRESS REPORTS AND OTHER REPORTS

The sponsor shall submit a complete progress report EFCA5 form (Section 5) per each investigator filled out with information about the study progress in his or her center, which shall be signed and dated by the investigator and the sponsor's legal representative, at least once a year as from the date of authorization by the agency.

For clinical trials on narcotic drugs, progress reports shall be submitted every six months as from the date of authorization by the agency.

The IDMC reports, if appropriate, shall be submitted with the progress reports, except when a change in the study conditions and risks takes place, in which case the reports shall be submitted within ten working days after obtaining them.

The sponsor shall inform A.N.M.A.T. about the following deviations from the protocol within a ten-day period after learning about them:

major deviations having affected participants' rights or safety;  
repeated minor deviations despite having warned the investigator about their occurrence.

The application for the addition or exclusion of an investigator or research center shall be submitted with the EFCA2 form (Section F) completed and signed and other supporting documents. Whenever an exclusion is requested, the reason for it shall be explained.

The study premature cancellation in one given center or in the country shall be immediately informed to A.N.M.A.T. including the pertaining justification.

The following changes throughout the study shall be informed to the agency with the study progress report:

changes in the REC member composition;

administrative changes, for example, the person responsible for the study or his or her contact data or the investigator's contact data.

The following changes or updates may not be informed to the agency:

start, duration and completion of the enrolment or random assignment period;

extension of the investigational product lot expiry date;

changes in the sponsor's monitoring program;

REC monitoring report, except for the case of major deviations (as described in 8.4).

8.9. Upon trial completion, the sponsor shall submit a complete final report EFCA5 form (Section F) per each investigator.

8.10. The sponsor shall submit the final result within one-year period after the study termination.

## SECTION C: GOOD CLINICAL PRACTICE GUIDE FOR CLINICAL PHARMACOLOGY STUDIES

### OBJECTIVE

With a view to enabling the agency to exercise its monitoring authority, this section sets forth the procedures that clinical pharmacology studies investigators and sponsors shall conduct pursuant to this regulation.

### INVESTIGATOR

The investigator is the person responsible for conducting a clinical pharmacology study in a research center. Whenever the investigator, plans, initiates and conducts an investigation on his or her own, he or she becomes the study sponsor and takes all the responsibilities implied thereby.

The investigator shall be suitably trained and experienced to conduct a clinical pharmacology study, as detailed in his or her Curriculum Vitae and proofs attached thereto.

The investigator may set up a team of qualified collaborators who are trained in all the applicable requirements to conduct the investigation, and may therefore, delegate some of his or her functions to them; but not his or her responsibilities. The collaborators' qualifications shall be documented in their updated Curricula Vitae.

The investigator shall maintain an updated list of his or her collaborators, indicating their name, delegated function, activities initiation date and signature registry.

The investigator and his or her collaborators shall know and respect the outlines set out in this Regulatory Guideline as well as the competent Health Authority requirements and the study protocol. The investigator and his or her collaborators shall be familiar with the information available concerning the investigational products.

The investigator shall verify and ensure that the research site is licensed to operate, that its infrastructure adjusts to the study requirements and that all the equipment, instruments and supplies to be used operate properly. Phase I, pharmacokinetics, bioavailability and bioequivalence studies may only be conducted in second or third level health institutions (for hospitalization), according to the regulation in effect set forth by the Ministry of Health. The level of each institution may be verified in its operating license.

In case of advertising in communication media for participant recruit purposes, the advertisements used shall be approved by the REC and submitted to the agency. The investigational product may not, implicitly or explicitly, be referred to as efficacious, safe or equivalent to or better than existing products in such advertisements.

The investigator and the research site shall be subject to monitoring, audit or inspection of the clinical study by the REC, sponsor and competent authorities.

## SPONSOR

The sponsor of the study is the physical person or legal entity that initiates, manages, controls and finances the study and takes all the responsibilities laid down in this regulatory guideline.

The sponsor shall count on qualified professionals for the design, planning, conduct, analysis and reporting of the clinical study, as well as on medical advisors to pursue matters concerning the investigational products and participants' safety.

The sponsor is responsible for selecting qualified investigators according to their education, training and experience; and research centers having all the resources needed for the proper conduct of the clinical pharmacology study.

The sponsor shall furnish the investigator with all the documents necessary to perform the study properly, such as, the protocol and investigational product monograph, among others. Likewise, the sponsor shall be responsible for training the investigator and his or her team on the study procedures, investigational products and applicable requirements.

The investigator is responsible for obtaining the authorization from the research site or institution authority before initiating the study; while the sponsor shall be responsible for obtaining the authorization from the agency before starting the study conduct.

For multi-site research studies, the investigator shall lay out a plan to validate and standardize all the measurement procedures in the various research sites.

The sponsor may summon an Independent Data Monitoring Committee (IDMC) composed of experts in the clinical study subject matter to review safety and efficacy partial results and evaluate and recommend whether the study should be continued, modified or cancelled. The IDMC members cannot be investigators of the study or sponsor's employees.

The sponsor shall implement and maintain a quality control and assurance process throughout the study stages, which shall be based upon standardized operational

procedures (SOPs), in order to ensure the study is being conducted and documented according to the protocol and this Regulatory Guideline and that data are being processed properly and are reliable.

The sponsor shall transfer some or all of his or her functions concerning the study to a contract research organization (CRO), provided that the latter is legally incorporated in Argentina and without prejudice of the legal responsibility attached to the sponsor regarding participants' care and data integrity.

The tasks and functions transferred to and accepted by the CRO, shall be laid down in a written agreement signed by the parties. The functions not specified in the agreement shall be discharged by the sponsor. The CRO shall fulfill all the obligations established for the sponsor under this Regulatory Guideline.

In the event the sponsor is a foreign company and delegates the conduct and performance of the study in Argentina to a CRO, the latter shall be subject to the regulations herein as the study sponsor and shall take all the responsibilities concerning administrative, misdemeanor and civil matters.

A clinical pharmacology study on an investigational product shall be conducted only if the sponsor takes out of an insurance policy or another form of guarantee set up in Argentina, in order to ensure participants' coverage for risks or potential damage.

Noncompliance of the protocol or the Regulatory Guideline herein by an investigator or sponsor's legal representative shall lead to an immediate remedial action by the sponsor.

When the sponsor identifies a repeated, persistent or serious violation of the protocol by an investigator, he or she shall suspend the study at the site and immediately report it to the REC and A.N.M.A.T.

## RESEARCH ETHICS COMMITTEE (REC)

### Evaluation requirement

Prior to the research initiation, the investigator is required to have a written authorization by a REC. To such end, the investigator shall provide the REC with all the information it requests, including the protocol and its amendments, informed consent documents and their amendments, other information to be provided to potential participants, participant enrolment method, last version of the investigational product monograph and any other information concerning the experimental products or procedures.

In case that the research site does not have its own REC or if the REC does not comply with the requirements set out herein, the study shall be evaluated by a REC belonging to another institution. The research site authority shall authorize the delegation of this function.

### REC evaluation objective and scope

The primary objective of the review by a REC of a clinical pharmacology study is to protect the dignity, rights, safety and well-being of the participants.

The REC shall provide an independent, competent and timely evaluation of the ethical, scientific and operational aspects of the proposed studies, which shall be based upon the current state of scientific knowledge and the Regulatory Guideline herein.

