CONSELHO NACIONAL DE ÉTICA PARA AS CIÊNCIAS DA VIDA
Presidência do Conselho de Ministros

OPINION ON

THE CLINICAL EVALUATION OF DRUGS

(4 / CNE / 93)

I - INTRODUCTION

1) Over the centuries, Medicine developed from a purely empirical activity, gathering observations, through successive trial and error, until it gradually, and with the aid of other fields of knowledge, achieved the status of a science, without ever losing its attributes of the humanities. The status of science implies an experimental knowledge with special required standards, since it centres on the human being, which is endowed with a dignity and a status of its own.

The clinical evaluation of new drugs, therefore, belongs to the vast field of direct research into life and the individual. This field of science also includes the chemical means used in radiological or radiochemical diagnosis and the specific medical devices, which include the mechanical means used in invasive diagnosis and in the treatment of many diseases, ensuring the substitution of tissues, structures and organs. At a more restricted level, the new drug study has the purpose of using defined chemical substances in the treatment of pathological situations, whether new compounds or new applications for already known substances.

2) Some of the problems arising in the field of clinical trials originate in the fact that these are placed in the confluence of fundamental principles resulting from human rights and a variety of technical aspects resulting from the need to obtain concrete results, scientifically proved, on a solid experimental basis, so that they can be applied to a greater number of patients.

3) The present opinion answers only to the governmental request made by the Minister of Health and focuses on two successive draft Statutes regarding CLINICAL TRIALS. This council deliberately does not assess, not considering it within its powers, aspects of a legislative nature and/or of a technical-juridical character. Therefore any reference to the draft Statute itself aims only to focus on the ethical aspects. Besides, we are conscious that the problems arising from the research in human beings are broader and would surpass the scope of the draft Statute.

4) The current new drug research is a highly complex, time consuming and expensive process. Therefore only large companies, almost all of them multinational, have the necessary human, technical and financial resources to carry them out. And this may not be without ethical problems, namely in what concerns competition and the search for immediate profit.

5) New drugs created in Universities or in other institutions where the purpose of research is non-profit making are exceptions.

6) One of the consequences of this situation is the appearance of "orphan diseases", for which there are no studies, or only rarely, on new drug therapies, either because of their rarity or because they do not create profit to compensate for the investment in the research. In view of the principle of solidarity with which the State has been entrusted, society should promote and support such research, and this has also a clear ethical aspect. On the other hand, some "orphan drugs" are known to be useful in the treatment of rare diseases and have been discovered by chance or sought after for reasons of prestige.

7) Developments in knowledge also brought about the production of drugs with the use of the new techniques created by genetic engineering, leading to the production of compounds identical to those synthesised in the human organism, such as insulin, erythropoietin, the antihemophilic factor, interferon, etc. These compounds create problems mainly in pre-clinical trials, since they are frequently specific and provoke allergic responses in laboratory animals. Nevertheless, they are identical to human compounds and do not give rise to any objections from a general ethical point of view, although they are subject to clinical study, just as happens with other products.

8) In this report, we analyse, in the following order:

The Scientific Aspects

The Ethical Aspects and their relationship with the draft Decree-Law 199/93

The General Aspects regarding the same draft Decree-Law.

II - SCIENTIFIC ASPECTS

1) The clinical evaluation of new drugs is only one aspect of research on human beings, along with other studies, such as new invasive diagnosis techniques or new surgery techniques, including the use of mechanical or biological means in the treatment of lesions or in the substitution of structures or organs. Apart from its specificity, the new drug study *in anima nobile* is of particular relevance due to its frequency and context in which it develops.

2) In order to place the clinical evaluation of new drugs, or of new applications for already known drugs, in its proper perspective, it is important to first present, in summary, the process by which drugs are discovered and developed.

Over time, pharmaceutics developed from the isolation of active principles extracted from plants traditionally used for therapeutic purposes, and, later, from the knowledge of their chemical structures, through the systematic search for biologically active molecules endowed with possible advantages or minor inconveniences, when compared to those produced by nature. In some cases, drugs have also been the product of findings that were either the result of mere chance or of astuteness on the part of the researcher while observing some unusual effect or some unexpected fact.

3) From the discovery of a new compound that, due to its chemical structure or for some other reason, is considered to have potential therapeutic application, a long process of research begins. This currently well defined and coded process is intended to evaluate two types of characteristics in the compound: its efficacy, depending on its pharmacodynamical properties, its safety, in regard to its toxicity, and the resulting benefits. These may be either absolute, in regard to the disease, or relative, when compared to other drugs already existing or applicable.

