BUNDESKAMMER DER GEWERBLICHEN WIRTSCHAFT

Bundeswirtschaftskammer

Bundeswirtschaftskammer · A-1045 Wien · Postfach

An das Präsidium des
Nationalrates
Parlament

Dr. Karl-Renner-Ring
1010 Wien

Ihre Zahl/Nachricht vom	Unsere Zahl/Sachbearbeiter	Bitte Durchwahl beachten	Datum
	SpG/59/92/Wr/Br Dr. Wrbka	Tel. 501 05/ Fax 502 06/ 4530 243	16.11.92

Betreff

Bundesgesetz mit dem das Arzneimittelgesetz geändert wird (AMG-Novelle 1992); Begutachtungsverfahren

Die Bundeskammer der gewerblichen Wirtschaft beehrt sich, 25 Kopien ihrer zu dem oben genannten Entwurf erstatteten Stellungnahme mit der Bitte um gefällige Kenntnisnahme zu übermitteln.

BUNDESKAMMER DER GEWERBLICHEN WIRTSCHAFT
GRUPPE GESUNDHEITSPOLITIK

Dr. Heinrich Wrbka

Anlage
25 Kopien

1100-01/89

BUNDESKAMMER DER GEWERBLICHEN WIRTSCHAFT

Bundeswirtschaftskammer

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Bundesministerium für Gesundheit,
Sport und Konsumentenschutz

Radetzkystraße 2
1031 Wien

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Die Bundeskammer dankt für die Übermittlung des Entwurfs einer Novellierung des Arzneimittelgesetzes und beehrt sich, in der Beilage eine gestraffte Stellungnahme zu den einzelnen Detailbestimmungen vorzulegen.

Grundsätzlich ist festzuhalten, daß der Entwurf in seiner übermittelten Fassung eine durchaus geeignete Basis für eine eingehende Expertendiskussion darstellt. Das angestrebte Ziel - eine möglichst nahe Angleichung an die Regelungen der EG - wurde über weite Strecken erreicht. Dennoch bedürfen einige Passagen einer eingehenden Beratung und Überarbeitung, um eine ausgewogene und beschlußreife Ausformulierung einer Regierungsvorlage zu erzielen.

Unbeschadet der oben erwähnten Detailanmerkungen (Beilage 1), stellen sich die wesentlichsten grundsätzlichen Forderungen der betroffenen Pharmawirtschaft wie folgt dar.

- Die sogenannten EG-Zulassungsverfahren (Mehrstaatenverfahren, Konzertierungsverfahren) bedürfen, wie dies mündlich bereits wiederholt ausführlich dargelegt wurde, einer eingehenden Überarbeitung. Hiebei ist natürlich auf die derzeit stattfindende Entwicklung in der EG und der EFTA Bedacht zu nehmen. Jedenfalls muß sichergestellt werden, daß durch eine zu starke Bindung an die EG-Verfahren, wie dies etwa derzeit in § 18 c des Entwurfes der Fall ist, eine nationale Zulassung nicht ausgeschlossen ist.

- Vernünftige gesetzliche Vorgaben für das sogenannte Co-Marketing sind unerläßlich.

- Im Zusammenhang mit der klinischen Prüfung, auf die im übrigen später noch näher eingegangen wird, ist anzumerken,

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daß drei Punkte ganz besonders zu thematisieren sind.

1. Es ist nicht einsichtig, warum nach Etablierung einer Ethikkommission, die alle Parameter einer geplanten klinischen Prüfung zu beurteilen hat, auch noch zusätzlich ein Gutachten des Arzneimittelbeirates einzuholen ist.

2. Die vorgesehenen Regelungen hinsichtlich des Abschlusses von diversen Versicherungen waren schon bisher Gegenstand von Diskussionen, die bislang zu keinen befriedigenden Lösungen geführt haben.

3. Der im Entwurf vorgesehene § 32 Abs. 3 wird mit allem Nachdruck abgelehnt. Die in dieser Regelung vorgesehene und mit Strafandrohung ausgestattete unentgeltliche Versorungspflicht von Probanden mit nicht zugelassenen Arzneispezialitäten durch den Sponsor verstößt gegen eine Reihe von Grundsätzen, die sowohl im Arzneimittelgesetz als auch im ASVG festgeschrieben sind. Darüber hinaus erscheint sie auch gegen verfassungsgesetzliche Grundsätze zu verstoßen.

- Als weiterer Schwachpunkt des Entwurfs wird der Komplex der Werbung angesehen. Als Stichworte dürfen das Fehlen der Erinnerungswerbung, die Unzulässigkeit, für Impfkampagnen zu werben, sowie die Regelung im § 51 Z 2 aufgezeigt werden.

- Ganz entschieden und mit allem Nachdruck wird der Entfall des derzeitigen § 59 Abs. 4a abgelehnt. Hier geht es um das Recht des Herstellers, bei der Behörde zu beantragen, daß ein Produkt - soferne es mit dem Grundsatz der Arzneimittelsicherheit vereinbar ist - vom Apothekenvorbehalt ausgenommen wird. In diesem Zusammenhang wird angemerkt, daß diese Regelung durch die Arzneimittelgesetznovelle 1988 neu formuliert wurde und damals schon eine Abschwächung der ursprünglichen Rechtslage war.

- Im Zusammenhang mit der Chargenprüfung erhebt sich die Frage, warum nicht ausländische Zertifikate direkt von der österreichischen Behörde anerkannt werden können.

- Vor allem für kleine und mittlere österreichische Unternehmen wird es aufgrund der neuen gesetzlichen Regelung in Zukunft unmöglich sein, neue "einfache" Arzneimittel zu entwickeln, bzw. bereits zugelassene zu adaptieren. Dies deshalb, weil im Regelfall gerade diese Unternehmen nicht in der Lage sein werden, den finanziellen Aufwand, der für die Durchführung einer klinischen Prüfung notwendig sein wird, zu verkraften. Es sollte daher überlegt werden, ob es nicht möglich wäre, eine Art Zwischenstufe zwischen Anwendungsbeobachtung und klinischer Prüfung einzuziehen. Dies kann natürlich nicht für "Hightech-Produkte" und ähnliches in Anspruch genommen werden.