Every clinical pharmacology study must be evaluated by a REC before its initiation and throughout its conduct, at least once a year until its completion. The REC may set shorter periods for evaluations as per the risks involved in the study.

The REC shall assess the suitability of the investigator to conduct the study according to his or her education and training in ethical and regulatory aspects and the research center suitability to host the study.

The REC shall make sure that potential participants give their consent without duress or undue influence and after having received all the information properly. The information about payments and compensations envisaged for the study shall be precise and easy to understand for participants.

The REC shall make sure of the compliance with the ethical principles applicable throughout the study conduct, by means of a monitoring mechanism for investigators.

#### Composition

The REC composition shall be such that enables a competent, unbiased and uninfluenced evaluation of the scientific, medical, ethical and legal aspects of the study.

The REC composition shall be cross functional, multi-sectored and balanced in terms of its members' age, sex and both scientific and non-scientific education. The number of members shall be adequate, preferably uneven, to ensure the fulfillment of its duty. It shall have a minimum of five full members and at least two alternate members for the cases of absence of the regular members.

The research center REC shall include an external member unrelated to the institution and who shall represent the interest of the community being assisted.

The members shall be frequently renewed in order to combine the advantages of experience with those of new perspectives. The REC member selection and replacement mechanism shall ensure the election impartiality and respect for the suitability and plurality criteria.

The REC shall elect a president among its members to lead meetings. The REC president shall be a person holding the experience, competence and qualifications to deal with and evaluate all the aspects of the investigations.

#### Operation

The REC holds the authority to approve, request amendments to, disapprove, discontinue or cancel an investigation on human health. The REC shall report its opinions in writing to the investigator, including the reasons for its decisions.

The REC shall make a list and keep it updated of its members, indicating their names, age, sex, profession or occupation, position at the REC and relationship with the institution.

The REC shall place in record its meetings, consultations and decisions, including the participating members and their voting results.

The REC shall request and make available for its members all the research documents necessary for a comprehensive evaluation including: the protocol and its amendments, the informed consent and its amendments, other information for participants, the investigator's updated curriculum vitae, enrolment mechanisms, a detail of the payments and insurance coverage envisaged for the participants and financing source of the study.

A member of the REC who is, in turn, an investigator in a project may not participate in any evaluations, consultations or decisions about such project.

The REC shall consult experts as to specific subject matters but they shall not have a right to decide on the project. The experts requested participation and opinion shall be documented.

The REC shall demand from the investigator the immediate report on all the relevant information about safety or protocol amendments increasing the risk for participants or those changes made with the purpose of eliminating the immediate hazards for them.

In case of administrative changes or changes that do not affect participants' safety, the REC may carry out a swift evaluation of such changes. The president or member in charge of the swift evaluation shall document it and inform the rest of the members about it.

The REC shall draft and update the standard operating procedures (SOP) to rule its composition and operation, including the following: member selection method; membership duration and criteria for renewal; sessions plan; means of summoning; quorum to hold sessions; specifications as to the type, format and opportuneness of the documents for project evaluation; procedures of evaluation, notification and appeal of opinions; procedures of study follow up and members' conflict of interest declaration.

The REC shall retain all the research relevant documents, such as the documents submitted for review, minutes of meetings, opinions and general communications for a ten-year period after the termination of the study and shall make them available for health authorities should they request them.

## INFORMED CONSENT

### General

The informed consent is the process that ensures that a potential participant decides to participate in a human health investigation voluntarily, without undue influence or duress, provided the investigation is consistent with the participant's values, interests and preferences.

The informed consent process shall be conducted by the investigator or a qualified sub-investigator authorized to do so in the function delegation form.

In case a potential participant cannot grant by him or herself the consent to a study, the informed consent shall be obtained from his or her legal representatives, in accordance to the Argentine legislation in the matter. Likewise, the participant's assent shall be requested after having provided him or her with information about the study, according to his or her understanding possibilities of such information. The participant's decision whether to participate or not shall be respected.

In case of a study potential participant's educational, cultural, social or economic vulnerability, the involvement of a witness unrelated to the investigator and his or her team shall be required. Said witness shall sign and date the consent form as a proof of his or her participation. The REC may set this requirement for all cases in centers where most patients are in a vulnerable situation.

A summary of the written information for the patient approved by the REC and the agency may be used in case of serious situations requiring immediate medical care. Spoken information shall be provided in the presence of an impartial witness, who shall

sign the written summary of the information and the consent signature page, together with the investigator.

#### Guidelines for obtaining the informed consent

The information consent documents include at least two sections: information pages for the participant and the signatures page. Any document intended to be used in the process shall be approved by the REC and the agency. The information section shall contain all the elements described in section B.5.1.

The informed consent shall be obtained prior to initiating the assessment of eligibility criteria or any other specific procedure of the study.

Oral or written information provided to the potential participant or his or her representative, in the cases under legal provisions, shall be submitted in a clear, precise, complete and truthful way; and in a practical language which shall be easily understandable for the participant, without including any expression that might lead the participant to believe he or she is not entitled to or waives any of his or her legal rights or that the investigator, institution or sponsor is released from liability by signing the consent. The written document shall guide the oral explanation.

The investigator or authorized sub-investigator shall provide the prospective participant or his or her legal representative with sufficient time and opportunity to assess all the options and make all the questions they might wish and receive satisfactory answers; and shall then verify through questions to the participant or legal representative that he or she fully understands the information provided.

After fulfilling the information process, the participant or his or her legal representative, in the cases legally foreseen, the investigator or authorized sub-investigator and the witness, if appropriate, shall sign and date two original consent signature pages, as a declaration of having been provided with the information and having understood it and made the decision to participate in the study freely and voluntarily. The participant or his or her legal representative shall receive one of the original signature pages and a copy of the written information section.

The process for obtaining the consent shall be documented in the participant's medical record, for which end the following shall be mentioned: date and time of initiation, that the participant was given sufficient time to reflect on and make questions, that the participant's understanding of the information was verified, that two original signature pages were signed and that one of them was given to the participant or his or her legal representative.

When the consent is given by a participant's legally acceptable representative or when a witness is required to carry out the process, the participant's medical record shall document the reasons for such situation and the fulfillment of the requirements applicable thereto. Likewise, the medical record shall inform both the presence and absence of the prospective participant's vulnerable condition.

All the new information or changes in the protocol that may affect the participant's safety or his or her decision to continue participating in the study shall be communicated verbally and in writing in order to obtain the consent. The new consent document shall be previously approved by the REC and the agency, unless the changes require swift implementation for safety reasons.

#### PROTECTION OF STUDY PARTICIPANTS

The investigator and the sponsor shall ensure that every participant will have access to their own information and to the study results once available and that their right to confidentiality will be protected at all times.

The investigator is responsible for obtaining the consent of all the participants, even when a sub-investigator was authorized to perform that action.

Since exposure to an investigational product during pregnancy implies risks for the embryo or fetus, the following measures shall be taken:

women of fertile age shall be warned about such risks, before giving their consent to participate in the study and about the need to immediately inform the investigator should they suspect of being pregnant at any time of the study;

the investigator shall run a pregnancy test prior to the admission to the study of every women of fertile age; and then regularly throughout the study;

a positive result pregnancy test shall imply the exclusion of the prospective participant or the preventive discontinuation of the investigational product administration, if appropriate. In case of pregnancy, the investigator shall guide the participant in obtaining proper care;

the sponsor and the investigator shall ensure the access to the necessary contraceptive methods for all the study participants.

