

## NATIONAL HEALTH COUNCIL

### RESOLUTION Nº 251, DATED 7 AUGUST 1997

Plenary of the National Health Council in its 15<sup>th</sup> Special Meeting, held on 5 August 1997, in the exercise of its competencies, as set forth in its by-laws, and the attributions in Law 8.080 and Law 8.142, respectively dated 19 September 1990 and 28 December 1990, Resolves:

To approve the following norms of research involving human beings in the thematic area of research with new pharmaceutical products, medicines, vaccines, and diagnostic tests:

#### I - PREAMBLE

**I.1** – This Resolution incorporates all provisions contained in Resolution 196/96 of the National Health Council on Guidelines and Norms Regulating Research Involving Human Beings, which this Resolution complements in the specific thematic area of research with new pharmaceutical products, medicines, vaccines, and diagnostic tests.

**I.2** – It also refers to the Resolution on the Common Market Group (GMC) Nº 129/96, signed by Brazil, which establishes the technical regulations for ascertaining [the implementation of] good practices in clinical research.

**I.3** – The norms, resolutions and regulations issued by the Health Surveillance Secretariat of the Ministry of Health (SVS/MS) should be fully complied with, and SVS/MS authorization is required to execute and subsequently follow up and control the technical development of research projects in [the area of] Clinical Pharmacology (Phases I, II, III, and IV of products not yet registered in the country) and Bioavailability and Bioequivalence. Research projects in this area should comply with the provisions of Law 6.360 (23 September 1976), regulated by Decree Nº 79.094 (5 January 1977).

**I.4** – In any clinical essay and particularly when there are conflicts of interests associated with new products, the dignity and well-being of the research subject must prevail over any other interests, whether economic, scientific, or of the community.

**I.5** – It is essential that all research in this thematic area be founded on recognized scientific norms and on knowledge based on *in vitro* laboratory experiments and pertinent literature.

**I.6** – It is necessary that the investigation of new products be justified and that such products actually result in significant progress when compared with existing products.

#### II - TERMS AND DEFINITIONS

**II.1** – Research of new pharmaceutical products, medicines, vaccines or diagnostic tests. It refers to Phase I, II or III research with these types of products or with products not yet registered in the country, even in Phase IV, when the research focuses on their use with modalities, indications, dosages, or paths of administration different from those established at the time registration was authorized, including their use in combinations, as well as bioavailability and bioequivalence studies.

**II.2** – The terms listed below, which are part of the Common Market Group Resolution (GMC Nº 129/96), are hereby incorporated into this Resolution.

#### **a – Phase I**

It is the first study with human beings, in small groups of usually healthy volunteers, of a new active principle or a new formulation, usually investigated using human volunteers. The purpose of such research is to establish a preliminary notion of the safety and pharmacokinetic profile, and, if possible, the pharmacodynamics profile [of the product].

#### **b – Phase II**

(Pilot-Scale Therapeutic Study)

The objectives of the Pilot-Scale Therapeutic Study are to demonstrate the activity [of the product] and to ascertain the short-term safety of the active principle in patients affected by a given disease or pathological condition. The research is carried out on a limited (small) number of individuals and is frequently followed by an administration study. It should also be possible to establish the dose/response ratio for the purpose of obtaining sound background for the description of the extended therapeutic studies (Phase III).

#### **c – Phase III**

Extended Therapeutic Study

These studies are performed on a large and varied number of patients, for the purpose of determining:

- the result of short-term and long-term risks/benefits of the active principle formulations and
- in a global (general) manner, the relative therapeutic value.

In this phase, the type and profile of the most frequent adverse reactions are studied, as well as the especial characteristics of the medication and/or therapeutic specialty, for example, clinically relevant interactions, main factors that modify the effect, such as age, etc.

#### **d – Phase IV**

This is research performed when the product and/or therapeutic specialty is commercially available.