- Als nicht gerade glücklich wird die Umsetzung der in der EG nicht einmal auf Richtlinienstufe stehenden GCP-Empfehlungen direkt im Gesetz selbst erachtet. Dies deshalb, weil es sich bei diesen Empfehlungen um wissenschaftliche Standards handelt, die einer permanenten Weiterentwicklung unterliegen. Darüber hinaus gibt es bereits jetzt schon Aktivitäten der WHO, weltweit einheitliche Standards zu schaffen (siehe Beilage 2). Seitens der Pharmawirtschaft wird die Auffassung vertreten, daß es vernünftiger wäre, im Arzneimittelgesetz nur die notwendigsten Rahmenbedingungen festzuschreiben und den sogenannten dynamischen Teil der GCP in flexibleren, rascher anzupassenden Instrumentarien (etwa in Verordnungen oder in Form von Anhängen) auszuformulieren.

Die dargelegten grundsätzlichen Bedenken bedeuten selbstverständlich nicht, daß die in der Beilage 1 angeregten Änderungsvorschläge nicht im Detail durchzuarbeiten sind. In diesem Zusammenhang erlaubt sich die Bundeswirtschaftkammer daran zu erinnern, daß das do Bundesministerium zugesagt hat, den vorliegenden Entwurf - so wie dies auch anläßlich der Novelle 1988 der Fall war - einer eingehenden Diskussion auf Expertenebene zuzuführen. Dies erscheint unerläßlich, um zu einer für alle Betroffenen optimalen Ausformulierung des Gesetzes zu gelangen.

BUNDESKAMMER DER GEWERBLICHEN WIRTSCHAFT

Der Präsident: Der Generalsekretär:

Beilagen wie erwähnt

BEILAGE 2

DRAFT 8.9.92

IFPMA Note
For the convenience of those who have studied the preliminary draft, (circulated under SM 147) this version has been annotated to indicate textural changes. These annotations have no other significance and can be disregarded by those studying the text for the first time.

WHO GUIDELINES FOR GOOD CLINICAL PRACTICE (GCP) FOR TRIALS ON PHARMACEUTICAL PRODUCTS

DIVISION OF DRUG MANAGEMENT & POLICIES
WORLD HEALTH ORGANIZATION

CONTENTS

INTRODUCTION

The purpose of these WHO Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products is to set globally applicable standards for the conduct of such biomedical research on human subjects. They are based on provisions already promulgated in a number of highly developed countries including Australia, Canada, EC Countries, Japan, Nordic Countries and the United States. These guidelines inevitably vary somewhat in content and emphasis, but all are consonant with regards to the prerequisites to be satisfied and the principles to be applied as a basis for assuring the ethical and scientific integrity of clinical trials. Indeed, they have provided a formal basis for mutual recognition of clinical data generated within the interested countries. Every care has been taken, in developing the WHO Guidelines as a practicable administrative tool for the broader constituency of WHO's Member States, to assure their compatibility with existing national and other provisions. It is hoped, on the basis of further consultation, to seek formal acceptance of the WHO Guidelines by Member States as a contribution to harmonization of standards internationally and to facilitating movement of pharmaceutical products internationally. No question arises, however, of challenging or usurping existing national regulations or requirements. The objective is to provide a complementary standard with international validity.

The guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research and drug regulatory authorities. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, these Guidelines not only serve the interests of the parties actively involved in the research process, they protect the rights and safety of subjects, including patients, and ensure that the investigations are directed to the advancement of public health objectives.

The Guidelines are intended specifically to be applied during all stages of drug development both prior to and subsequent to product registration, but they are also applicable in whole or in part, to biomedical research in general. They should also provide a resource for editors to determine the acceptability of reported research for publication and, specifically, of any study that could influence the use or the terms of registration of a pharmaceutical product. Not least, they provide an educational tool that should become familiar to everyone engaged in biomedical research and to every newly-trained doctor.

DEFINITION OF TERMS

Definitions given below apply specifically to the terms used in this guide. They may have different meanings in other contexts.

Adverse Event
Any untoward medical occurrence that may present itself during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse Reaction
A response to a pharmaceutical product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. In clinical trials, injuries caused by overdosing, abuse/dependence and interactions with any other product should be considered as an adverse reaction.

Audit
A systematic examination, carried out independently of those directly involved in the trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the CRFs are consonant with those found in hospital files and other original recordings.

Case Report Form (CRF)
A document designed to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification and audit.

Clinical Trial
Any systematic study on pharmaceutical products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. Description (in brief) of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below:

a) Phase I
These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic/pharmacodynamic profile of the active ingredient in humans.

b) Phase II
The purpose of these therapeutic pilot studies is to demonstrate activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. The trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. This phase also aims at the determination of appropriate dose ranges/regimens and (if possible) clarification of dose/response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

c) Phase III
Trials in larger (and possibly varied) patient groups with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, as well as to assess its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age, etc.). The design of trials should preferably be randomized double-blind, but other designs may be acceptable, e.g. long-term safety studies. Generally, the circumstances of the trials should be as close as possible to normal conditions of use.

d) Phase IV
Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, assessment of therapeutic value or treatment strategies. Although methods may differ, phase IV studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

Contract
A document, dated and signed by the investigator/institution and the sponsor that sets out any agreements on financial matters and delegation/distribution of responsibilities. The protocol may also serve as a contract when it contains such information.

Contract Research Organization (CRO)
A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

Ethics Committee
An independent body (a review board or a committee; institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance.

Final Report
A comprehensive description of the trial after its completion including a description of experimental (including statistical) methods and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethics, statistical and clinical appraisal.

Good Clinical Practice
Good Clinical Practice is a standard for clinical studies which encompasses the design, conduct, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the diagnostic/therapeutic/prophylactic product under investigation are properly documented.

Good Manufacturing Practice (GMP)
That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled in conformity with quality standards appropriate for their intended use and as required by the product specification. Any reference to GMP in this document should be understood as a reference to the current WHO GMP Guidelines.

Informed Consent
A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

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Inspection
An officially-conducted examination (i.e. review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and / or at the site of the sponsor in order to verify adherence to Good Clinical Practice as set out in this document.

Investigational Product
Any pharmaceutical product (see definition) or placebo being tested or used as reference in a clinical trial.

Investigator
A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person legally allowed to practice medicine/dentistry.