An investigator who is a doctor of medicine or a dentist, as appropriate, shall be responsible for all the participants' health care related decisions throughout the study.

Should the study put at risk the integrity or health of the participants, for example, due to an adverse reaction or a therapeutic failure, the investigator shall take all the precautions to halt the exposure to the risk.

The use of a placebo control shall be properly justified both from the methodological and ethical points of view. The use of a placebo in terminal diseases shall be accepted in case of inefficacy of all the existing treatments.

The investigator and the sponsor shall ensure that the participant will receive proper medical care in case of injury related to the investigation. In the case of diagnose of an inter-current disease caused by a research related procedure, the investigator shall guide the participant in obtaining the necessary health care.

Participants requiring to continue their treatment after the study completion shall have access to the intervention that turned out to be beneficial or to an alternative intervention or another proper benefit, which shall be approved by the REC for the time it decides or until such access is ensured by any other means.

#### AGREEMENTS AND FINANCING

The sponsor is responsible for affording all the research costs, including study treatments and procedures. In clinical studies with a therapeutic benefit, the sponsor may make payments to the participants for any inconveniences and their time. However, such payments may not become an undue influence by being disproportionate in such a way that the patient is persuaded to run unnecessary risks. Payments shall be apportioned according to the study characteristics.

The sponsor shall ensure medical care and an insurance coverage or the setting up of any other form of guarantee in the country, in case of injury to participants resulting from the study.

The investigation financing shall be documented in a written agreement signed by the sponsor, the investigator and/or the institution hosting the study, which shall show in detail the commitment of the parties to fulfill the obligations set out in the Regulatory Guideline herein.

The REC shall check any financial agreement and foreseen payment for the participants as provided for in 7.1. The sponsor shall verify that the REC approved them prior to research initiation.

The investigator shall declare his or her potential financial conflicts of interests to the REC prior to initiating the investigation and at any time said conflicts arise.

The approval or authorization of the study shall not release the sponsor, the investigator or the host institution from any legal responsibility they might bear in case of participants incurring damages as a result of their participation in the study.

## INVESTIGATIONAL PRODUCT

### Manufacture, packing and labeling

The sponsor shall ensure that all the investigational products are manufactured according to GMP, if appropriate, and packed in a safe manner to prevent contamination or deterioration during transportation or storage.

The label shall be written in Spanish and contain, at least, the following printed information or, whenever appropriate, there shall be space left to complete said information on it:

study identification, sponsor and investigator;

product name, or if blinded, the corresponding code;

dosage form, route of administration (may be excluded in solid forms) and concentration or potency per unit, were it the case of an open study;

lot number or code to identify the manufacturing and packing process;

participant's code and number of visit or date of product administration.

The following information shall be included in the label whenever the primary packing size allows for it, or otherwise, in the secondary packing or a leaflet attached:

the name, address and telephone number of the person who should be contacted for information about the product, the study and the emergency decoding (sponsor, CRO or investigator);

basic storage conditions;

expiry date (month/year);

special instructions for the product administration;

a "clinical investigation exclusive use" statement;

a "keep away from the reach of children" statement if the product is given to the participant.

In case of updating the investigational product expiration date, an additional label shall be placed on the packing which shall contain the lot number, the old expiration date and the new one. The re-labeling process may be carried out at the authorized manufacturing site or at the research center, in which case, the study monitor shall

perform said procedure and a sponsor representative shall review its result. Such process shall be documented on the sponsor's lot record and the research center product accountability records.

If the formulation of the investigational product or its comparators were modified during the study, the new pharmacokinetics or dissolution studies, according to the pharmaceutical form, shall be available prior to using the new the formulation, in order to ensure therapeutic equivalence. Topical and gaseous drugs are exempted from said requirement, provided the API concentration is the same. All product modifications require a protocol amendment and approval by the REC and A.N.M.A.T.

#### Information

All clinical studies shall be based on safety and efficacy information obtained from clinical and non-clinical studies. Such information shall support the product proposed use as to its indication, pharmaceutical form, route of administration, dose and population to be treated.

The sponsor shall submit an investigation product monograph updated with complete data concerning the safety, efficacy, route of administration and treated population of pre-clinical or previous clinical studies on the investigational product. The information contained in the information leaflet shall suffice, in the case of an API already registered at the agency.

The sponsor shall set out the required conditions concerning temperature, humidity, protection from light, etc., for the proper conservation of investigational products and any other supply necessary for its administration. The protocol shall also indicate procedures for handling, storing and returning the unused products to the sponsor and/or their final disposition at the research center, pursuant to the regulations in effect.

The sponsor shall set forth the development and control guidelines and use procedures to be applied to studies of products not defined or governed by GMP or GLP standards, for example, biological products. Said guidelines and procedures shall be subject to approval by the agency.

#### Supply and handling

The sponsor shall be responsible for handling the investigational product from the moment it departs from the manufacturing site or when it is cleared from Customs until it is delivered to the research site and from the time he or she takes away the unused or expired product until its destruction. The investigator shall be responsible for managing the product domestically and shall be supervised by the sponsor who shall be jointly and severally liable.

The sponsor shall be responsible for providing study participants with free-of-charge investigational products throughout all the study and for ensuring their timely delivery and the retrieval of failed, expired or unused products.

Before delivering the investigational products to the investigator, the sponsor shall make sure that the REC has approved it and the agency and jurisdictional health authority have authorized it.

The investigator shall be responsible for the investigational products to be used as per the protocol. The investigator or his or her delegate shall instruct every participant on the rightful use of the investigational product(s), make sure participants understand such instructions and then verify in every clinical visit that the instructions are followed.

If a blinding method is used in the study, the sponsor shall set out a decoding procedure for emergency situations and the investigator shall do his or her utmost to preserve the blind, unless it becomes necessary to identify the product for participant's safety reasons. In such case, the investigator shall document and justify the procedure and immediately report it to the sponsor and the REC.

The investigator shall have an inventory of the investigational products documenting the following: reception from the sponsor, dispensation to participants, reception of the remains and return of unused products to the sponsor. Said function may be delegated to a BSc in Pharmacy or any other team member qualified and authorized to do so.

The inventory of investigational products at the center shall indicate the participant's code, product name or code, lot or serial number, expiry date, delivery and reception date and the respective quantities. The inventory shall enable to verify that the products were dispensed only to participants and that they used the products according to the protocol. Final accountability shall show a coincidence among the products received, the products used and the products returned to the sponsor. Otherwise, differences shall be accounted for in writing.

Investigational products shall be stored in a locked safe place, with the exclusive access of authorized personnel and in the room conditions set out by the sponsor and the applicable regulations.

The sponsor shall keep an analysis and description record of every investigational product batch and reserve an adequate quantity of samples for an eventual re-confirmation of specifications until the study data analysis is completed or until the regulatory authority decides that should be the case.

Investigational products destruction shall be carried out according to the legislation in force concerning hazardous residues. The sponsor shall be primarily responsible for the destruction of unused products and shall retain the destruction certificate.