Today, one of the most relevant aspects in drug policy is the cost/benefit relation, which is more and more important as the new compounds are being the object of greater demands on efficacy and safety, with a natural increase in the research involved, and, at the same time, there is a gradual decrease in health's available resources, in its curative aspect.

Thus laboratory studies are carried out, involving research as diverse as trials in isolated cells, in isolated organs, in anaesthetised or conscious living animals and in enzymatic systems *in vitro*, with the purpose of analysing possible changes in the various organs and systems of the

organism. These changes are evaluated through the quantitative and qualitative study of innumerable biological parameters.

If the compound should compare favourably to others already known and endowed with some analogous properties, it goes on to the next phase, which is the study of its toxic effects on animals, not only in what concerns immediate effects but also in what concerns changes resulting from its prolonged administration in high doses, including the risk of provoking neoplasia. Possible disturbances in the reproductive process are also studied, both in regard to the fertility of animals and to the possibility of the compound inducing malformations in the fetus.

Once this basic information has been acquired, and if the compound should pass the successive eliminatory tests, it is studied in biological models as similar as possible to human diseases from which there is potential improvement or cure through the spectrum of actions evidenced by the substance. Throughout this research process, various animal species are used so that interspecific differences can be evaluated and the consequent extrapolation of animal data to the human being can be facilitated.

This preclinical study of a new compound goes on for some years, usually between five and ten.

4) The clinical study begins only after the compound's spectrum of activity and relative innocuousness have been well demonstrated.

5) This study has three fundamental purposes:

First, to verify if the same type of responses already known from the experiments with laboratory animals are observed in the human being.

If the effects are similar, the trials may continue. Should any unexpected but potentially advantageous response arise, it becomes necessary to further the observations in animals, possibly involving new experimental models.

The second purpose is to verify if the pharmacological effects indeed lead to an effective therapeutic applicability, which implies an evaluation of the organism's tolerance for the compound, of the necessary doses and of the compound’s behaviour within the organism.

The third purpose is to demonstrate that the compound is safe enough to be currently applied to humans. Safety is always evaluated in relation to potential benefits. Thus drugs designed to be used in current and less serious situations must be proportionally more innocuous than drugs designed to treat more serious diseases.

6) Clinical trials are traditionally undertaken in four phases that gradually succeed each other, in particular without a clearly marked transition between Phases III and IV.

7) In Phase I, the substance is administered to a small number of individuals, usually healthy volunteers. In the beginning, the doses are quite small, the results from the research on laboratory animals serving as a reference. They are gradually increased in order not only to determine the relationship between the observed effects and the administered doses but also to establish the adequate dosage.

These trials are designed to study the induced effects, as well as the behaviour of the substance within the organism, the relationship between the administered dose and the concentrations in the blood, the development of these concentrations during a period of time, the mechanisms of the compound’s biotransformation within the organism and the routes through which the substance and its metabolites are eliminated.

The detection of these biotransformation or degradation products is very important and, sometimes, it becomes necessary to try them out on laboratory animals, for they may still be biologically active or toxic.

It is also of great importance to know the routes of elimination of the drug, for it may condition the use of this substance with certain types of patients.

These trials generally take from 9 to 24 months.

One of the problems that occur in this first phase of administration to humans of substances recently discovered, though already extensively studied in animals, has to do with the fact that the subjects are healthy volunteers. Although an extreme example, this is especially the case in potentially dangerous substances, such as anti-neoplastics, or in substances designed to treat clinical situations in which the disease induces considerable changes in the normal functioning of the organism and may lead to responses quantitatively different from those observed in a healthy individual.

The use of healthy volunteers is not universally accepted. Therefore some prefer to study the compound in patients that may immediately benefit from the administration of the new substance.

8) Trials in Phase II consist of the administration of the compound under study to small groups of patients carefully selected and under tight surveillance.

This phase is designed to determine the compound's eventual therapeutic effect in this specific situation, its pharmacological profile and the optimum dosage, as well as to gather information on the substance's biotransformation and elimination mechanisms in this particular type of patient and to track down any abnormal or undesirable effects that may have not been detected in healthy individuals but may appear more frequently or intensively in patients. These trials may be regarded as pilot trials. They are frequently designated open-ended and do not include comparison with placebos or with other already known drugs.

These trials take from 12 to 24 months and, should they not lead to the exclusion of the compound, they continue almost imperceptibly throughout Phase III.

9) Trials in Phase III are extended to a larger number of patients, allowing for the verification of the drug's efficacy under conditions of current practice, as well as for the detection of rarer, abnormal or undesirable effects, which can only be observed in larger groups of people.