Investigator's Brochure
A collection of data for the investigator consisting of all the relevant information on the investigational product(s) known prior to the onset of a clinical trial including chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data in animals as well as in man and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the information must be updated.

Monitor
A person appointed by the sponsor, and responsible to the sponsor, for the monitoring and reporting of progress of the trial and for verification of data.

Patient files
Hospital files, consultation records or special subject file allowing the authenticity of the information presented in case record forms to be verified and, where necessary, allowing them to be completed or corrected. The conditions regulating the use and consultation of such documents must be respected.

Pharmaceutical product
Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and presented in a dosage form suitable for administration to humans.

Principal investigator
The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicentre trials.

Protocol
A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator/institution involved and the sponsor. It can, in addition, function as a contract.

Quality assurance relating to clinical trials
Systems, processes and quality control procedures which have been established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOP), reporting, and professional/personnel qualifications.

Raw data
Raw data refers to all records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, recorded data from automated instruments or exact, verified copies in the form of photocopies, microfiches etc. The term can also include photographic negatives, microfilm or magnetic media.

Serious Event
An event that is associated with death, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

Sponsor
An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

Standard Operating Procedures (SOP)
Standard, detailed, written instructions for the management of any defined situation occurring during the clinical trial. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

Trial Subject
The trial subject may be:

a) a healthy person volunteering in a trial,
b) a person with a condition unrelated to the use of the investigational product,
c) a person (usually a patient) whose condition is relevant to the use of the investigational product;

who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control.

1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

1.1 Justification for the trial

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks/benefits of a particular clinical trial be thoroughly considered and that the chosen solutions be scientifically sound and ethically justified.

1.2 Ethical principles

All research involving human subjects should be conducted in accordance with four basic ethical principles, namely justice, respect for persons, beneficence and non-maleficence as defined by the current revisions of the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS). These principles must be fully known and followed by all engaged in conducting clinical trials throughout all phases (see chapters 3 and 4).

1.3 Investigational product

Preclinical studies that provide sufficient evidence of potential safety and eventual clinical application of a pharmaceutical product are a necessary prerequisite for a clinical trial. Similarly, the chemical and pharmaceutical studies prior to a clinical trial should establish adequate quality of the trial product. The pharmaceutical, preclinical and clinical data should be adapted to the appropriate phase of the trial. In addition, a compilation of information on safety and efficacy collected in previous and ongoing clinical trials elsewhere with the investigational product is vital for the planning and conduct of subsequent trials.

1.4 Investigator and site(s) of investigation

All investigators should have appropriate expertise, qualifications and competence to undertake a proposed study. Prior to the trial, agreement on monitoring and auditing procedures, and also on standard operating procedures (SOP), should be established. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial (see chapter 4).

1.5 Regulatory requirements

Countries in which clinical trials are performed should have regulations by which these studies can be conducted. All parties involved in a clinical trial should comply fully with the existing national regulations or requirements. In those countries where regulations do not exist or require supplementation, the competent government officials may designate, in part or in whole, the present WHO Guidelines for Good Clinical Practice as the basis on which clinical trials will be conducted. The use of these guidelines should not prevent their eventual adaptation into national regulatory law. Neither should they be used to supersede an existing national requirement in those cases where the national requirement is more rigorous.

2. THE PROTOCOL

The clinical trial should be carried out in accordance with a protocol agreed and signed by the investigator and sponsor. Any change(s) appearing later should be appended as amendments and be similarly agreed on and signed by the investigator and sponsor.

The protocol should state the aim of the trial and the procedures to be used; the reasons for proposing that it should be undertaken on human subjects; the nature and degree of any known risks; the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent.

The protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigator(s) and sponsor.

A model list of items to be contained in a protocol is given in Appendix I.

3. PROTECTION OF TRIAL SUBJECTS

The personal integrity and welfare of the trial subjects as defined in the Declaration of Helsinki is the ultimate responsibility of the investigator who must also take into consideration the scientific validity of the trial for which all involved are responsible.

3.1 Declaration of Helsinki

The current revision of the Declaration of Helsinki (Appendix 2) is the accepted basis for clinical trial ethics, which must be fully known and followed by all engaged in research on human beings. Independent assurance that subjects are protected can only be provided by an ethics committee and freely-obtained informed consent.

3.2 Independent ethics review board/committee

The aim of the work of the ethics committee is to ensure the protection of the rights and welfare of human subjects involved in research, and provide public reassurance, *inter alia* by previewing trial protocols. The work of the ethics committee should be guided by the Declaration of Helsinki and governed by national and other relevant international requirements.

The ethics committee should have documented policies and procedures as a basis for its work, which should include the authority under which the committee is established, the number and qualifications of members elected, a definition of what it will review and its authority to intervene and maintain records of its activities. The frequency of meetings and how it interacts with the investigator and/or sponsor should be defined.

The sponsor and/or investigator must consult the relevant ethics committee(s) regarding suitability of a proposed clinical trial protocol (including annexes) and of the methods and material to be used in obtaining and documenting informed consent of the subjects.

The ethics committee must be informed of all subsequent protocol amendments and of any serious adverse events occurring during the trial, likely to affect the safety of the subjects or the conduct of the trial. The ethics committee should be asked for its opinion if a re-evaluation of the ethical aspects of the trial appears to be called for.

Subjects must not be entered into the trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures and documentation in writing.

When receiving the submission for a clinical trial the ethics committee should consider the following:

a) the acceptability of the investigator for the proposed trial, on the basis of sufficient information made available to the committee, in terms of his/her qualifications, experience, supporting staff, and available facilities.

b) the suitability of the protocol in relation to the objectives of the study and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others, as well as the efficiency of its design, i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects.

c) the means by which patients will be admitted and by which necessary/appropriate information will be given, and by which consent is to be obtained.

d) the adequacy and completeness of the information in lay language to be given to the subjects, their relatives, guardians and, if necessary, legal representatives presented in writing to the ethics committee. All written information for the subject and/or legal representative must be submitted in its final form.

e) provision for compensation/treatment in the case of death or other loss or injury of a subject, if attributable to a clinical trial, and details of any insurance or indemnity to cover the liability of the investigator and sponsor.

f) the extent and form of payment through which the sponsor will remunerate/compensate organizations, investigators, and trial subjects involved.

g) acceptability of major amendments in the protocol.