This research is based on the characteristics under which the medicine and/or therapeutic specialty was authorized. These are usually post-commercialization surveillance studies that aim at establishing the therapeutic value, [verifying] the emergence of new adverse reactions and/or confirming the frequency of known adverse reactions, as well as the treatment strategies.

The same ethical and scientific norms applied in the research in the previous phases should be used in Phase IV research.

Once a medicine and/or therapeutic specialty is already commercially available, the clinical research performed to explore new indications, new methods of administration, or new combinations (associations), etc. shall be considered research of a new medicine and/or therapeutic specialty.

#### **e – Pharmacokinetics**

As a rule, it is all the modifications a biological system causes on an active principle.

In operational terms, it is the study of kinetics (quantitative relation between the independent variable 'time' and the dependent variable 'concentration') of the absorption, distribution, biotransformation, and excretion of medicines (active principle and/or its metabolites).

#### **f – Pharmacodynamics**

It is all the modifications an active principle causes in a biological system. From a practical standpoint, it is the study of the biochemical and physiological effects of medicines and their action mechanisms.

#### **g – Margin of Safety**

It is the pharmacodynamics indicator that expresses the difference between the toxic dose (for example, the DL 50) and the effective dose (for example, the DE 50).

#### **h – Therapeutic Margin**

It is the ratio of the maximum tolerated dose, also toxic dose, to the therapeutic dose (toxic dose/therapeutic dose). In clinical pharmacology, the therapeutic margin is used as equivalent of the Therapeutic Indicator.

### **III – RESPONSIBILITY OF THE RESEARCHER**

**III.1** – The unremittable and untransferable responsibility of the researcher to [comply with] the terms of Resolution 196/96 is hereby reaffirmed. All obligations provided for in said Resolution are equally reaffirmed, particularly the guarantee of conditions [required] to care for research subjects.

**III.2** – The researcher shall be responsible for:

**a** – submitting a complete research project to the Research Ethics Committee (CEP), in the terms of Resolution 196/96 and this Resolution;

**b** – maintaining a file for each research subject, for a period of five years, after the end of the research, due compliance being given to the confidentiality and secrecy of the records;

**c** – submitting a detailed report as requested or established by the CEP, the National Research Ethics Committee (CONEP), or the Health Surveillance Secretariat (SVS/MS);

**d** – informing the CEP of any occurrence of collateral effects and/or unexpected adverse reactions;

**e** – communicating also any proposed changes in the project and/or justification of interruptions, keeping in abeyance until the matter is appreciated by the CEP, except in urgent cases to safeguard the safety of research subjects; in the latter case, the CEP should be notified immediately afterwards;

**f** – making available to CEP, CONEP and the SVS/MS all duly required information;

**g** – continuously analyzing the findings, throughout the research, for the purpose of detecting, as soon as possible, the advantages of one treatment over another or preventing adverse effects on research subjects;

**h** – submitting regular reports within the time periods established by the CEP, with at least one report every six months and one final report;

**i** – providing the patient's physician and the patient him/herself access to the results of tests and treatment whenever requested and/or indicated; and

**j** – recommending that no individual be selected as research subject before a year has passed from his/her participation in another research, unless that individual were to directly benefit from it.

#### **IV – RESEARCH PROTOCOL**

**IV.1** – The protocol must include all items stipulated in Chapter VI of Resolution 196/96, in addition to the basic pharmacological information appropriate to the phase of the research project, in compliance with Res. GMC 129/96 - Mercosul – including the following.

**a** – Specifications and rationale of the clinical research phase in which the study is to be carried out, demonstrating that prior phases have been concluded.

**b** – Description of the pharmacological substance or product being investigated, including its chemical formula and/or structure, in addition to a brief summary of relevant physical, chemical and pharmaceutical properties. Any structural similarity to other known chemical compounds should also be mentioned.