Most clinical trials are carried out in this Phase, which is designed to demonstrate not only the absolute benefit of the drug, when compared it, for example, to a substance inert in the organism or deprived of any effects and regarded as a placebo, but also its relative benefit, when compared to other drugs already known and currently in use.

All of these trials imply very rigorous experimental parameters in order to avoid, as far as possible, the influence of mere chance or the interference of subjective factors on the part of the doctor or the patient, and also to allow for the statistical analysis of the obtained results. This analysis will largely determine the number of patients to be submitted to the compound under study, and the lower the differences and higher the variability of the results, the larger the number of patients.

In this experimental structure, it is of great importance, not only scientifically but also ethically, to establish desired goals very clearly so that the trial can be shortened if these goals can be quickly accomplished and not indefinitely extended if they are not achieved.

On the other hand, some compounds require the use of special experimental protocols. It

is not acceptable, for example, from an ethical point of view, to compare a compound potentially useful in the treatment of neoplasia to an inactive placebo, leaving a group of patients at the mercy of the spontaneous evolution of a clearly fatal illness.

Trials in Phase III are carried out on groups of hundreds or thousands of patients, who are frequently studied by various groups of researchers in various institutions or countries. Nevertheless, they all follow a common methodology in order to make the global analysis of the results possible. These are usually called multicentric trials.

The evaluation of the compound's efficacy and safety underlies the whole course of the research. There are no fixed or critical quantitative levels for each of them. Greater risks can be accepted in cases of a more serious illness or of a fatal prognosis, in cases where a high level of therapeutic efficacy is clearly shown, in cases where efficacy is defined as the reduction in the individual's incapacity caused by the disease or as the reduction in mortality, in cases where different clinical tests prove that efficacy and, finally, when there is no knowledge of other drugs or therapies to treat the disease.

Permission to sell the drug is granted by the authorities responsible for Public Health and requires demonstration of quality throughout the manufacturing process, of clinical efficacy, of safety during use and of the cost/benefit relation, if the new compound should be compared to others already existing.

10) Finally, trials in Phase IV are part of a surveillance process following the marketing of the drug. These studies take place under conditions of current therapeutic application of the drug and also follow a rigorous methodology, although a highly detailed report of the analysed elements is not required. The high number of patients under observation allows for the detection of rare, undesirable effects, as well as for the careful analysis of the best administration technique and the most appropriate doses. We can therefore explain why some compounds that have been in use for many years are withdrawn from the market when it becomes obvious that they carry with them more risks than benefits, or when new drugs appear which are clearly more advantageous than the previous ones.

III - ETHICAL ASPECTS REGARDING THE DRAFT DECREE-LAW 199/93

1) The ethical aspects of the new drug research are similar to those of any research on humans, with some particular features inherent in the very nature of the experiment.

2) Thus, following the guidelines established in the Helsinki Declaration and in its later revisions, various general ethical principles are applied, namely the freedom of the human being, the respect for the person, safeguarding his physical and mental integrity, justice, the pursuit of the Good and the elimination of unnecessary risks in the search for the best solution for suffering.

3) Contrary to other fields where ethical aspects concerning life and health are still being discussed, clinical trials already have well defined rules, both proposed by the World Health Organisation and adopted by the European Community. The texts are very similar and are both entitled "Good Clinical Practice".

Therefore the assessment of all and any national legislation on this matter has an already established referential framework, which is assumed to be underlying the following opinion.

4) In a general way, we can consider three complementary and absolutely linked

perspectives, which concern:

A) The protection of the patient's rights.

B) The doctor-researcher.

C) The places where the trials are undertaken.

5) Comments ensuing from the CNECV analysis of the draft Decree-Law 199/93 focus on these three perspectives and, in order not to lose the global idea of the most relevant ethical-doctrinal aspects, they shall be pointed out whenever they relate to those aspects and as these are being exposed.

A) Aspects concerning the protection of the patient's rights.

1) Not only do ethical aspects concerning the patient's protection originate in the respect for individual freedom but they also involve, in every case, the pursuit of the patient's well-being, avoiding unnecessary risks.

These principles make us ponder carefully on situations likely to bring more benefits to third parties or to society than to the patient himself. In any clinical trial, the person's individual well-being must prevail over the interests of science and society. This concern is present both in the "Basic Principles" (Num. 5) of the Helsinki Declaration (1964, completed in Tokyo in 1975 and in Venice in 1983) and in its principles of "Non-Therapeutic Biomedical Research on Human Beings" (Num. 4).

