FEDERICO ALBERTO ARGÜELLES TELLO, Sanitary Authorization Commissioner of the Federal Commission for the Protection against Sanitary Risks, and in accordance with the provisions of articles 1, 2 section VII, 3 section IX, section XXII, 17 Bis, 24, 32, 46 , 47, 48, 51, 51 Bis 1, 51 Bis 2, 74, 74 Bis, 75, 77 Bis 1, 96, 97, 98, 99, 100 fractions I, III, IV, V and VI, 102 fraction V, 103, 166 Bis 3 fraction VI, 166 Bis 3, 166 Bis 11. 166 Bis 15, 166 Bis 16, 166 Bis 17, 166 Bis 18, 166 Bis 19, 166 Bis 20, 192 Quintus, 200 Bis, 323, 324, 326, 332, 333 section V, 350 Bis 3 and other applicable relatives of the General Health Law, 3, 11, 14, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31,32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58 section I, 63, 64, 70 section II, 71, 100 section III, 109, 113, 116, 119 and 120 and other applicable regulations of the General Law of Health in Matters of Research for Salt you, 14 sections I, II, III and XIV and other applicable relatives of the Regulation of the Federal Commission for the Protection against Sanitary Risks, and

CONSIDERING

That any clinical study in any research phase for the use of health supplies, procedures or experimental activities in human beings or biological samples of human beings, for its realization, must adhere to the provisions of the General Health Law, the Regulation of the General Law of Health in the Matter of Research for Health, in the guidelines of the *International Conference of Harmonization* for Good Clinical Practices (CH-E6-R1), and other applicable provisions, which must be duly reflected in the Research Protocol and other documents necessary for its authorization.

That any research, trial or clinical study, in any of its phases, for the use of health supplies, procedures or experimental activities in human beings or biological samples of human beings, for scientific research purposes, must have authorization from the Federal Commission for the Protection against Sanitary Risks (COFEPRIS).

That a clinical study is any investigation that involves human beings or biological samples derived from human beings, where it is intended to discover or verify the clinical, pharmacological and/or pharmacodynamic effects of an investigational product and/or medical devices, and/or to identify the adverse reactions of an investigational product, and/or the absorption, distribution, metabolism and excretion of an investigational product in order to establish its efficacy and safety. The term clinical trial or study and health research are considered synonymous.

That it is the power of COFEPRIS, within the scope of its competence, to monitor and verify authorized clinical studies, which must comply with scientific and ethical principles.
nationally and internationally accepted, such as the Nuremberg Code, the Declaration of

Helsinki, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Council for International Organizations of Medical Sciences *(CIOMS)* and the World Health Organization (WHO), the Guidelines for Good Practice Clinic, of the International Conference on Harmonization *(ICH)* among others, as well as in the Mexican Sanitary Legislation on Research for Health, such as: The General Law of Health, the Regulation of the General Law of Health in Health Research, the Official Mexican Standards on the matter and other provisions established by the Ministry of Health (SSA), where the guidelines and principles to which health research in Mexico must be submitted have been established.

That in all research in which the human being is the subject of research, the criterion of respect for their dignity, the protection of their rights and well-being should prevail over any other interests of science and society;

That the investigation must adhere to the principles of the Declaration of Helsinki in force, norms related to Human Rights, and other applicable national and international ethical principles;

That all those involved in the research such as: sponsors; Contract Research Organizations (OIC / or CRO for its acronym in English); researchers and collaborators; Research Ethics Committees or Biosafety Committees (CEI); manufacturers of investigational products; authors, editors and publishers, and others involved, must comply with national and international ethical standards and Good Clinical Practices (ICH-E6-R1).

That the sponsors, authors, editors and publishers must comply with the ethical obligations established in this regard, they will be obliged to publish the positive, negative and inconclusive results of the research or otherwise they must be available to the public, and they will be responsible for the integrity, truthfulness and accuracy of your postings. In addition, the sources of financing, affiliations, contracts or agreements with other institutions, and any conflict of interest must be established in the publication; For all the above, I have to issue the following:

GUIDELINES TO COMPLY WITH GOOD CLINICAL PRACTICES IN RESEARCH TO HEALTH

1. DEFINITIONS

Without prejudice to the provisions of the General Health Law and its Regulations, for the purposes of these Guidelines shall be understood as:

1.1 **Good Clinical Practices:** to the standards related to the design, conduct, monitoring, auditing, registration, analysis and reporting of data from a clinical trial in

human, which ensures that the data and results reported are true and accurate; and that the rights, integrity and confidentiality of the subjects are protected.