The ethics committee should give its opinion and advice in writing within a reasonable time, clearly identifying the trial protocol, the documents studied and date of review. A list of those present at the committee meeting, including their professional status, should be attached.

3.3 Informed consent

The principles of informed consent in the current revision of the Declaration of Helsinki should be implemented in each clinical trial.

a) Information should be given in both oral and written form whenever possible. No subject should be obliged to participate in the trial. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to enquire about details of the trial. The information must make clear that the trial is a research procedure, participation is voluntary and that refusal to participate or withdraw from the trial at any stage is without prejudice to the subject's care and welfare. Subjects must be allowed sufficient time to decide whether or not they wish to participate.

b) The subject must be made aware and consent that personal information may be scrutinized during audit/inspection by competent authorities and properly authorized persons/sponsor, and that participation and personal information in the trial will be treated as confidential and will not be publicly available.

c) The subject must have access to information about insurances and other procedures for compensation and treatment should he/she be injured/disabled by participating in the trial. The subject should know the circumstances under which the investigator or the sponsor might terminate the subject's participation in the study.

d) If a subject consents to participate after a full and comprehensive explanation of the study (including its aim, expected benefits for the subjects and/or others, reference treatment/placebo, risks and inconveniences – e.g. invasive procedures – and, where appropriate, an explanation of alternative, recognized standard medical therapy), this consent should be appropriately recorded. Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent (consent). In either case, the signature confirms that the consent is based on information which has been given, and that the subject has freely chosen to participate without prejudice to legal and ethical rights while reserving the right to withdraw at his/her own initiative from the study at any time, without having to give any reason. However, in case the reason for withdrawal relates to adverse event(s) the investigator should be informed.

e) Careful consideration should be given to members of a group with a hierarchical structure – such as medical, pharmacy and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. In such cases the willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of benefits or that refusal might provoke a retaliatory response from senior members of the hierarchy. Other vulnerable people whose mode of consent also needs special consideration include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency rooms, some ethnic minority groups, homeless persons, nomads and refugees.

f) If the subject is incapable of giving personal consent (e.g. unconscious or suffering from severe mental illness or disability), the inclusion of such patients in a trial may be acceptable if the ethics committee is, in principle, in agreement and if the investigator is of the opinion that participation will promote the welfare and interest of the subject. The agreement of a legally valid representative that participation will promote the welfare and interest of the subject should also be recorded by a dated signature. If neither signed informed consent nor witnessed signed verbal consent are possible, this fact must be documented stating reasons by the investigator.

Only (open-label) emergency treatment with the investigational product may be appropriate in those cases where consent cannot be obtained.

g) In a non-therapeutic study, i.e. when there is no direct clinical benefit to the subject, consent must always be given by the subject or that of a legally valid representative and their signature obtained.

h) The trial subjects should be informed that they have access to appropriate (indicated) persons to obtain further information, if necessary.

i) Any information becoming available during the trial which may be of relevance for the trial subjects must be made known to them by the investigator.

4. RESPONSIBILITIES OF THE INVESTIGATOR

4.1 Medical care of trial subjects

The investigator is responsible for adequate and safe medical care of those subjects who participate for the duration of the trial and the investigator must ensure that appropriate medical care is maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made.

4.2 Qualifications

The investigator should:

- be an appropriately-qualified person legally allowed to practice medicine/dentistry;
- have good knowledge and experience of the field of medicine defined by the protocol;
- have the qualifications and competence in accordance with national regulations as evidenced by an up-to-date curriculum vitae and other credentials;
- be experienced in clinical trial research methods or receive scientific support from an experienced colleague;
- be aware of available relevant data and literature and all information provided by the sponsor;
- have access to human and other resources to assume full responsibility for the proper conduct of the trial.
- be aware of and comply with national regulatory and legal requirements.

4.3 Selection of trial subjects

The investigator is responsible for ensuring the equitable selection and adequate number of suitable subjects. It may be necessary to secure the cooperation of other physicians in order to obtain a sufficient number of subjects. In order to assess the probability of an adequate recruitment rate for subjects for the study it may be useful to determine prospectively or to review retrospectively the availability of the subjects. A check should be made by the investigator whether subjects so identified could be included according to protocol.

4.4 Compliance with the protocol

The investigator should agree and sign the protocol with the sponsor and confirm in writing that he/she has read, understands and will work according to the protocol and Good Clinical Practice.

The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to the trial subjects. Any change should be in the form of a protocol amendment, appended to the original protocol and signed by the investigator and sponsor. Major amendments, with justification, should be submitted to and implemented after approval of the ethics committee (see Section 3.2) and drug regulatory authority.

4.5 Information to subjects and informed consent

The investigator is responsible for giving adequate information to subjects about the trial. The current version of the Declaration of Helsinki (Appendix 2), and International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) should be followed. The nature of the information that should be given is dependent on the complexity of the study, the nature of the investigational pharmaceutical product and its stage of development.

Information should be given in both oral and written form in the language understandable to the subject. It should be noted in the protocol how it is to be recorded that information has been given and when and by whom it will be given.

Informed consent should be obtained according to the principles as described in Section 3.3.

The investigator should supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about contact personnel who can assist in an emergency situation.

4.6 The investigational product

The investigator should be thoroughly familiar with the properties, effects, and safety, including pre-trial data, of the investigational pharmaceutical product(s) as described in the investigator's brochure or in the literature. The investigator should be aware of all relevant new data on the product that appears during the course of the trial as required.

4.7 Site of the trial, facilities and staff

Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. Selection of the site is dependent on the stage of development of the product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial as required.

Facilities should be available to meet all possible emergencies.

The investigator should ensure that he/she has sufficient time to conduct and complete the trial, and that other commitments or trials do not divert essential subjects or facilities away from the trial in hand.

The investigator should provide adequate information to all staff involved in the trial.

The investigator should notify or obtain approval for the trial from relevant local hospital (medical, administrative) management in compliance with existing regulations.

4.8 Notification to drug regulatory authority

As governed by national regulations, the investigator, sponsor, or investigator jointly with the sponsor, should give notification of the trial to, or obtain approval from, the drug regulatory authority. The investigator should ensure that any submission must be in writing, be dated and contain sufficient information to identify the protocol.

4.9 Review by an ethics committee

Prior to its commencement, the investigator must ensure that the proposed trial has been reviewed and accepted by an independent ethics committee (see Section 3.2).