> Article 3 (2) refers to clinical trials as only *"being undertaken on human beings if the results of the trials should allow to conclude that the risks to be taken by the person undergoing the experiment are proportional to the benefits estimated to that same person"*. Nonetheless, it seems obvious that, in the paragraph written in these words, this proportionality can only refer to the "diseased" person (to refer to the "healthy" person it could not say "benefits to that same person") and, therefore, cannot be applied to trials in healthy volunteers. A more comprising formulation must be found, without prejudice - so as to avoid the creation of an anti-ethical concept - of taking proportionality into account when considering the risks to the human body.

2) There is also a principle of justice that may influence the choice or the exclusion of certain types of diseases or patients. This is the reason why, for example, trials in certain minority groups, such as prisoners, non-Caucasian races, unemployed or poor people, and so on, are not permitted, except for situations in which the study may be of particular interest to those groups. Another aspect that must be taken into account is the possible discrimination of women in fertile age, whenever compounds are under study, whose effects on the development of the human embryo are not yet known, even if laboratory research should have already demonstrated the absence of risks to the fertility of experimental animals and the absence of teratogenic effects. The alternative may consist in compelling an effective contraception, although this may also involve risks or interfere with the results.

3) The respect for the integrity of the individual also includes safeguarding professional secrecy and protection of data, even when these are stored in magnetic media, transmitted through any other means or published for scientific purposes.

> What is now laid down in Article 10 on "data protection" (*All those who participate in clinical trials or who in any way may know about them are obliged not to reveal any personal data to which they may have access*) already includes in this important obligation the whole number of people who, as experience has already shown, are in

fact in possession of the elements to preserve. That is also ethically correct.

Nevertheless, it is not logical to require [as in Article 14 (3) - b)] that both the "Promoter" and the "Monitor" make the results of the experiments available. Such requirement should be placed on the "Monitor" alone. In fact, they are naturally connected, as is referred in Article 15 (1) (*the monitor is the individual designated by the promoter to conduct the clinical trial ...*), and that is sufficient.

On the other hand, it should also be mentioned that, according to the rules of "Good Clinical Practice", even though the obtained results are kept secret, the files may be consulted by duly credentialed and authorised people, or by people with authority to carry out the verifications or audits.

4) The patient's freedom, as a fundamental element of the human being, must be always respected. This respect reveals itself in practice in two confluent lines of action: first, the patient must be provided with the necessary information to give informed consent; second, he must be given the possibility to abandon the trial at any time and without being penalised for it in any way.

It is therefore highly advantageous, and this is absolutely relevant, to have avoided (contrary to the first draft Decree-Law) the difficult and fluid matter of cases in which trials without previous consent would be permitted (as per Articles 6, 8 (2) and 13 (3) of the first draft Decree-Law, which disappeared in the second one). In fact, the situation would become difficult to control and there would always be the risk of fraud.

5) The information must be provided in a clear and trustworthy manner, which implies that the doctor-researcher must know the patient and his problems directly and must be able to establish a personal relationship with him. Only then is it possible to inform the patient about the various aspects relating to the trial. The information must also be understandable within the patient's cultural context, without going into unintelligible technical detail but instead pointing out all those aspects that might be relevant to the patient so as to form an adequate and complete opinion.

Therefore what is laid down in Article 8 (2), since it generally consists of exclusively technical elements presented in an unintelligible language for almost all clinical experimental subjects, does not appear to contribute in any adequate manner to the desired informed opinion, thus replacing in an administrative way the relationship between the doctor and the patient or volunteer. Furthermore, what is laid down in various subparagraphs of Article 8 (2) seems irrelevant from the ethical point of view for the good performance of the experiment. Some of them may also create the conditions for potential conflict between the patient and the doctor or the institution in which the research is to take place (*the researcher must also provide the clinical experimental subject with the information, in writing, mentioned in subparagraphs a, c, d, e, f and h of Article 5 (2), namely: a) The names and addresses of the promoter, of the researcher responsible for the experiment and of his collaborators, as well as their respective curricula; b) The researcher's wage and the payments in money or in goods to be made by the promoter to the establishments in which the experiment takes place, for collaborating in its performance; c) The drug's generic name and composition and the identification of the entity who prepared the samples; d) The name of the physician responsible for the quality of the drugs to evaluate*; *e) The type and definition of the clinical experiment, the selected technique and its purposes; f) The place and service where the clinical experiment is to take place and its respective duration; h) The precautions to be taken in the course of the trial and foreseeable adverse reactions).*

Besides, since the type of effective consent is rigorously defined (Article 9 (1): *consent to participation in clinical experiments should be free, informed and expressly*

given in writing; and Article 8 (3): *the consent obtained without complying with what is set down in the preceding paragraphs is not valid*), it appears that clinical trials with people who cannot give direct consent (minors, incapacitated or disabled people) are not permitted, that is, no person has the right to give consent on the other person's behalf.