1.2 Research Center: any health care establishment belonging to the public, social or private sectors, whatever its name, that can carry out preventive, diagnostic, therapeutic, and rehabilitation activities, as well as third parties authorized to carry out studies of drug interchangeability, aimed at maintaining or reintegrating people's health status and carrying out training and development activities for health personnel, as well as research on human beings; are all those in which research is carried out on human beings and/or their products and that, in accordance with the General Health Law, Regulations and other applicable provisions, are required to have a Research Ethics Committee.

1.3 Research Ethics Committee: it is an autonomous, institutional, interdisciplinary, plural and advisory body to evaluate and rule on research protocols in human beings, whose objectives are; Contribute to safeguarding the dignity, rights, safety and well-being of all current and potential research participants; Act in the interest of research participants and the communities involved, taking into account national and international regulations on research ethics, and ensure that the benefits and burdens of research are distributed among groups and classes of research. society, taking into account age, gender, economic status, culture, and ethnic considerations.

1.4 Principal Investigator: the health professional who is responsible for conducting, coordinating, directing and supervising the execution of research for health in human beings and who has the appropriate academic training and experience to do so;

1.5 Contract Research Organization (OIC, or *CRO* for its acronym in English): that natural or legal person hired by a sponsor to whom one or more of the activities related to health research is transferred through a contract that is sponsored in the country. Responsibility for all activities remains with the sponsor;

1.6 Sponsor: to the natural or legal person who expresses himself in writing, to finance totally or partially a research project or protocol;

1.7 Research Product; to any pharmaceutical form containing an active ingredient or placebo, or product of biological or biotechnological origin, as well as the medical device that is used or tested in a clinical study, including a registered product when it is used or packaged in a different form with which was authorized, or when it is tested for indications that have not been authorized, or when it is used to obtain further information about its authorized use. Applies to new entities

chemical and biological, generic, new formulations, product combinations, biosimilars, medical devices with or without the release of any active ingredient;

1.8 Research Subject: the individual who grants his or her informed consent in writing, by himself or through his legal representative, so that certain procedures are performed on his person for research purposes for health in human beings;

1.9 Phases of clinical research: includes the sequence of studies that are carried out from the first administration of any input for human health until data are obtained on its efficacy and therapeutic safety until conclusive data on its efficacy and therapeutic safety; so referred to in the regulations.

2 RESEARCH ETHICS COMMITTEE

That Article 41 Bis of the General Health Law defines the "Research Ethics Committee" (CEI), as the body responsible for evaluating and ruling on research protocols involving human beings and biological samples from human beings, following the recommendations of an ethical nature that correspond, as well as to elaborate guidelines and institutional ethical guides for health research, having to follow up on their recommendations.

The main objective of the CEI is the review, evaluation and, where appropriate, approval of the research proposal and its supporting documentation, paying special attention to the feasibility of the study and with respect to the rights of the research subject, the research documents to be evaluated should include, but not be limited to: Research protocol; Informed Consent Letter; Investigator's Manual; Amendments to previously approved documentation; targeted advertising for recruitment; information directed to the research subject and other required documentation.

The following functions are the responsibility of the Research Ethics Committee; I. The review, evaluation and opinion of the Research Protocols that involve human beings and biological samples derived from human beings, II. Formulate and follow up on the ethical recommendations that correspond to the Research Protocols, III. Prepare guidelines and institutional ethical guides in the field of health research, attached to current regulatory provisions, IV. Advise researchers for optimal ethical performance of their protocols, V.
Present in the first thirty calendar days of the year, an annual report of activities to the owner or director of the Establishment, VI. Participate with other Committees, in the joint evaluation of research protocols when warranted, and VII. Assist in the application of the Law, the Regulations and the other applicable provisions regarding health research.