4.10 Serious adverse events/reactions

As governed by national regulations, the investigator is responsible for notifying (with documentation) the health authorities, the sponsor and, when applicable, the ethics committee immediately in the case of serious adverse events/reactions, and must take appropriate measures to safeguard subjects (see also Section 7).

4.11 Financing

The relationship between the investigator and the sponsor (in matters such as financial support, fees, honorarium payments in kind, etc.) must be stated in writing in the protocol or contract.

4.12 Monitoring, auditing and inspection

The investigator must accept and be available for periodic visits by the monitor/s and accept the implications thereof (see also Section 6). In addition, the investigator must accept the auditing and/or inspection procedures by the authorities and by persons appointed by the sponsor for quality assurance.

4.13 Record keeping and handling of data (see Section 8).

4.14 Handling and accountability of pharmaceutical products for trial (see Section 10).

4.15 Termination of trial and final report

In the case of premature termination of the trial, the investigator must inform the drug regulatory authority and ethics committee where applicable. Reasons for termination must be stated.

After completion of the trial, a final report must be drawn up. The report should be dated and signed by the investigator to verify responsibility for the validity of the data.

5. RESPONSIBILITIES OF THE SPONSOR

5.1 General role of the sponsor

The sponsor may be a pharmaceutical company, but may also be an investigator, a principal investigator or an independent institution or organization that initiates, funds, organizes and oversees the conduct of a trial. When the sponsor is a foreign company or organization it should have a local representative to fulfil the appropriate local responsibilities as governed by national regulations.

The sponsor is responsible for the overall adequacy and reliability of the data and information that are presented to the investigator before the start of the clinical trial or that become available during the trial, as well as responsible for the pharmaceutical product(s) involved.

The sponsor, investigator, or both, are responsible as stipulated in the national regulations for the necessary contacts with the drug regulatory authority and independent ethics committee, such as notification or submission of the trial protocol, reporting adverse events and submitting reports on the trial.

In clinical trials in which the investigator is a sponsor, he/she is responsible for the corresponding functions, including monitoring.

The sponsor should set up a system of quality assurance (including independent auditing) for the conduct of the trial as defined in Section 13. Such a system should operate independently of those conducting the trial.

The sponsor must establish written detailed standard operating procedures (SOP) to comply with Good Clinical Practice.

The sponsor should agree and prepare a written contract/agreement with the investigator prior to the trial, setting out the distribution of responsibilities.

Both the sponsor and investigator must agree on and sign the protocol as an agreement of the details of the clinical trial and the means of data recording (e.g. case report form (CRF)). Any major amendment to the protocol should be submitted with its justification to the ethics committee and drug regulatory authority, should be approved by the ethics committee, and should be agreed to by both the sponsor and the investigator before the amendment is implemented; any such agreement should be documented.

The sponsor may transfer responsibilities for any or all obligations to a scientific body (commercial, academic or others), or to a contract research organization (CRO). Any such transfer should be stated in writing.

5.2 Particular responsibilities of the sponsor

a) to select the investigator, taking into account the appropriateness and availability of the trial site and facilities, and be assured of the investigator's qualifications and availability for the entire duration of the study; to assure the investigator's agreement to undertake the study as laid down in the protocol, and according to these guidelines of Good Clinical Practice, including the acceptance of verification procedures, audit and inspection.

b) to inform the investigator of the chemical/pharmaceutical, toxicological, pharmacological and clinical data (including previous and on-going trials), which should be adequate to justify the nature, scale and duration of the trial, as a prerequisite to planning the trial and to bring to the attention of the investigator any relevant new information arising during the trial. All relevant information must be included in the Investigator's Brochure which must be supplemented and/or updated by the sponsor whenever new pertinent information is available.

c) to submit notifications/applications to the relevant authorities (where required) and to ensure the submission of any necessary documents to the ethics committee, and to ensure communication of any modification, amendment or violation of the protocol, if the change may have impact on the subject's safety or the outcome of the trial, and to inform the investigator and relevant authorities about discontinuation of the trial and the reasons for discontinuation.

d) to provide and supply the fully characterized, properly coded and labelled investigational pharmaceutical product(s) prepared in accordance with principles of Good Manufacturing Practice (GMP), and suitably packaged in such a way as to protect the product from deterioration, and that any blinding procedure is ensured.

Sufficient samples of each batch and a record of analyses and characteristics must be kept for reference so that if necessary an independent laboratory is able to re-check the investigational product(s), e.g. for quality control or bioequivalence.

Records of the quantities of investigational pharmaceutical products supplied must be maintained with batch/serial numbers. The sponsor must ensure that the investigator within his/her institution is able to establish a system for adequate and safe handling, storage, use, return and destruction of the investigational product(s).

e) to appoint and ensure the on-going training of suitable and appropriately trained monitors and their clinical research support personnel.

f) to appoint appropriate individuals and/or committees for the purpose of steering, supervising, data handling and verification, statistical processing and trial report writing.

g) to consider promptly, jointly with the investigator(s), all serious adverse events and take appropriate measures necessary to safeguard trial subjects, and to report to appropriate national authorities according to their requirements.

h) to inform promptly the investigator(s) of any immediately relevant information that becomes available during a trial and ensure that the ethics committee is notified by the investigator(s) if required.

i) to ensure the preparation of a comprehensive final report of the trial suitable for regulatory purposes whether or not the trial has been completed. Submissions of safety updates and annual reports may be required by the authorities.

j) to provide adequate compensation/treatment for subjects in the event of trial-related injury or death, and to provide indemnity (legal and financial cover) for the investigator, except for claims resulting from malpractice and/or negligence.

k) to agree with the investigator(s) on the allocation of responsibilities for data processing, breaking of the code, statistical handling, reporting of the results, and publication policy.

6. MONITOR

6.1 General role of the monitor

The monitor is the principal communication link between the sponsor and the investigator. The monitor is appointed by the sponsor and should be accepted by the investigator. The number of monitors may depend on the complexity of the trial and types of centres involved.

The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, its annexes and amendments. The monitor should have adequate medical, pharmaceutical and/or scientific qualifications. The qualifications most appropriate for a monitor will depend on the type of trial and the type of product under investigation.

The monitor or some other responsible person who has been notified by the sponsor and is known to the investigator, should always be available at any time to the investigator for consultation or reporting of adverse events.