**c** – Detailed preclinical information is required to justify the phase of the project, including a report on the experimental studies (materials and methods, animals used, laboratory tests, pharmacodynamics data, margin of safety, therapeutic margin, pharmacokinetics, and toxicology, in the case of drugs, medicines, or vaccines). The preclinical results must be accompanied by a discussion of the relevance of the findings in connection with the expected therapeutic effects and possible undesirable effects in human beings.

**d** – The preclinical toxicology data should include the study of acute toxicology, subacute toxicology with repeated doses and chronic toxicity (repeated doses).

**e** – The toxicology studies should be performed in at least three animal species, one of which must be a non-rodent mammal; both sexes must be included in the studies.

**f** – In studying acute toxicity, two paths of administration must be used, one of which must be related to that recommended for the therapeutic use being proposed and the other must be a path that will ensure the absorption of the pharmaceutical product.

**g** – In subacute toxicity, repeated dose and chronic toxicity studies the path of administration should be related to the proposed therapeutic use and the experiment should last at least 24 weeks.

**h** – In the preclinical phase, the toxicity studies should also include an analysis of the effects on fertility, embryo-toxicity, mutagenicity, oncogenic (carcinogenic) potential, and other studies, according to the nature of the pharmaceutical product and the therapeutic proposal.

**i** – Depending on the importance of the project, in view of the lack of time and in the absence of other therapeutic methods, the CEP may approve projects that have not fulfilled all clinical pharmacology phases; in this case, approval must also be obtained from CONEP and the SVS/MS.

**j** – Information about the status of the research and product registration in the country of origin.

**k** – The detailed clinical information obtained during the prior phases, as regards safety, pharmacodynamics, effectiveness, and dose-response observed in studies using human beings, whether healthy volunteers or patients. If possible, there should be a separate summary of each study, with a description of the objectives, design, method, results (safety and effectiveness), and conclusions. In the case of a large number of studies, the summary must encompass groups by phase, in order to facilitate a discussion of the results and their implications.

**l** – Justification for the use of a placebo and possible suspension of treatment (washout).

**m** – Access to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter, if there is no sponsor, in the event its superiority to the conventional treatment is proven.

**n** – In multiple center studies the researcher must, to the extent possible, participate in the design of the project. If this is not possible, the researcher must formally state that he/she agrees with the existing design and that he/she will follow it.

**o** – The sponsor must provide the researcher all data about the pharmaceutical product.

**p** – Funding must not be tied to the *per capita* payment of the subjects effectively recruited.

**q** – The protocol must be accompanied by the terms of consent. In the case of subjects not fully capable of self-determination, in addition to the consent from the individual legally responsible for the proposed research subject, it is necessary to take into account the expressed wishes of the proposed research subject, even when not fully capable (for example, the elderly) or not fully developed (for example, children).

**r** – In the case of research on psychiatric patients, whenever possible consent should be obtained from the patient him/herself. It is mandatory that the level of capability to express free and informed consent of each psychiatric patient be established by a psychiatrist other than the researcher involved in the project.

In the case of drugs with psychopharmacological action, a critical analysis must be made of the possible risks of causing dependency.

**IV.2** – Including healthy subjects in research.

**a** – Justifying the need to include healthy subject in the research project. Critical analysis of the risks involved.

**b** – Description of how the recruitment will take place; no dependency situation should exist.

**c** – In the case of drugs with psychopharmacological action, a critical analysis of the risk of causing dependency is necessary.

## **V – ATTRIBUTIONS OF THE CEP**

**V.1** – The CEP and the researcher will be jointly responsible for maintaining ethically correct conducts throughout the project and during the implementation of the research. In addition, they should take the following actions.

**a** – Issue a consolidated report explaining the scientific basis of the research project and its relation with the studies in prior phases, including the preclinical phase, with emphasis on safety, toxicity, adverse reactions or effects, effectiveness, and results.