2.1 The CEI must function in accordance with the provisions of the General Health Law, the Regulations of the General Health Law on Research for Health (LGSMIS), the Regulations of the General Health Law on the Provision of Services of Medical Attention (RLGSMPSAM), the Provisions, Guidelines and Guides issued by the National Bioethics Commission (CNB), what is established in the Good Clinical Practices (ICH-E6-R1), and other applicable provisions;

2.2 The CEI must register with COFEPRIS, through the procedure called COFEPRIS-05-038 “Registration of Research, Ethics and Biosafety Commissions having previously completed the self-assessment process before the CNB;

2.3 The CEI must at all times avoid any conflict of interest in the evaluation of all information related to health research, for which they must implement a procedure for filling out, signing and keeping the "Form of no conflict of interest", of all the participants in the CEI session, in addition, in the event that any member declares a potential conflict of interest, they must refrain from participating in the analysis and evaluation of the information, which must be recorded in the minutes of the corresponding session, as as established by the “National Guide for the Integration and Operation of Research Ethics Committees”, issued by the CNB;

2.4 The CEI must establish and implement a "general policy on the confidentiality of the information" that they receive and evaluate, for the members of the Committee, as established in the "National Guide for the Integration and Operation of Ethics Committees in Research”, issued by the CNB;

2.5 The REC must establish and implement a “code of conduct” for the members of the Committee;

2.6 The CEI must establish and implement its “Operating Procedures Manual”, where each and every one of the activities carried out by the CEI is established, as well as an updated list of the members that make up said CEI; these procedures as well as the list of members must be sent to the CNB, and may be requested by the researcher, the sponsor and/or the regulatory authorities;

2.7 The operating expenses of the Committee must be financed by the Establishment, without this implying a conflict of interest in the functions of the Committee.

3 PRINCIPAL INVESTIGATOR

3.1 The main investigator has the obligation to know and apply what is established in the regulations and in the Good Clinical Practices (ICH-E6-R1) before, during and after conducting the investigation, and all his activities will be based on the standards national and international ethics, always taking care of the health and integrity of the research subject, including the confidentiality of the research project as well as adherence to the clinical protocol;

3.2 It is the duty of the principal investigator to protect the life, dignity, integrity, right, privacy, provide medical assistance, and safeguard the health of the subjects who participate in the proposed investigations, applying their knowledge and ethics to fulfill this duty over any other interest. ;

3.3 The investigator must keep any agreement, contract, or record that stipulates the responsibilities, attributions, and functions of all those involved in the investigation, in accordance with the provisions of the Good Clinical Practices (ICH-E6-R1)

3.4 The principal investigator is responsible for keeping track of the reception, storage, distribution, administration, destruction or return of the product under investigation and other supplies required for the investigation in accordance with the provisions of the investigation protocol;

3.5 The principal investigator has the responsibility to report and guarantee the quality and validity of the data obtained during the investigation.

3.6 The principal investigator is responsible for reporting any adverse event arising from the investigation in accordance with the provisions of NOM-220-SSA1-2002, "Installation and operation of pharmacovigilance" and other applicable provisions;

3.7 The principal investigator is responsible for preparing, integrating, using, archiving and ensuring the safeguarding of the clinical file of the subject under investigation in accordance with the provisions of NOM-168-SSA1-1998, "Clinical File", as well as in Good Clinical Practices (ICH-E6-R1) and Good Documentation Practices (BPD); Thus, the minimum storage time indicated by NOM-168-SSA1-1998, “Clinical File”, which is 5 years, will be understood.

3.8 The principal investigator is responsible for selecting his work team who must have the knowledge, education and training in Good Clinical Practices (ICH-E6-R1) and in the investigation process in which each individual is involved;

3.9 The principal investigator is responsible for customizing the informed consent form provided by the sponsor or preparing it, as well as for conducting the process of obtaining informed consent or, where appropriate, for delegating it to staff of his or her team trained to carry out this activity and registered for this purpose;

3.10 The main investigator is responsible for providing the research subject with contact information (24-hour phone number, email, contact name) for emergency cases and, in cases where it is warranted, requesting the breaking of the blind to the sponsor (if necessary). You must provide contact information for the sponsor, 24-hour telephone, email, contact name) by a treating physician other than the principal investigator;

3.11 The principal investigator must notify the Secretariat of the recruitment status of the subjects, indicating at least the date of recruitment of the first subject, as well as semi-annual reports on the recruitment status.