## REPORTS AND NOTIFICATIONS

The investigator shall immediately notify the sponsor of all the serious adverse events (SAE), including relevant laboratory abnormalities, as per the procedures and terms established by the sponsor. Additional information enabling to determine the SAE relation with the investigational product shall be furnished, as soon as available.

The investigator shall notify the REC, within the period set out by the latter, of all the SAEs and other events significantly affecting the study and/or the risk for participants.

The investigator shall report the study progress to the REC at least once a year. The progress report shall contain, at least, the number of enrolled, followed up and withdrawn participants, the encoded list of participants, serious adverse events and their alleged relation with the investigational product as well as the participants' safety related relevant deviations from the protocol observed throughout the period.

The sponsor shall notify of all the unexpected and serious ADR related to an investigational product to all the investigators of all the ongoing studies of the product within a fourteen-day period after learning about them. The investigators shall report said unexpected and serious ADR to the REC within the period it sets forth for such purpose.

The sponsor shall be responsible for timely submitting the study reports and for reporting to the agency the unexpected and serious ADR and any other safety related

information of an investigational product, within a ten-working-day period after having learnt about them.

#### CHANGES DURING THE STUDY

The changes made to an approved protocol shall be justified according to their potential impact on the participants and the study scientific validity. Said changes require approval by the REC and the agency prior to their implementation unless they were performed to preserve participants' safety.

The study participants or their representatives shall be informed about the changes affecting their safety or that may modify their decision to continue in the study and shall give their signed and dated consent prior to the implementation of such changes.

Administrative amendments shall be notified to the REC and the agency, in the subsequent progress report and to the study participants, when appropriate; but shall not require an approval or written consent.

#### CLINICAL DATA RECORD-KEEPING

The sponsor shall set out the proper procedures for obtaining and recording participants' clinical data, including the encoding system that will enable to preserve their identity confidentiality.

The investigator shall be responsible for the reliability, legibility, consistency and opportuneness of clinical data records both in medical records (source documents) and clinical data forms (CDF).

Both participants' clinical data and the description of procedures related to them, for example, the obtainment of the informed consent, pre-study evaluation, inclusion in the study, randomized assignment result, instructions for using the investigational product, treatment initiation and termination, control of product delivery and return, as well as the information provided to the participant, shall be documented in the same format as are the medical notes used for the rest of the patients receiving medical care at the center.

The investigator shall be responsible for preserving the confidentiality of every participant's identity. No data of the participant's identity shall be contained in any document transmitted, reported or taken away from the host institution.

The changes or corrections of any of the study records shall not conceal or delete the original datum. Corrections shall be dated and signed with their author's initials.

In case of using electronic direct data transmission automated devices to perform study-related exams such as an electrocardiogram and a spirometry, an identifiable printed source document of the process shall be obtained and filed in the medical record.

In case of using an electronic format for clinical data record-keeping and transmission, the system used shall comply with integrity, accuracy, reliability, confidentiality and consistency requirements.

Electronic record-keeping systems shall enable:

the recording of all the editions of individual data, including the author and the edition date and without eliminating the original data;

a restricted access to enter or edit data;

the obtainment of a data back-up copy;

the protection of treatment blind during data entry and processing, if appropriate.

The sponsor shall use an SOP to manage electronic systems and a list of the persons authorized to discharge such function.

The study final results must be always related to the study clinical data, even when the variables were transformed at processing.

## ESSENTIAL DOCUMENTS OF THE STUDY

### Documents file and retention

Document filing shall be set out from the beginning of the study, both at the research center and the sponsor's office. All the documents mentioned in the Regulatory Guideline herein are subject to monitoring and auditing by the sponsor and to inspection by the agency and shall be available whenever required by them.

The investigator and the sponsor shall retain the study documents in a locked safe place with access limited to authorized personnel and shall take the necessary steps to prevent their accidental loss or destruction.

All the study documents shall be retained for ten years after the date of the last visit of the last patient enrolled in the center.

Essential documents required prior to the study initiation:

a copy of A.N.M.A.T. Regulatory Guideline herein;

a current version of the Declaration of Helsinki;

a valid investigational product monograph and other safety information;

a protocol approved by the REC and the agency;

amendments prior to the study initiation approved by the REC and A.N.M.A.T., if any;

blank copies of the clinical data forms;

an informed consent document approved by the REC and the agency;

a model of recruitment advertisements approved by the REC, if any;

a letter of commitment from the investigator and his or her team to comply with the protocol (study title) and to abide by the Declaration of Helsinki and A.N.M.A.T. Regulatory Guideline for GMP-CPS;

a proof of approval by the REC of the study indicating the approved documents: protocol and which version, informed consent and which version, recruitment advertisements and others;

a dated list of the REC members and positions;

the Regulation or note whereby A.N.M.A.T. authorizes the study and research center;

the notes whereby the agency authorizes the protocol or informed consent amendments;

the proof whereby the agency was informed about the recruitment advertisements;

an investigator's function delegation form to his or her team members;

the investigator's and his or her team's curricula vitae;

a proof of the investigator's and his or her team training on the study;

a list of the normal laboratory values to be used in the study;

a copy of the laboratory quality accreditations and/or study findings quality control certificates;

a curriculum vitae of the person responsible for the laboratory;

the instructions for obtaining and sending samples, if appropriate;

the instructions for handling and storing the investigational product, if not included in the protocol;

the instructions for blind handling and blind breaking procedures, if not included in the protocol;

a center monitoring plan;

a baseline monitoring visit report;

#### Essential documents required during the study

The following documents shall be available during the study:

the current investigational product monograph, had it been updated;

amendments to the protocol approved by the REC and the agency, if any;

amendments to the informed consent approved by the REC and the agency, if any;

new clinical data forms, had there been any changes;

new recruitment advertisements approved by the REC and the agency, if any;

the REC approval notes of protocol amendments, if any;

the REC approval notes of informed consent amendments, if any;

the REC approval notes of new recruitment advertisements, if any;

the REC approval notes of other documents, if appropriate;

the agency approval notes of protocol amendments, if any;

the agency approval notes of informed consent amendments, if any;

the proof whereby the agency was informed about the recruitment advertisements, if any;

the research team new members' curricula vitae, if appropriate;

research team new members' commitment letter, if appropriate;

an updated list of functions delegation, had there been any changes;

updated laboratory values, had there been any changes;

a copy of updated laboratory accreditation and/or its quality control certificate;

updated instructions for obtaining and sending samples, had there been any changes;

a proof of the calibration of parameter measuring instruments of the study;

the notifications to the sponsor of SAEs;

the notifications to the REC about the SAEs occurred in the center;

the notifications to the REC about the unexpected and serious ADR occurred in the centers;

the notifications to the REC about the unexpected and serious ADR occurred in other centers;

other safety notifications;

the progress reports submitted to the REC and A.N.M.A.T.

a list of prospective, included and withdrawn participants;

a chronologic participant enrolment list;

a participants' identification list;

proofs of reception of the investigational product and a proof of its return to the sponsor;

investigational product accountability forms;

investigational product storage temperature control records;

monitoring visit forms;

monitor's reports or notes;

other relevant notifications to and from the REC, the sponsor and the agency;

signed informed consents;

source documents such as medical records, laboratory and pharmacy records, participants' diaries, imaging and technical reports, electrocardiograms, etc.

completed and signed clinical data forms.