The monitor should follow a predetermined written set of standard operating procedures (SOP). The main responsibility of the monitor is to oversee progress of the trial and to ensure that this is conducted and reported in accordance with the protocol. A written record should be kept of the monitor's visits, telephone calls and letters to the investigator.

Any unwarranted deviation from the protocol or any transgression of the principles embodied in Good Clinical Practice should be reported promptly by the monitor both to the sponsor and the interested ethics committee.

6.2 Particular responsibilities of the monitor

a) to work according to a predetermined standard operating procedure (SOP), visit the investigator before, during and after the trial to control adherence to the protocol and assure that all data are correctly and completely recorded and reported, and that informed consent is being obtained and recorded for all subjects prior to their participation in the trial;

b) to ensure, prior to the trial, that the trial site has adequate premises including laboratories, equipment, staff, and that an adequate number of trial subjects is likely to be available during the trial;

c) to ensure that all staff assisting the investigator in the trial have been adequately informed about, and will comply with the details of, the trial;

d) to enable/ensure prompt communication between the investigator and sponsor at all times;

e) to ensure that all CRFs are correctly filled out, in accordance with original observations and to clarify with the investigator any errors/omissions;

f) to ensure that all errors/omissions are corrected/commented on and that the investigator signs and dates the final edited CRFs. In addition, that these procedures are carried out continuously during the entire course of the trial;

g) to check that the supplies, storage, dispensing and return of investigational pharmaceutical product(s) are safe and adequate and properly documented and in accordance with local regulations and, where applicable, the trial protocol;

h) to assist the investigator in any necessary notification/application procedure;

i) to assist the investigator in reporting the data and results of the trial to the sponsor;

j) to submit a written monitor report to the sponsor (stating the findings and if actions were taken) after each visit and after all relevant telephone calls, letters and other contacts with the investigator (audit paper trail concept).

7. SAFETY MONITORING

The occurrence of adverse events must be monitored carefully and recorded in detail during the course of the trial.

7.1 General requirements

The trial protocol should clearly state method(s) by which adverse events will be monitored. It should also describe how this information is to be handled and analysed by the investigator and sponsor, and their responsibilities to report to each other and to the regulatory authority(s). The sponsor should provide adverse event reporting forms.

National regulations may require the sponsor and/or the investigator to report certain types of adverse events/reactions (e.g. serious, previously unknown, etc.) to the regulatory authority and ethics committee. If required, all such reports should be accompanied by an assessment of causality and possible impact on the trial and on future use of the product.

7.2 The investigator

The investigator has to report adverse events to the sponsor immediately and to the regulatory authority and the ethics committee in accordance with national regulations. Normally, adverse events associated with the use of the product must be reported to the regulatory authority within specified time limits.

Reports on adverse events submitted by the investigator to the drug regulatory authority should contain both subject and trial identification data (i.e. unique code number assigned to each subject in the trial).

When reporting adverse events to the sponsor, the investigator should not include the names of individual subjects, personal identification numbers or addresses. The unique code number assigned to the trial subject should be used in the report and the investigator should retain the code. The name of the investigator reporting the adverse events should be stated.

After the trial has ended, all recorded adverse events should be listed, evaluated and discussed in the final report.

7.3 The sponsor

During the conduct of the trial, the sponsor has to report adverse events/reactions to the drug regulatory authority according to national regulations.

The sponsor is responsible for reporting adverse events/reactions with the trial product to the local health authority as required by national regulations and to the other investigators involved in clinical trials of the same product.

The sponsor should also report as soon as possible to the investigator as well as internationally and nationally to drug regulatory authorities any trial with the same product that has been stopped anywhere in the world due to action taken by any regulatory authorities, or any other withdrawals from the market for safety reasons.

8. RECORD KEEPING AND HANDLING OF DATA

The aim of record keeping and handling of data is to record, transfer, and where necessary convert efficiently and without error, the information gathered on the trial subject into data which can be used in the report.

All steps involved in data management should be documented in order to allow for a step-by-step retrospective assessment of data quality and study performance (audit paper trail concept). Documentation is facilitated by the use of check-lists and forms giving details of action taken, dates and the individuals responsible.

A basic aspect of the integrity of data is the safeguarding of "blinding" with regard to treatment assignment. It starts with the randomization of patients into treatment groups. It is maintained through all steps of data processing up to the moment when the decision to break the code is formally taken.

In the event of electronic data handling, confidentiality of the data base must be secured by safety procedures such as passwords and written assurances from all staff involved. Provision must be made for the satisfactory maintenance and back-up procedures of the data base.

8.1 Responsibilities of the investigator

a) The investigator undertakes to ensure that the observations and findings are recorded correctly and completely in the CRFs and signed by the appropriate person after delegation according to the protocol.

b) If trial data are entered directly into a computer, th must always be an adequate safeguard to ensure validation including a signed and dated print-out an ck-up records. Computerized systems should be validated and a detailed description for their use be produced and kept up-to-date.

c) All corrections on a CRF and elsewhere in the hard copy raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction, dated and initialled by the investigator or the authorized person. For electronic data processing, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions.

d) If data are altered during processing, the alteration must be documented.

e) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ importantly from previous values must be evaluated and commented upon by the investigator.

f) Data other than those requested by the protocol acquired in the course of monitoring adverse events or recurrent or new illness may appear on the CRF clearly marked as additional/optional findings, and their significance should be described by the investigator.

g) Units of measurement must always be stated, and transformation of units must always be indicated and documented.

h) The final report of the trial should be drawn up as defined in the protocol and be signed by the sponsor/monitor/investigator(s) and the responsible statistician.

i) For a period of time defined by national regulations, the investigator should maintain a confidential record to allow the translation of the unambiguous code used to conceal the identity of the individual subjects of the trial (subject identification code).

8.2 Responsibilities of the sponsor and monitor

a) When using electronic data-handling the sponsor must use validated, error-free data processing programmes with adequate user documentation.

b) Appropriate measures should be taken by the monitor to avoid overlooking missing data or including inconsistencies. If a computer assigns missing values automatically, this should be made clear.

c) When electronic data handling systems or remote electronic data entry is employed, SOPs for such systems must be available. Such systems should be designed to allow correction after loading, and the corrections made must appear in an audit file.

d) The sponsor must ensure the greatest possible accuracy when processing data. If data are transformed during processing, the transformation must be documented and the method validated. It should always be possible to compare the data print-out with the original observations and findings.

e) The sponsor must be able to identify all data entered pertaining to each subject by means of an unambiguous code.

f) The sponsor must maintain a list of persons authorized to make corrections, and protect access to the data by appropriate security systems.