**b** – Approve the justification of the use of a placebo and washout.

**c** – Request partial and final reports from the main researcher establishing the schedule (on a six-monthly basis at least) according to the characteristics of the research. Copies of the reports must be forwarded to the SVS/MS.

**d** – If announcements in the media are to be used to recruit research subjects, such advertising must be authorized by the CEP. No indication may be given, whether implicitly or explicitly, that the product being investigated is effective and/or safe, or that it is equivalent to or better than other existing products.

**e** – Convene the research subjects for follow up and evaluation.

**f** – Require that the top management of the institution start an inquiry, suspend or interrupt the research and communicate the fact to CONEP and the SVS/MS.

**g** – Any infringement of ethical principles or evidence of fraud of any nature should lead the CEP to request the creation of an Inquiry Committee and to communicate the results[of such inquiry] to CONEP, SVS/MS and other agencies (top management of the Institution, pertinent Regional Councils).

**h** – Communicate the occurrence of serious adverse events to CONEP and the SVS/MS.

**i** – Communicate to the Institution the occurrence or existence of administrative responsibility problems that may interfere with the ethical conduction of the research; report to CONEP and the SVS/MS immediately and, as the case may be, to the Regional Councils.

**V.2** – The National Health Council hereby delegates to the CEP authority to approve, from the point of view of ethics, research projects involving new pharmaceutical products, medicines and diagnostic tests, with the provision that the following documents be submitted to CONEP and the SVS/MS:

**a** – a copy of the consolidated report approving the research project, together with a completed header page,

**b** – official conclusion on the partial and final reports on the research and

**c** – other documents required by CEP, CONEP or the SVS.

**V.3** – In research that includes patients submitted to emergency or urgency situations, the CEP must previously approve the conditions or limits for obtaining free and informed consent; in addition, the researcher must inform the research subject, on a timely basis, about his/her participation in the project.

**V.4** – Assess whether all adequate measures are being implemented in the case of research with human beings whose capability for self-determination is impaired or limited.

## **VI - OPERATIONALIZATION**

**VI.1** - CONEP will exercise its competencies in the terms of Resolution 196/96, with emphasis on the following activities:

**a** – organizing an information and follow up system (item VIII.9.g of Resolution 196/96) on the basis of the data supplied by the CEPs (consolidated approval report, duly completed header page, partial and final reports, etc.);

**b** – organizing a system to evaluate and follow up the activities of the CEPs. The system should enable peers, i.e. members of the various CEPs, to exchange information and experience, with reports to CONEP. It should also comply with the specific regulations issued by CONEP;

**c** – informing the appropriate authorities, particularly the Health Surveillance Secretariat of the Ministry of Health, with a view to appropriate action, proven violations of the ethical standards in the execution of research projects; and

**d** – supplying the various bodies of the Ministry of Health, particularly the Health Surveillance Secretariat, the information required to fully exercise their respective competencies as regards the research covered in this Resolution.

**VI.2** – The Health Surveillance Secretariat/MS shall exercise its attributions in the terms of Resolution 196/96, with especial emphasis on the following activities.

**a** – Reporting, in writing, to CONEP any indication of violation of ethics observed or detected during the execution of the research projects covered in this Resolution.

**b** – Supply, upon request or when pertinent, the information required for the full exercise of the competencies of CONEP.

**c** – In the case of research involving situations for which there is no recognized treatment (“humanitarian use” or “compassionately”), the release of the product may be authorized as an emergency measure, after CEP approval and ratification by CONEP and the SVS/MS.

**d** – Standardizing its internal operational procedures with a view to exerting effective health control of the products object of clinical research.

**CARLOS CÉSAR S. DE ALBUQUERQUE**  
President of the National Health Council

I hereby ratify CNS Resolution Nº 251, dated 7 August 1997, in the terms of the Decree on the Delegation of Competency dated 12 November 1991.

**CARLOS CÉSAR S. DE ALBUQUERQUE**  
Minister of Health of Brazil