Essential documents required at study completion

The following documents shall be available upon study conclusion:

investigational product final accountability;

proofs of the investigational product destruction, if destroyed at the center;

full list of participants' identification;

final report submitted to the REC and the agency;

close-out monitoring visit report;

dated close-out notification by the sponsor.

## MONITORING

The sponsor shall be responsible for implementing a regular and ongoing quality control of the clinical study denominated monitoring.

The sponsor shall select monitors who have the proper scientific and/or clinical knowledge to perform the duty and train them on the investigational product, protocol, consent documents, sponsor's SOP and applicable rules and regulations.

The sponsor shall set out and document in a plan the type and scope of the monitoring process, based on considerations such as the objective, design, number of participants and variables to be assessed.

The monitor shall comply with the monitoring plan and respect all the procedures established by the sponsor for the monitoring process.

The monitor shall verify that:

the rights and well-being of human subjects are protected at all times;

the investigation is conducted per the protocol and the REC and the competent regulatory authority requirements;

the investigator and his or her team are qualified to perform the study and that they have the proper resources throughout the study conduct;

the approval by the REC and the authorization by the competent authority were obtained;

the investigator uses the last version of the protocol and informed consent approved by the REC and authorized by A.N.M.A.T. ;

all the participants´ written consents were obtained prior to their inclusion in the study;

the investigational products supply and storage are appropriate and sufficient;

the investigational products are administered to the right participants as per the conditions set forth in the protocol;

participants have been provided with correct and adequate instructions for using, handling, storing and returning the investigational products;

the reception, use and return of investigational products at the research site are properly controlled and recorded;

the end disposition of unused investigational products complies with the sponsor´s requirements and the applicable regulation;

the investigator has all the documents and supplies needed to properly conduct the investigation;

the study personnel carry out the specific functions assigned to each of them;

the participants included in the study meet the eligibility criteria;

the participants rate of recruitment is adequate;

the source documents, CDF(s) and inventories of the investigational products are precise, complete, legible, consistent and timely; and that participants´ confidentiality is preserved;

the investigator submits, in due time and manner, the reports and notifications required from him or her, including the AE, SAE and unexpected and serious ADR;

that deviations from protocol, REC requirements or the applicable regulation, including changes in the use of products, procedures or visits not performed and participants´ withdrawals or loss are properly documented, explained and notified to the REC and the sponsor.

After the monitoring visit, the monitor shall inform in writing the errors and deviations thereby detected to the investigator and indicate the appropriate measures to prevent their repetition.

The monitor shall submit a written report to the sponsor after every visit to the research site. The report shall include date, place, name of the monitor, investigator and present

team members and a detail of the documents reviewed and the findings, deviations, actions taken or pending and the recommendations proposed to assure their compliance.

The sponsor shall document the monitoring report review and follow-up.

#### AUDIT

The sponsor shall implement an audit process as part of the study quality assurance system in order to ensure that all the steps of such process, including data recording, analysis and data reporting, were taken accurately as per the protocol, SOPs and regulatory requirements.

For conducting audits, the sponsor shall appoint auditors who are independent from the clinical study and its data management, upon their qualification credentials and experience.

The sponsor shall set out an audit plan for clinical pharmacology studies based on the type, importance, complexity, number of participants and research risks, including the investigator selection criteria and centers to be audited.

The auditor's findings shall be documented and reported to the sponsor.

The sponsor shall ensure that audits on clinical studies and data management systems are performed in compliance with their SOP(s).

The audit reports shall be provided to A.N.M.A.T., were it to request them or whenever there is evidence of serious non-compliance or throughout a legal procedure.

#### SUSPENSION OR CANCELLATION OF THE STUDY

A study may be suspended or cancelled by the investigator, the host institution, the sponsor, the REC or the agency. In such cases, the reason shall be justified and notified to the other stakeholders.

The sponsor shall suspend the research in a center where serious or repeated protocol deviations having affected participants' safety were detected and he or she shall inform such event to the agency.

Participants shall be immediately informed about the study suspension or cancellation and shall be provided with medical care according to their needs. The sponsor shall provide an alternate treatment for the participants for as long as the REC decides.

If the sponsor suspends or cancels the clinical development of an experimental drug, he or she shall notify of such decision and justify it to all the investigators, host institutions and A.N.M.A.T.

## SECTION D: INSPECTIONS OF CLINICAL PHARMACOLOGY STUDIES

### OBJECTIVE

This section describes the procedures that should be followed in inspections of clinical pharmacology studies within A.N.M.A.T. competence, with a view to verifying the compliance of this Regulatory Guideline.

### SCOPE AND AUTHORITY

Studies inspections are mainly aimed to investigators and research centers. However, A.N.M.A.T. may establish the need for performing inspections of other involved parties such as the sponsor and the contract research organizations (CRO).

A.N.M.A.T. inspectors are empowered to enter the research center and have direct access to the investigational product, study filed documents and participants' medical records. The inspections of clinical pharmacology studies may also include external institutions carrying out specific procedures of the study that were contracted by the investigator, sponsored party or CRO.

### INSPECTION PROCESS

The inspection process comprises the study and inspector selection, the inspection planning and the inspection notification, conduct, reporting and result.

Inspections may be performed prior to the study initiation, during its conduct or after its conclusion.

### SELECTION OF THE STUDY AND THE INVESTIGATOR

The study selection criteria shall be as follows:

- inclusion of vulnerable population;
- priority for research initial phases;
- high risk investigational products studies;

The investigator selection criteria shall be the following:

- a high recruitment rate as compared to other investigators of the study;
- a high or low incidence of serious and unexpected ADR as compared with the rest of the study investigators;
- the investigator's background in previous studies;
- his or her participation in a significant number of studies;
- any relevant information included in safety and/or progress reports that merits an inspection, in the view of the agency;
- a complaint about the investigator's inappropriate behavior.

### INSPECTOR SELECTION

A.N.M.A.T. Director of the Drug Evaluation Office (DEO) shall select the inspector or inspectors to conduct the inspection.

The Director of the Drug Evaluation Office shall ensure:

- the appropriate number of inspectors to perform the inspection;

the inspectors' suitability based on their education and training in studies scientific and regulatory aspects;

the absence of potential financial conflicts of interest with the study investigators, research sites or sponsor;

the supply of a proper identification document for inspectors;

inspectors' access to all the study information needed to carry out the inspection, including at least, the protocol, amendments, informed consents and serious and unexpected ADRs reports as well as the study progress and previous inspections reports.

## PLANNING AN INSPECTION

When planning an inspection, the designated inspectors shall:

analyze the information provided by the Drug Evaluation Office ;

thoroughly know the study objectives, inclusion and exclusion criteria, foreseen visits and analytical procedures, investigational product information, its safety data and special handling and storage requirements as well as the allowed and unallowed concomitant drugs;

consider the observations made during the study evaluation prior to the authorization and/or the study and investigator selection criteria;

create an inspection plan specific for the study and the investigator to be inspected , which shall be approved by the Inspections Coordinator and the DEO;

create an inspection form including the list of study documents to be reviewed, the guidelines to obtain the informed consent, the verification of clinical records, the investigational product circuit and the facilities of the research center to be visited.