4 SPONSOR

4.1 The sponsor or, as the case may be, the OIC/CRO, has the obligation to know and apply what is established in the Good Clinical Practices (ICH-E6-R1);

4.2 In case of delegating the activities related to the investigation to a third party (OIC/CRO or other), the sponsor must establish in writing each and every one of the activities delegated; being at all times the absolute responsible for all activities;

4.3 The sponsor is responsible for ensuring that the manufacturing of the product under investigation and other supplies required for the investigation comply with the provisions of the Good Manufacturing Practices, in NOM-059-SSA1-1993, "Good manufacturing practices for manufacturing establishments". the chemical-pharmaceutical industry dedicated to the manufacture of medicines", in NOM-164-SSA1-1998, "Good manufacturing practices for drugs", and other applicable regulations, in NOM-073-SSA1-2005, "Stability of drugs and medicines", and other applicable regulations; as well as international guidelines for the cases in which it applies;

4.4 The sponsor is responsible for establishing the labeling of the product under investigation, considering what is established in NOM-072-SSA1-1993, "Labeling of medicines", when applicable, or if applicable, the labeling must contain at least the following information:

- Protocol identification number;
- Company name and address of the manufacturer;
- Batch number, identification code, pharmaceutical form;
- Expiration date;
- Storage conditions;
- The following legends: "Forbidden for sale", "Use permitted only for research", "Keep out of the reach of children";
- Language in Spanish;
- Warning symbols or pictograms apply.

4.5 The sponsor and/or the OIC/CRO, where appropriate, is responsible for selecting each research center, ensuring that it has:

- The authorization for its operation by COFEPRIS.
- Human and material resources (areas, equipment, etc.) necessary for the investigation;
- Resources and area for emergency care, or, if applicable, a written agreement with the health institution that will attend the emergency, which must comply with the provisions of the

NOM-206-SSA1-2002, “Regulation of health services”. That establishes the criteria for operation and care in the emergency services of medical care establishments;

- Restricted and protected storage area for the product under investigation and other supplies required for the investigation, with adequate controls of temperature, humidity, and other conditions according to what is established by the manufacturer;
- Clinical analysis laboratory where the biological samples derived from the investigation will be analyzed, whether national or foreign, where the biological samples will be analyzed. The laboratory must comply with the provisions of the Good Clinical Laboratory Practices, in NOM-166-SSA1-1997 "For the organization and operation of clinical laboratories", and in other applicable legal regulations; as well as international guidelines for the cases in which it applies;

- Research Ethics Committee, which will evaluate, approve and monitor the research; The CEI must comply with the provisions of section 2.0 of this document;

4.6 The sponsor must establish Standard Operating Procedures (SOP) or Standard Operating Procedure (SOP), in writing for each stage of the investigation;

4.7 The sponsor must establish in writing each of the functions, responsibilities as well as such as the financial agreement with the Principal Investigator;

4.8 The sponsor must ensure the timely delivery, in good condition and free of charge, of each and every one of the treatments, procedures, clinical tests, and other procedures related to the study, to the research subject;

4.9 The sponsor must ensure and control the quality of the research, in such a way that it follows up on compliance with the research protocol and the previously established PNO's or POE's, through periodic monitoring visits and audits, and where appropriate compliance with the reports derived from inspections or verifications by the Regulatory Authority;

4.10 The sponsor or, as the case may be, an OIC/CRO is responsible for continuous monitoring of the study, which must be established based on its nature;

4.11 The sponsor or, as the case may be, an OIC/CRO must ensure that the monitoring of the study is carried out in accordance with the guidelines established in the Good Clinical Practices (ICH E6-R1);

4.12 The sponsor will be responsible for supplying only the amount of supplies necessary to carry out the study, ensuring that none of these will be commercialized or used for purposes other than research;

4.13 The sponsor or, as the case may be, an OIC/CRO must establish the declaration of financing, sponsorship, affiliations, contracts or agreements with other institutions involved, management of any conflict of interest, incentives, amount and payments for the subjects;

4.14 The sponsor must establish a financial fund or have insurance that covers serious adverse events derived from the medication or procedures of the research study.

4.15 The OIC/CRO of foreign origin must have an established domicile in Mexico and the authorization or notice according to the activities they carry out in the country.

5 HEALTH SURVEILLANCE

These Guidelines will be subject to sanitary surveillance by the Federal Commission for the Protection against Sanitary Risks.

TRANSIENT

FIRST. These guidelines will enter into force the day after their publication on the COFEPRIS website.

SECOND. These guidelines are subject to modification or addition through the Sanitary Authorization Commissioner.

Mexico City, on the thirty-first day of May, two thousand and twelve.- **The Sanitary Authorization Commissioner of the Federal Commission for the Protection against Sanitary Risks, Dr. Federico Alberto Argüelles Tello.**