8.3 Archiving of data

The investigator must arrange for the retention of the subject identification codes for a sufficient period of time for reasons of safety and efficacy as instructed by the national regulations. Patient files and other source data must be kept for a period of time required by the local rules for hospitals, institutions or private practice. The sponsor or owner of the product must make appropriate arrangements for retention of all other documentation pertaining to the trial in a form which can be retrieved for future reference. Archived data may be held on microfiche or electronic record, provided that hard copy is available.

The protocol, documentation, approvals and all other documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out, must be retained by the sponsor. Data on adverse events must always be included.

All data and documents should be made available if requested by relevant authorities.

9. STATISTICS AND CALCULATIONS

The use of qualified biostatistical expertise is necessary before and throughout the entire trial procedure, commencing with the design of the protocol and CRFs and ending with completion of the final report and/or publication of results.

Where and by whom the statistical work should be carried out is agreed upon between the sponsor and the investigator and recorded in the protocol.

9.1 Experimental design

The scientific integrity of a clinical trial and the credibility of the data produced depend first on the design of the trial. In the case of comparative trials, the protocol should, therefore, describe:

a) an *a priori* rationale for the targeted difference between treatments which the trial is being designed to detect, and the power to detect that difference, taking into account clinical and scientific information and professional judgement on the clinical significance of statistical differences;

b) measures taken to avoid bias, particularly methods of randomization, when relevant, and selection of patients.

9.2 Randomization and blinding

In case of randomization of subjects the procedure must be documented. Where a sealed code for each individual treatment has been supplied in a blinded, randomized study, it should be kept both at the site of the investigation and with the sponsor.

In the case of a blinded trial the protocol must state the conditions under which the code is allowed to be broken and by whom. A system is also required to enable access to the information on treatment received by individual subjects in the case of an emergency. The system must only permit access to the treatment schedule of one trial subject at a time. If the code is broken, it must be justified and documented in the CRF.

9.3 Statistical analysis

The type(s) of statistical analyses to be used must be specified in the protocol, and any other subsequent deviations from this plan should be described and justified in the final report of the trial. The planning of the analysis and its subsequent execution must be carried out or confirmed by an identified, appropriately qualified and experienced statistician. The possibility and circumstances of interim analyses must also be specified in the protocol.

The investigator and monitor must ensure that the data are of the highest quality possible at the point of collection and the statistician must ensure the integrity of the data during processing.

The results of analyses should be presented in such a manner as to facilitate interpretation of their clinical importance, e.g. by estimates of the magnitude of the treatment effect/difference and confidence intervals, rather than sole reliance on significance testing.

An account must be made of missing, unused or spurious data excluded during statistical analyses. All such exclusions must be documented so that they can be reviewed if necessary.

10. HANDLING AND ACCOUNTABILITY OF PHARMACEUTICAL PRODUCTS

The sponsor is responsible for ensuring that the pharmaceutical product(s) supplied for the trial (investigational product, or reference products including placebo) are of appropriate quality and subject to quality assurance procedures (see 5.2 d).

10.1 Supply and storage

The arrangements made by the sponsor to supply the investigator with investigational pharmaceutical products for the trial should be described in the protocol. The manner in which investigational products are recorded, delivered, dispensed and stored should be detailed. Records should contain information about the shipment, delivery, receipt, disposition, return and destruction of any remaining pharmaceutical products. The investigator must not supply the investigational product to any person not targeted to receive it. Preferably a local pharmacy or the pharmacy department of the hospital should assume responsibility for storage, delivery, return and keeping records of the investigational pharmaceutical product(s). If it does, the procedure in the pharmacy must be documented to make auditing possible.

10.2 Packaging and labelling

The sponsor is responsible for the correct packaging and labelling of the pharmaceutical products used. The investigational products should be labelled in compliance with instructions from the national drug regulatory authority and the label should state that the product is for clinical research purposes only.

In blinded trials, the package should be labelled in a way that does not reveal the identity of the product. In an emergency it must be possible to determine the identity of the actual treatment received by an individual subject.

In blinded trials all investigational product(s), including reference products and placebos used, should be indistinguishable by appearance, taste, smell and other physical characteristics. If changes are made to the control product formulation, the need for a comparative *in vivo* bioavailability and dissolution test or other *in vitro* studies should be considered.

10.3 Responsibilities of the investigator

The investigator is responsible for ensuring:

- safe handling of the investigational products during and after the conduct of the trial, preferably in cooperation with a hospital pharmacy/pharmacy;
- that the investigational product is used only in accordance with the protocol and only for subjects included in the trial and by designated staff responsible to the investigator;
- that dosage and instructions for use are correct and that every subject involved understands them properly;
- that unused investigational products are returned to the pharmacy or sponsor or destroyed, and that records of these activities are kept according to the protocol.

10.4 Responsibilities of the sponsor and monitor

The sponsor is responsible for:

- ensuring that the package of investigational product(s) is of a size suitable for the trial and adequate for the trial subjects;
- keeping sufficient samples from each batch used in the trial as a reference for future re-checking and control and as provided in national regulations;

During the study visits the monitor should check:

- that the pharmaceutical products for the trial are used exclusively within the limits defined by the protocol;
- that supply records of investigational products are in order and that there are sufficient supplies;
- the expiry dates of batches;
- storage conditions of the pharmaceutical products for the trial;
- the handling of returned and/or unused pharmaceutical products.

11. ROLE OF DRUG REGULATORY AUTHORITY

The role of governments is to provide the legal framework for clinical trials. The aim should be twofold; to protect the safety and rights of the subjects participating in a trial and to allow only trials which may lead to conclusive data. This could be done by several means, including the specification of the competence needed for investigators and the demand for approval by relevant scientific/ethics committees. Regulatory authorities should have a

mandate to revise or terminate trials. The system must allow for on-site inspection of the quality of the data obtained, with due concern to subject confidentiality.