## INSPECTION ANNOUNCEMENT

Inspections shall be announced to the sponsor and/or principal investigator at least fifteen running days before it is conducted, in order to ensure the availability of the research team and documentation at the time of the inspection conduct.

The previous inspection announcement may not be made if the visit is decided upon relevant information included in the safety reports and/or progress reports or upon a complaint about the investigator's inappropriate behavior.

The inspection shall be announced by means of a certified return receipt letter.

## INSPECTION CONDUCT

### General considerations

Inspectors shall appear at the site to be inspected and get in contact with the investigator or his or her delegate at the announced date and time.

Inspectors shall:

verify the compliance with the protocol and its amendments authorized by A.N.M.A.T.;

verify that participants' rights and safety were protected;

evaluate data quality and integrity.

The documents obtained or produced from the inspections of clinical investigators shall be available only for A.N.M.A.T. and, when appropriate, for the investigators and sponsor involved.

Both inspector and any other A.N.M.A.T. personnel related to clinical investigators activities shall maintain confidential the information they access to during the inspections.

#### Initial interview

In the initial interview the inspector shall show his or her official identification and explain the type and scope of the inspection as well as the procedures that will be conducted therein.

The investigator's team members and the sponsor's agents may be present at the initial interview.

The inspectors shall request information (who, what, when, where, how) about the delegation of the following functions to the investigator's team members:

informed consent obtainment;

prospective participants assessment;

participants' selection and random assignment;

clinical data obtainment and evaluation;

clinical data forms filing out;

study drug reception, return and management.

The inspector may interview the investigator's team members and, if appropriate, participants at the beginning of or during the inspection.

#### Inspection conduct

The inspectors shall identify and review all the source documents and other documents essential for the study.

Likewise, the inspectors may inspect the facilities of the research center or those of the external institutions where study-related procedures are performed.

The handwritten or electronic notes taken by the inspectors during the inspection shall be filed in the inspection dossier at the agency and shall serve as a support for inspection report accuracy.

The inspectors shall request and take copies of the study records or investigational product samples, if they deem it appropriate.

The inspectors may interview the study participants, should they find it necessary. Such interviews shall be documented in records different from the inspection records. The interview records shall contain the participant's identification, the interview objective, the questions made and the answers provided by the participants. The interview records shall be filed in the inspection dossier at the agency and the investigators shall access them upon previous justified request to and express authorization by the agency.

The inspectors may interrupt the study and shall immediately communicate such decision to the DEO, if they were to identify serious deviations from the regulations or serious risks for the participants.

#### RECORD REVIEW PROCEDURES

The inspectors shall review the investigator's essential documents under Section C of the Regulatory Guideline herein.

The inspectors shall verify the recruit mechanisms in the medical record of each participant and the absence of duress and undue influence in the recruit.

The inspectors shall verify the following in the informed consent process:

that the consent obtainment process fulfills all the rules set forth herein;

that the informed consent used was approved by the REC and A.N.M.A.T.;

that all the informed consent forms were signed and dated by the participants or their legal representative and the investigator or authorized sub-investigator;

that the empowerment to represent the participant is documented in the medical record, had the informed consent been obtained from the participant's legal representative;

that a written assent was obtained in the case of persons under age and within the lower age limit determined by the REC;

that the informed consent was obtained by the investigator or sub-investigator authorized in the function delegation form; that the informed consent was obtained prior to evaluating the eligibility criteria or any other study specific procedure;

that the consent obtainment is documented in the participant's medical record, including the initiation date and time, that they were provided with time to reflect on and make questions, which the questions made were, that the participant's understanding of the information was verified and that two originals were signed and one of them was given to the participant;

that in the case of a participant being in a situation of cultural, educational, social or economic vulnerability, the consent was obtained in the presence and with the signature of an impartial witness and that the mechanism was documented in the participant's medical record.

The inspectors shall verify that the participants gave their consent to all the informed consent amendments and the latter had been approved by the REC and the agency at the time of using them and that all the process requirements were fulfilled.

The inspectors shall compare the protocol and amendments approved by the REC and the agency with the protocol filed by the investigator in relation to:

inclusion and exclusion criteria;

clinical data type and obtainment frequency;

treatment dose, frequency and route of administration;

randomized assignment and blinding procedures.

The inspectors shall review the source documents and verify the following:

that participants exist and that all the procedures under the protocol were performed to them;

that participants met the eligibility criteria at the time of their inclusion in the study;

that participants were administered the study treatments per the protocol;

that all SAE were notified to the sponsor;

that clinical data were obtained and notified correctly and completely.

According to the inspection plan set out, the inspectors shall verify:

the informed consents;

the serious adverse events and the serious and unexpected ADR;

the participants withdrawn from the study;

the eligibility and treatment evaluation criteria in a relevant sample;

if a major deviation is detected in a study procedure, for instance, errors in the treatment administration, that procedure shall be reviewed in a larger sample.

The inspector shall verify that participants receive for free the study products and procedures as well as the payments foreseen for them, by means of the payment receipts or invoicing to the investigator or the sponsor for study examinations.

The inspectors shall verify that the investigational and comparator products:

are labeled as per the Regulatory Guideline herein;

are stored under the room conditions set out by the sponsor;

are non-expired products and that the expired products are stored in a separate place or were returned to the sponsor;

were received at the center by authorized personnel;

are administered to participants according to the assignment set forth in the protocol;

are administered to participants in the doses, frequency, route of administration and duration established in the protocol;

unused, expired or not stored under the required conditions are returned to the sponsor or correctly destroyed, if appropriate.

The inspectors shall review the reception and distribution records of the investigational and comparator products to verify the following:

the products identity;

the products distribution circuit in relation to the date of reception, dispensation and return, identity, lot numbers, dates of expiration and quantities of the products;

the agreement between the accountability forms, the source documents and the clinical data recording forms.

## INSPECTION RECORD

Upon conclusion of the inspection, the inspectors shall write a record in which they shall document the type of review and its scope regarding the specific records reviewed, the observations and findings, and the problems solved and not solved during the inspection. If there were observations unanswered or not clarified, the

inspected party shall provide the pertaining answers or clarifications within a ten-working-day period after the inspection.

The inspection record shall be written in a clear and objective way; and the observations shall meet the requirements set forth in the Regulatory Guideline herein. The copies obtained of the investigator's records shall be attached to the inspection record as a proof of the observations made. The inspection record text shall make reference to the documents attached.

Three original inspection records shall be signed by the investigator and/or a sub-investigator, the inspectors and the sponsor's agent. An original record shall be given to the investigator and another one to the sponsor's agent while the third original record shall be retained by the inspectors and filed in the inspection dossier at A.N.M.A.T.

#### INSPECTION TECHNICAL REPORT

Once all the pending issues are dealt with, the inspectors shall write a final technical report of the inspection in print and digital format, including a clear and objective description of the inspection findings based on the inspection record.

The technical report shall document the observations made during the inspection and describe in detail the type and scope of the inspection and the answers provided by the parties during the inspection in an orderly manner.

The technical report shall conclude with a proposal of Inspection Result and of the measures deemed appropriate as per such Result.

The final technical report shall be submitted to the Director of the DEO, who will notify the inspected party of such report, if appropriate.

#### INSPECTION RESULT

The inspection result may be communicated to the inspected party during the inspection exit interview or by means of a summoning of the said party to the Drug Evaluation Office premises or by means of a notification that shall be given at A.N.M.A.T. reception desk.