This restriction was probably introduced after being considered the best way to prevent abuse, since consenting on one's own behalf is very different from consenting on someone else's.

However, at the ethical level, such restriction seems dubious, and not even the Helsinki Declaration goes so far (see Num. 11 of its Basic Principles). It needs no more than to ponder on situations in which these people, as patients, are prevented from receiving the benefits from the trials. Permission to give consent on someone else's behalf should be granted in case of disease, and only then, and not in the case of "healthy", incapacitated people. There is still a gap to be filled by the therapeutic clinical trial in the field of mental health.

On the other hand, it is worth pointing out and pondering on the fact that the same Helsinki Declaration (Num. 5 of its principles on "Medical Research Associated with Medical Care") foresees that "if the doctor finds it essential not to obtain the patient's informed consent, his specific reasons for it should be set down in the Protocol and previously transmitted to the independent Committee". However, this is still a very delicate matter, even though the Ethics Committee's compulsory opinion is always an important guarantee.

6) The patient should also be informed about the existing mechanisms and the compensation and treatment procedures in case of lesion or incapacity resulting from his participation in the trials.

After being informed, the patient, or the person liable for him, should be allowed to ponder on the details of the experiment, the estimated benefits, eventual risks, undesirable effects, and others, in order to give his voluntary and conscious consent.

The draft Decree-Law 199/93 is omissive in this respect.

7) Consent may, in certain cases, be presumed, following a principle of solidarity, whenever a common superior good such as life itself is in question. In other cases, it may also be given by the family, based on their knowledge of the patient and of what his opinion on the situation would be if he were in the condition to freely give his consent.

These are very complex aspects, especially when they concern minors or incapacitated people, who may not have a capacity of discernment or whose capacity may be affected in any profound way.

For these reasons, trials in healthy children, should there be no immediate benefits, appear to be ethically illicit; similarly, only in situations of serious mental illness and when there are justified immediate benefits should trials be authorised.

The authorisation must be given by the legal representative.

8) In terms of procedure, the consent must be registered and, when possible, signed by the patient and/or by an independent witness.

Trials in minors or in patients unable to give consent, which, as it has been already said, are only permitted if they should be for the benefit of the subject, will depend on the effective legal representative's decision. Approval from an entity strange to the trial, such as the institution's Ethics Committee, must also be obtained.

The above mentioned Community rules also refer that, in case of trials that do not result in direct clinical benefits for the patient, the informed consent must be always signed by the patient himself.

9) The trial is always described in a Protocol, along with a detailed account of the various aspects already mentioned. It will serve as the basis for the opinion of the Ethics Committee when authorising the trial.

> The provisions of Article 5 (4) (*The clinical experimental subjects' identification and the proof of their respective consent shall be appended to the protocol*) are only possible *a posteriori*, after the trial has been concluded. It seems therefore impossible to regard it as one of the elements to submit to the Ethics Committee in order to obtain its approval of the trial, although it should be included in the final *dossier*.

10) In the rules of "Good Clinical Practice" adopted by the European Community, there are sixteen chapters on the protocol, in which we can find general information such as the name of the trial, the names and identification of the researchers, the promoter's identification (if he should exist) and the identification of the institution in which the trial is to take place. Apart from this description, there must also be a presentation of the purposes and reasons for the trial, the problem to solve, as well as the ethical implications of the proposed research, from general aspects to the way the information is to be given to patients or healthy volunteers and their consent is to be obtained.

11) The Protocol must also mention the study's development through time and its justification, as well as the phase of the trial and the adopted experimental structure. It must also include an exhaustive description of the criteria for selecting the individuals, and for excluding them, and of their acceptable reasons for abandoning the trial during its course.

A detailed presentation of the product, the administration technique and the compounds used as standard for comparison, placebo or referential active drug is also required.

12) Another group of questions relates to the way in which the treatment is to be evaluated: what kind of effects should be looked for and measured? What undesirable effects can be expected? What laboratory tests are to be undertaken? And when in the trial? How are the results to be analysed from the statistical point of view? What rules are to be followed when controlling the quality of the observations?

The draft Protocol also requires an explicit presentation of the procedures to follow when registering observed effects, undesirable effects and their treatment, and when protecting confidential data.

13) Finally, the Protocol must also include a presentation of the financial elements involved, defining who is to finance the trial, how the financial resources are to be distributed between the institution and the researchers, which forms of compensation are to be adopted with regard to patients or volunteers, and so on, including insurance against injury or loss resulting from the trials.

The Protocol must also determine who is liable for the institution's additional expenses resulting from the trial, such as an eventual extension of the hospitalisation period or tests that can only be justified by the fact that the patient is subject to a trial.