11.1 General responsibilities

The national drug regulatory authority should ensure that the protocols of clinical trials, submitted in advance for its review, are in accordance with existing national regulations and instructions.
Under national regulations and on the basis of its review of clinical trial protocols and/or reports, the regulatory authority may propose revisions or request additional data on a clinical trial or may terminate a trial.
The regulatory authority should be able to check on supervision of the conduct of the trial by requesting reports on the monitor's interaction with the investigator.

It should also be possible for the authorities to check the reliability and quality of reported results.

The drug regulatory authority should file the subject identification code list submitted by the investigator/sponsor at the same time as the signed final report.

National regulations should stipulate ways to report and handle misconduct discovered in connection with clinical trials.

11.2 Inspections

Under national regulations the regulatory authority might inspect the conduct of a clinical trial by on-site visits. Such an inspection should consist of a comparison of the procedures and practices of the clinical investigator with the commitments set out in the protocols and reports submitted to the drug regulatory authority by the investigator or the sponsor.

Inspections may be carried out either routinely, randomly or for specific reasons.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The data archives should be tested for retrieval.

12. QUALITY ASSURANCE FOR CONDUCT OF CLINICAL TRIAL

The sponsor is responsible for the implementation of a system of quality assurance in order to ensure that all sites, data and documents are available for verification.

All observations and findings should be verifiable in order to ensure the credibility of data and to assure that the conclusions presented are derived correctly from the raw data. Verification processes must, therefore, be specified and justified. Statistically controlled sampling may be an acceptable method of data verification in a trial.

Quality control must be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The sponsor's audit should be conducted by persons/facilities independen those carrying out the trial.

Any or all of the recommendations, requests or documents addressed in this Guideline or in national regulations may be subject to, and must be available for, an audit through the sponsor or a nominated independent organization and/or competent authorities (inspection).

Sponsor and investigational sites, facilities and laboratories, and all data (including patient files) and documentation must be available for institutional and independent sponsor audit as well as for inspection by competent authorities.

13. CONSIDERATIONS FOR MULTICENTRE TRIAL

See Appendix 3.

APPENDIX I

MODEL LIST OF ITEMS TO BE CONTAINED IN A CLINICAL TRIAL PROTOCOL

The trial protocol should, where relevant, be required to cover the following points:

1. Title and justification for the trial.

2. Statement of rationale, objectives and purpose of trial.

3. Site of the trial, name and address of the sponsor.

4. Name, address and qualifications of each investigator.

5. Description of the type of trial (controlled, open), trial design (parallel groups, cross-over technique), blinding technique (double- blind, single-blind), randomization (method and procedure).

6. Description of trial subjects. Criteria for inclusion and exclusion of potential trial subjects and process of recruitment, types, methods and time of allocation of subjects.

7. Number of trial subjects needed to achieve the trial objective based on statistical considerations.

8. Description of and justification for route of administration, dosage, dosage interval and treatment period for the pharmaceutical product being tested and the product being used as a control.

9. Any other treatment that may be given or permitted concomitantly.

10. Clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out.

11. Description of how responses are recorded. Description and evaluation of methods of measurement, times of measurements, follow-up procedures.

12. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.

13. Methods of recording and reporting adverse events/reactions, provisions for dealing with complications.

14. Procedures for the maintenance of subject identification code lists, treatment records, randomization list and/or case report form (CRF). Records should permit easy identification of individual patients/ participants and permit auditing and reconstruction of data.

15. Information on establishment of the trial code, where it will be kept and when, how and by whom it can be broken in the event of an emergency.

16. Measures to be implemented to ensure the safe handling and storage of pharmaceutical products, and to promote and control compliance with the prescribed and other instructions.

17. Description of methodology on the evaluation of results, (e.g. statistical methods) and on the report on patients/participants withdrawn from the trial.

18. Time schedule for completion of the trial.

19. Information to be presented to the trial subjects including how trial subjects will be informed about the trial and how and when consent will be obtained.

20. Staff instructions, i.e. statement of how the staff involved are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.

21. Ethical considerations and measures relating to the trial.

22. Medical care after the trial and modalities of post-trial treatment should be defined.

23. Statements regarding financing, insurance, liability, and delegation/distribution of responsibilities, i.e. when serving as a contract.

24. List of literature referred to in the protocol.

APPENDIX 2

WORLD MEDICAL ASSOCIATION

DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,
35th World Medical Assembly, Venice, Italy, in October 1983 and
41st World Medical Assembly, Hong Kong, in September 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers — either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX 3

CONSIDERATIONS FOR MULTICENTRE TRIALS

Because a multicentre trial is conducted simultaneously by several investigators at different sites following the same protocol, some special administrative arrangements are normally needed. Ideally, the trial should begin and end simultaneously at all sites.

A number of aspects are rendered more complex in multi-centre trials such as:

- the elaboration, discussion and written acceptance of the protocol and its annexes by all investigators;
- ethics committee(s), and the number of committees to be consulted;
- the organization of initial and intermediary meetings of parties involved;
- implementation of the trial;
- the randomization procedure;
- ensuring that the quality of the product is maintained during distribution and storage in different locations;
- the training of investigators to follow the same protocol;
- standardization of methods for evaluation and analyses of laboratory and diagnostic data (e.g. set-up of an external quality control system for laboratory assays);
- control of adherence to the protocol including measures to terminate participation of sites if necessary;
- role of monitor(s);
- centralized data management and analysis;
- drafting of the final report;
- publication.

A multicentre trial therefore may require a special administrative system, the scale of which will depend on the number of trial sites involved, study end-points and present knowledge of the investigational pharmaceutical product. One or several committees may be set up or the necessary functions may be performed by one or more designated person(s). The functions, responsibilities and mandate of the committee(s) or person(s) should be described in the trial protocol, as should the procedure for nomination.

The responsibility for commencement and overall performance of the trial could be the task of a committee/person. A second committee/person could be appointed to provide advice on policy matters and supervision of data. A third committee/person should have access to the results obtained in the trial, including adverse events. It should be stated in the protocol if and under what circumstances and how this committee/person can break the code. Interaction between these committee(s)/person(s) is necessary.

A coordinating committee could also be set up or a co-ordinator appointed with responsibility for the control of the practical performance and progress of the trial and maintaining contacts with the regulatory authorities and ethics committees.

This system will provide adequate assurance that the study will be planned and conducted according to acceptable scientific standards.