The Inspection Results shall be as follows:

No Action Indicated (NAI): no objectionable conditions or practices were found during the inspection;

Voluntary Action Indicated (VAI): conditions or practices requiring corrective measures by the investigator or sponsor, but that do not require any action by A.N.M.A.T. were found during the inspection;

Official Action Indication (OAI): actions by A.N.M.A.T. are required.

In the event an OAI is required, the director of the Drug Evaluation Office shall be empowered to take the following preventive measures:

temporary suspension of the study recruitment at the center;

temporary suspension of the study inspected at the center;

restriction on the investigator to conduct new studies.

In the cases under 12.3., the investigator shall commit him or herself in writing before the director of the DEO to implement the corrective actions indicated to him or her.

After that, he or she will be allowed to re-initiate or initiate, as appropriate, the enrolment of up to three participants. A new inspection shall verify the compliance of the investigator's committee and enable him or her to continue or not the recruit and/or the conduct of the study.

In the event an OAI, the agency may adopt one or more of the following final measures, simultaneous or consecutively, after assessing the inspection technical report and the recommendation of the director of the DEO:

final suspension of the study recruit at the center;

final suspension of the study inspected at the center;

suspension of all the studies conducted at the center;

suspension at all the centers nationwide of the inspected study;

indication to the sponsor of monitoring intensification at the center;

indication to the sponsor of a change of investigator at the center;

indication to the sponsor to reject all the data generated at the center;

notification to the competent authority or professional association granting the investigator's professional licensure, as well as to the sanitary authority of the jurisdiction and the REC that approved the study:

administrative and/or legal sanction to the investigator, sponsor or CRO and prior initiation of the corresponding administrative inquest.

Noncompliance of the Regulatory Guideline herein, may give raise to the initiation of an administrative inquest, without the need to require additional information from the inspected party.

## SECTION E: GLOSSARY

**AUDIT:** a systematic and independent examination of the study related activities and documents to determine whether the activities evaluated were performed and the data were accurately recorded, analyzed and reported as per the protocol, SOP(s), GCP and A.N.M.A.T. Regulatory Guideline for GCP-CPS.

**AUTONOMY:** a person's self-determination capacity to make a decision voluntarily, as per only his or her own values, interests and preferences provided that he or she has the necessary information to assess all the options. By definition, an autonomous person is able to give his or her informed consent without needing any protection other than the assurance that all the necessary information is provided to him or her. In addition, those individuals having a diminished or inexistent autonomy are in a vulnerable situation, and, therefore, require special protections. A person's autonomy is considered diminished in case of cultural, educational, social or economic disadvantage, for example, in the case of ethnic minorities, refugees or illiterate, subdued, homeless or impoverished persons. For such cases, the additional protection is the presence of an impartial witness who assures that all the rights and interests of those persons are respected during the informed consent obtainment process. The absence of autonomy takes place when a person is legally or mentally incapable of giving his or her consent voluntarily. In said cases, the consent shall be obtained from his or her legal representative pursuant to the Argentine legislation in the matter.

**BIOAVAILABILITY:** the capacity of a pharmaceutical form of releasing an API in the site of action at the proper speed to obtain a sufficient concentration, and at the timely moment to enable it to exert its action. Since, generally, the concentration cannot be determined in bio-phase in human beings and assuming the existence of balance in the concentrations in serum and bio-phase, the fraction of a drug reaching the systemic circulation of the extravascularly administered dose of a given pharmaceutical form, shall be accepted as bioavailability.

**BIOEQUIVALENCE:** two drugs or medicinal products are biologically equivalent when, upon the existence of chemical equivalence, they have a similar bioavailability if administered to the same person in an equal dosage regimen.

**GOOD CLINICAL PRACTICE (GCP):** an international ethical and scientific quality standard for the design, conduct, recording and reporting of the trials involving the participation of human subjects. Compliance with this standard provides a public assurance that the participants' rights, safety and well-being are protected, in accordance with the Declaration of Helsinki; and that the trials data are reliable.

**GOOD MANUFACTURING PRACTICE (GMP):** a standard to assure a uniform manufacture that meets the requirements of product identity, activity and purity.

**GOOD LABORATORY PRACTICE (GLP):** a laboratory organization and activity related standard under which studies are planned, conducted, recorded, controlled and presented. It aims at assuring the quality and integrity of all the data produced during a given study as well as to tighten the study related safety.

**RESEARCH ETHICS COMMITTEE (REC):** a body acting within its competence scope, which is independent from the sponsor and investigator and is constituted by medical or scientific professionals and non-medical or non-scientific members and whose function is to provide public assurance of the protection of the rights, dignity, safety and

well-being of a study participants, by means of, among other things, the review of the study protocol, informed consent process and the investigator's suitability.

**INDEPENDENT DATA MONITORING COMMITTEE (IDMC):** an external board set up by the sponsor to evaluate, at set time intervals, a clinical study progress, safety data and critical points for efficacy assessment, in such a way that it may recommend the study continuation, modification or suspension.

**CONFLICT OF INTEREST:** a conflict of interest takes place when a professional primary interest such as the patients' well-being or the validity of a scientific research study may be affected by a secondary interest such as economic gain, professional prestige or personal rivalries.

**INFORMED CONSENT:** a process by means of which a person confirms his or her decision to participate in a human health research study, after having been informed of all its relevant aspects. The informed consent is documented by means of signing a specific form to such purpose.

**SOURCE DATA:** the information about clinical findings, observations or other activities, which is necessary for the reconstruction and evaluation of the clinical study. Said information is documented in original records or their copies certified by the person responsible for them, which are called source documents. The source data must be attributable, readable, accurate and contemporary.

**PERSONAL DATA:** information of any type related to certain or ascertainable physical persons or legal entities.

**ESSENTIAL DOCUMENTS:** documents that individually or collectively enable the evaluation of a study conduct and of the quality of the data produced thereby.

**SOURCE DOCUMENTS:** original documents and records of the clinical data used in a study, such as the medical records, laboratory or pharmacy records, imaging reports and images, participants' diaries, data recorded on automated instruments, magnetic devices or microfilm and photographic negatives. The certified exact copies of the above mentioned documents are included in this definition.

**INFORMED CONSENT AMENDMENT:** a written description of the formal changes or clarifications of the documents or consent form. The changes of expected benefits and risks envisaged for participants or that may affect their decision to continue with the study require approval by the REC and A.N.M.A.T.

**PROTOCOL AMENDMENT:** a document of changes or clarifications of a study protocol. The amendments may be: (a) substantial, when they describe changes in the design, population, procedures or investigational product and require approval by the REC and A.N.M.A.T.; or (b) unsubstantial or administrative when they reflect, for example, only changes of the contact data.

**CLINICAL STUDY:** a set of activities with the purpose of obtaining generalizable knowledge about human health to be applied in medicine, sciences of life and their related technologies. Clinical studies may be observational or experimental, according to whether the investigator intervenes or not in the variable under study.

**EXPERIMENTAL CLINICAL STUDY (synonym: clinical trial):** a study in which the investigator selects participants upon inclusion and exclusion criteria, actively intervenes on the independent or predicting variable and observes and analyzes the changes made in the dependent or outcome variable as a consequence of the

intervention. Controlled clinical trials entail the concept of hypotheses contrast with a null hypothesis. The interventions may encompass synthesis drugs, biological products, medical devices, surgical techniques, etc. Said studies are considered as of “major risk” to participants.