14) As a generally accepted ethical principle, the participation of a healthy volunteer or a patient in a clinical trial should be free.

In spite of possible practical difficulties, it seems advisable to establish that "*under no circumstance can the subjects' participation in clinical experiments be paid for*" [Article 12 (1)].

As to the possibility of "compensation" or "reimbursement for expenses, injury or loss", it is ethically correct to have that compensation supervised (Article 12 (3): *whenever there should be, in accordance with the previous paragraph, compensation for expenses, injury or loss, the respective amounts and their justification must be periodically reported, in writing, to the entity with jurisdiction to give authorisation).*

However, it appears that this matter, for that reason and as it has been mentioned before, should also be submitted to the Ethics Committee, which is particularly able to "read between the lines" on the effective nature of those "expenses", "injury" or "loss".

Furthermore, it seems more accurate, therefore avoiding misinterpretations, to speak only of "refunding of expenses" in this Article, and not mention any "injury" or "loss" [Article 12 (2): *What is set down in the previous paragraph does not affect the reimbursement for any expenses, injury or loss that the subject might have borne for having participated in the trial*; and the above cited Article 12 (3)], for it is the expenses that must be controlled. As to the "injury" or "loss", which relate to the institution of civil/penal liability, what is said in Article 17 (1) is sufficient (*Without prejudice to the relevance, in terms of civil, penal and disciplinary liability, of the facts in question, the violation of the provisions of the present statute is punished...)*, as is better explained below.

15) Before the trial begins, each intervening element's share in liability must be clearly established in the Protocol.

The liability system applied to the violation of obligations inherent in the clinical trials' system has been improved in the second draft Decree-Law (but we do not comment on the lowering of the fines' sum, a politic matter that is not within our jurisdiction).

As it has already been said, what is laid down in the above cited Article 17 (1) is important and should be maintained, even though it may be considered unnecessary. We must not forget that, according to our legal system, "legal rights violated by means of offence to the body or to the health are at the owner's free disposal in so far as the fact does not contradict good morals, and that "in order to decide if the offence to the body or to the person's health actually contradicts good morals, the agent's and the offended person's motives and purposes, as well as the means used and the offence's estimated extent shall be all taken into consideration" (Portuguese Penal Code, Articles 149 and 38).

B) Ethical aspects regarding the doctor-researcher:

1) Ethical aspects concerning the doctor regarded as a researcher relate, in the first place, to his qualifications, which include not only his legal capacity to practice the necessary acts in the course of the trial, assuming full liability for them, but also his scientific and technical capacities, especially in the trial's field of study, so as to ensure his correct evaluation of the risk/benefit relation and his careful selection of the patients that are admitted to the trials.

2) However, although these aspects can be demonstrated by his Curriculum Vitae, they

will not do without total professional integrity and a high ethical standard. Only then can the rights of patients and volunteers participating in the trial be properly safeguarded.

The requirement of "professional qualifications" in Article 2 should be praised, for it ensures the dignity and seriousness of the process, considering that the person's fundamental rights are in question (Paragraph 1: *Clinical experiments can be conducted only by doctors with adequate scientific qualifications and research experience, especially in the field of the proposed clinical trial)*.

3) This respect towards the patient reveals itself in a particular manner in the doctor-patient relationship, the patient being as clearly and completely informed as possible so as to give his duly informed consent.

All the above mentioned aspects may be regarded as included in the ethical principles of the medical profession.

4) Although special emphasis has been given to the doctor-researcher's role as the person responsible for the clinical trial, the same fundamental required conditions are applied to all health professionals, or others, who in any way may participate in the trial or collaborate with the leading researcher.

C) Ethical aspects regarding the places where the trials are undertaken:

1) Aspects regarding the places where the trials are undertaken are also of great importance, especially in what concerns hospital institutions, particularly for trials in Phases I and II, or when very toxic compounds are used.

However, as to Article 4 of the draft Statute, it must be clearly foreseen that clinical trials may be performed on an "ambulatory basis", although we may consider it to be implicit in the adopted words (*Clinical experiments can take place only in public health establishments or in private health units properly licensed...*). In fact, they are frequently undertaken on this basis (naturally depending on the type of illness). The "ambulatory basis" may be regarded as implicit in this article's words only in so far as it is associated to a "health unit", but it must also be permitted on a medical office basis, although always subjected to the same authorisation requirements. In these cases, it seems obvious that, instead of an Ethics Committee, the Medical Association of the respective country [*] must be necessarily heard.

As for the rest, the new practice of requiring a new opinion from the Ethics Committee whenever the Protocol should undergo alterations is correct, the researcher having, among other obligations, the responsibility of (Article 14 (2)-c): *Proposing to the Administrative Organ of the health institution, upon authorisation from the promoter and from the Head of Division*[**] *and having heard the Ethics Committee, any alterations to the protocol eventually resulting from the clinical experiments' partial data, and also the responsibility of promoting any changes or the interruption of the experiments whenever there should be justified reasons for it.).*

We are pleased that the content of the verifications entrusted to the Ethics Committee has been well defined (Article 7 (2)-a): *The researcher's and his collaborators' experience and qualifications, having in mind the performance of the proposed experiment; b) The technical and attendance conditions under which the experiment is undertaken; c) The Protocol's adequacy to the purposes of the*

[*] in Portugal, *Ordem dos Médicos*

[**] in Portugal, *Director de Servico* (Director of Service)

experiment, pondering particularly on possible benefits and predictable risks; d) The fulfilment of ethical obligations assumed in the protocol or resulting from the national or international rules that control the performance of clinical trials; e) The appearance of reasons that may justify the suspension or the revocation of the authorisation granted for the performance of clinical trials.). They should be completed with our suggestions.

2) Clinical trials imply the existence of adequate human and technical means to intervene in good time and with the right measures in case of serious reactions likely to result in death, or even if only justifying the patient's admittance into a health unit for a complete understanding of the situation.

This is the meaning of what is set down in Article 4 (2) of the draft Decree-Law *(Experiments with drugs that, due to their nature or to the characteristics of the disease, may represent a serious risk to the patient's life or health must be carried out in health units into which the patient can be admitted and with the adequate technical, material and human conditions to ensure a permanent control of the experiments and allow for possible, necessary operations).*

In the draft Decree-Law, there is no information as to the grounds or the way in which public or private health establishments' competence to carry out the clinical trials is to be recognised.

3) From the ethical point of view, it also becomes necessary, and all the produced texts agree in this respect, that a liable authority exists with capacity to authorise the trials on the institution's behalf. This authority is currently designated Ethics Committee or Council. Not only must it give its opinion on the clinical trial's scientific validity and on the researchers involved, but it must also include among its members not only health professionals but also jurists, religious representatives from the main religious orders in the area, social workers, etc.

In regard to Ethics Committees, a dichotomy arises from the beginning: the idea of having Ethics Committees in the institutions as a previous condition for the licensing of clinical trials contradicts what is set down in another paragraph of the draft Statute, according to which they may be replaced by the Regional Consulting Committees of the Medical Association.

On the other hand, it seems absolutely necessary that, in order to have "*private health units properly licensed"* [Article 4 (1)], these must have a properly structured Ethics Committee.

Therefore the condition required in Article 6 (1) -b *(In private health units, upon the Ethics Committee's favourable opinion)* seems to contradict what is laid down in Article 7 (4): "*If there should not be an Ethics Committee, the powers conferred upon it by the present draft Statute are to be exercised by the Regional Ethics Committee of the Medical Association".* It is therefore accepted that there may not be an Ethics Committee, even though the Regional Ethics Committee of the Medical Association does not have the desirable plural constitution.

Despite the Medical Association's undeniable respectability and scientific quality, its general supplementary participation appears to free from responsibility the health unit that might wish to admit the clinical trials. This aspect is especially apparent in trials carried out on an "ambulatory basis".

These reflections do not mean that the present Decree-Law, laying down transitorily, cannot recognise Ethics Committees already vested with those powers (it would be a way of giving them prestige) and the Medical Association's intervention only

while there is no legislation on Ethics Committees (see Article 7 (3): *Ethics Committees' composition, jurisdiction and functioning are established in a specific Statute).*

As to this matter, we must say that it would be appropriate if the legislator, also laying down transitorily, undertook to publish the above mentioned legislation, consulting the CNECV in due time.

In regard to clinical trials, Article 7 (1) correctly establishes that *" (...) supervision of their performance, especially in what concerns ethical aspects and the drugs' safety and efficacy, shall be the responsibility of the Ethics Committee"*, although the Ethics Committee may not be the most appropriate entity to supervise possible non-ethical aspects.

But we do not know how this supervision can be carried out, nor do we see how it would be possible, therefore making it preferable to suppress the paragraph, at risk of it being no more than a fantasy, thus creating a false sense of security.

It is more correct and realistic to limit the Statute to the necessary intervention of Ethics Committees in certain important acts pertaining to the performance of the clinical trial. It would be the only possible way for them to carry out that supervision.

And so, Ethics Committees should primarily ensure that ethical values are respected, without having to necessarily get involved in the scientific aspects of the experiments.