**CLINICAL PHARMACOLOGY STUDY:** a systematic scientific study conducted with drugs or biological products in volunteer, healthy or unhealthy human subjects, with the purpose of discovering or verifying their therapeutic effects and/or identifying adverse reactions and/or studying the absorption, distribution, metabolism (biotransformation) and excretion of their active principles in order to determine their efficacy and safety.

**PHASE I STUDY:** an initial introduction of a new drug researched in human subjects to determine its metabolism, pharmacological actions, secondary effects with increasing doses and, if possible, to obtain early evidence about its efficacy. It includes the study of variations among sub-populations and interactions with other drugs and the intake of food. These studies must justify the use of the product in Phase II. Typically, Phase I studies are closely monitored and may be conducted in volunteer healthy subjects or, occasionally, in patients.

**PHASE II STUDY:** the efficacy and safety of the dose ranges are determined in this phase. Likewise, the dose-response ratio is determined, whenever possible, in order to obtain a broad background for the design of widened therapeutic studies (Phase III).

**PHASE III STUDY:** a study conducted in large and varied groups of participants in order to determine both short-term and long-term risk-benefit balance of the proposed formulation(s) and the relative therapeutic value, in general.

**PHASE IV STUDY:** a study conducted after the drug and/or medicinal product is marketed in order to determine its therapeutic value, the appearance of new adverse reactions and/or the confirmation of the already known adverse reactions frequency as well as the treatment strategies.

**VACCINE CLINICAL STUDY:** a systematic and scientific study conducted in volunteer, healthy or unhealthy human subjects in order to determine the tolerance, safety, immunogenicity and/or efficacy of a vaccine. It has three phases: (a) Phase I: first study conducted in human beings to evaluate the tolerance, safety and biologic effects; (b) Phase II: a study determining the immunogenicity caused by a vaccine; and (c) Phase III: a controlled clinical study, with a high number of volunteer participants which aims to assess the effectiveness of a vaccine for the prevention of a disease and its safety in a more thorough way.

**MULTI-CENTER STUDY:** a clinical study conducted according to only one protocol but in more than one place or institution and, therefore, conducted by more than one investigator.

**ADVERSE EVENT (AE):** any adverse medical occurrence in a patient or subject of a clinical study of a health intended product or therapeutic procedure and which does not have a necessary causal relation with this treatment. An adverse event may be any unfavorable and unintended sign, including laboratory abnormal findings and symptoms or diseases temporally associated with the use of the investigational product, whether related or not with it.

**SERIOUS ADVERSE EVENT (SAE):** any unfavorable occurrence throughout and within the research of a diagnostic or therapeutic product or procedure that results in death, is life-threatening, requires in-patient hospitalization or prolongation of the

existent hospitalization, results in persistent or significant incapacity or disability or that is a congenital anomaly or a birth defect or that is medically significant as per medical criteria. The above mentioned is applicable without the need for an alleged causal relation existence between the product or treatment administered and the adverse event.

**CLINICAL DATA FORM (CDF):** a printed, digital or optical document designed to keep record of all the clinical data required as per protocol, about each participant of the study and that shall be reported to the sponsor.

**CONTROL GROUP:** a group used as a comparator that indicates what happens when the treatment under study is not applied.

**ACTIVE PHARMACEUTICAL INGREDIENT:** a natural, biological or synthetic chemical substance having a specific pharmacological effect and that is used in human medicine.

**INSPECTION:** an official review conducted by the competent authority of the documents, facilities, records and any resource considered as related to the clinical study and that may be located in the research center, sponsor's or contract research organization (CRO) facilities or in other sites deemed appropriate.

**INSPECTOR:** a person designated by the competent health and/or regulatory authority to conduct the study-related inspections.

**INSTITUTION OR RESEARCH CENTER:** any government or privately owned agency or medical or dental facility where clinical studies are conducted.

**INVESTIGATOR:** a professional responsible for conducting the clinical trial at the research center. If the trial is conducted by a team, the investigator is responsible for the team and is denominated the principal investigator. The principal investigator may delegate functions to his or her team, but not his or her responsibilities. The investigator-sponsor is the physical person initiating, managing financing and conducting, on his or her own or together with others, a clinical study, having under his or her responsibility the management, dispensation and use of the investigational product.

**INVESTIGATIONAL PRODUCT MONOGRAPH:** (Synonym: Investigator's brochure) a compilation of clinical and non-clinical data of drugs, investigational medical products or procedures relevant for their study in human beings.

**MONITORING:** action of overseeing the process of a clinical study and ensuring that it is conducted, recorded and reported in accordance with the protocol, SPO(s), GCP and applicable regulatory requirements.

**CONTRACT RESEARCH ORGANIZATION (CRO):** a physical person or legal entity contracted by the sponsor to perform one or more of his or her functions or activities related to the study.

**STUDY PARTICIPANT:** a healthy or unhealthy individual participating in a clinical pharmacology study as a research subject.

**SPONSOR:** a physical person or legal entity responsible for initiating, managing, controlling and financing a clinical study.

**PLACEBO:** a pharmacologically inert substance used as a substitute of the investigational product with the aim of acting as a comparator in a clinical

pharmacological study, as long as the ethical criteria of participant protection is respected.

**VULNERABLE POPULATION:** an individual or a group of individuals whose wish to participate in a clinical trial may be unduly influenced by the justified or unjustified expectation of the benefits associated with his or her participation (undue influence) or by the threat by the investigators or any other unequal relation in case the individual refuses to participate (duress).

**COMPARATOR PRODUCT:** a marketed or investigational product or a placebo used as a reference in a clinical study.

**INVESTIGATIONAL PRODUCT:** a pharmaceutical form of an active substance under investigation, including products holding a marketing authorization when used or combined in the formulation in a form other than the authorized one or for the treatment of an unauthorized indication.

**PROTOCOL:** a document describing the history, fundamentals, objectives, design, methodology ethical considerations, statistical aspects and organization of a study.

**ADVERSE DRUG REACTION (ADR):** an untoward and unintended response to a medicinal product at any dose. In clinical experience and before the approval of a new medicinal product or of its new uses, particularly, when the therapeutic dose cannot be determined, any reaction implying causal relation between a medicinal product and an adverse event as a reasonable possibility, that is to say, that the relation may not be ruled out, must be considered an adverse drug reaction.

**UNEXPECTED AND SERIOUS ADVERSE DRUG REACTION (UNEXPECTED SADR):** an adverse reaction that results in death, is life-threatening, requires in-patient hospitalization or prolongation of the existent hospitalization, results in persistent or significant incapacity or disability and whose nature of seriousness is not consistent with the product information written in the investigational product monograph or any other documentation.

**LEGAL REPRESENTATIVE:** a person authorized under the Argentine Civil Code or the applicable laws, who acts as the representative of a prospective participant in a clinical study to grant the informed consent to the study.

**IMPARTIAL WITNESS:** a person independent from the investigator and his or her team who participates in the informed consent obtainment process as an assurance that such process respects the rights and interests of a prospective participant who is vulnerable due to his or her cultural, educational, social or economic situation.