One of the ways for the Ethics Committee to exercise the powers vested in it is by being considered one of the addressees of the final report to which the Promoter is bound [and Article 13 (2) - g) does not foresee its presentation to it: *Presenting the final report to the Administrative Organ of the health establishment, as well as to the* Instituto de Farmácia e do Medicamento *(Pharmacy and Drug Institute*)]; and also by being consulted for the purposes of Article 12 (3) *(When there should be, in accordance with the previous paragraph, compensation for expenses, injury or loss, the respective amounts and their justification must be periodically reported, in writing, to the entity with jurisdiction to give the authorisation)*.

As for the rest, the new practice of requiring a new opinion from the Ethics Committee whenever the Protocol should undergo alterations is correct, the researcher having, among other obligations, the responsibility of [Article 14 (2) - c)] *"Proposing to the Administrative Organ of the health institution, upon authorisation from the promoter and from the Head of Division and having heard the Ethics Committee, any alterations to the protocol eventually resulting from the clinical experiments' partial data, and also the responsibility of promoting any changes or the interruption of the experiments whenever there should be justified reasons for it".*

We are pleased that the content of the verifications entrusted to the Ethics Committee has been well defined (Article 7 (2)-a): *The researcher's and his collaborators' experience and qualifications, having in mind the performance of the proposed experiment; b) The technical and attendance conditions under which the experiment is undertaken; c) The Protocol's adequacy to the purposes of the experiment, pondering particularly on possible benefits and predictable risks; d) The fulfilment of ethical obligations assumed in the protocol or resulting from the national or international rules that control the performance of clinical trials; e) The appearance of reasons that may justify the suspension or the revocation of the authorisation granted*

for the performance of clinical trials.). They should be completed with our suggestions.

IV - GENERAL ASPECTS REGARDING THE DRAFT DECREE-LAW

1) In general terms, the draft Decree-Law follows the rules of "Good Clinical Practice" quite closely and is acceptable from the point of view of the ethical grounds pertaining to the research on the human being. Therefore comments ensuing from its detailed analysis in the CNECV are aimed only to make explicit some of the aspects in it.

The considerable improvement in the conception and development of the draft Statute, when compared to the previous one, has been particularly pointed out in the CNECV. Nevertheless, given its language inaccuracies and imperfections, there is still the need for a careful revision of the text at the formal level, in order not to risk an unclear understanding of it, which would naturally reflect on its good performance at the ethical level (e.g., in Article 4 (1), should be written *"public health establishments"* and *"requirable"* instead of *"required"*; in Article 4 (2), should be written *"therapeutic interventions"*; in Article 5 (2), a reference to the "Monitor" is missing; in Article 5 (2) - g), it would be more clear to say, for example, *"a prevision as to the participants, their profile, the criteria..."*; several types of words are incorrect, there are incorrect references to other articles, and so on.

2) Since it is not incumbent on the CNECV to analyse the chosen juridical technique, any references to the articles are aimed only to locate the several aspects in discussion.

3) In general, the CNECV considers the use of various definitions to be clearly advantageous for a better understanding of concepts, namely in Article 1 (2) *(For the purposes of the present Statute, the clinical drug evaluation is understood to be the systematic study of drugs in healthy or unhealthy human beings with the purpose of investigating or verifying their effects and/or of identifying possible side-effects and/or of studying their absorption, their distribution, their metabolism and their excretion, so as to determine their efficacy and safety)*, Article 13 (1) *(The promoter is the person responsible for the promotion and financing of the clinical trial)*, Article 14 (1) *(The researcher is the specialist-doctor responsible for the conduction and performance of the clinical trial)* and Article 15 (1) *(The monitor is the individual designated by the promoter to conduct the clinical trial, to report its evolution, to verify the information gathered and also to keep him permanently informed)*. The word *"benefit"* should be added to the references on efficacy and safety.

4) The CNECV considers the setting of "required conditions" in Article 3 to be very important, although we cannot be sure that the modern tendency to replace trials in laboratory animals with other laboratory models will actually provide any relevant elements for a possible clinical application. Similarly, laboratory trials cannot provide information on the cost/benefit relation because of the evident inexistence in animals of pathological models for various clinical situations. But, for doctrinal and teleological strictness, it seems essential to lay down in Article 3 (2) (paragraph 2 goes to 3) that "In any clinical trial, the person's individual well-being must prevail over the interests of science and society". Such concern is present both in the "Basic Principles" (Num. 5) of the Helsinki Declaration (1964, completed in Tokyo in 1975 and in Venice in 1983) and in the principles of "Non-Therapeutic Biomedical Research on Human Beings" (Num. 4).

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THE REPORTER, THE PRESIDENT,

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