وزارة الصحة والسكان

قرار رقم ٤٣٥ لسنة ٢٠٠٦

بشأن المدونة المصرية لأساليب التصنيع الجيد للمستحضرات الحيوية والأمصال واللقاحات

وزير الصحة والسكان

بعد الاطلاع على القانون رقم ٤١٥ لسنة ١٩٥٤ فى شأن مزاولة مهنة الطب ؛

وعلى قرار رئيس الجمهورية رقم ٣٨٢ لسنة ١٩٧٦ بإنشاء الهيئة القومية للرقابة والبحوث الدوائية ؛

وعلى قرار رئيس الجمهورية رقم ٣٩٨ لسنة ١٩٩٥ بإنشاء الهيئة القومية للبحوث والرقابة على المستحضرات الحيوية ؛

وعلى قرار رئيس الجمهورية رقم ٢٤٢ لسنة ١٩٩٦ بتنظيم وزارة الصحة والسكان ؛

قـــرر :

مادة ١ - اعتماد مدونة منظمة الصحة العالمية لأساليب التصنيع الجيد للمستحضرات الحيوية المرفقة كمدونة مصرية لأساليب التصنيع الجيد للأمصال واللقاحات والمستحضرات الحيوية .

مادة ٢ - يتم تطوير المدونة وفقًا للتعديلات التى تجريها منظمة الصحة العالمية تمشيًا مع التطورات الحديثة فى مجال تصنيع المستحضرات الحيوية .

مادة ٣ - تقوم الهيئة القومية للبحوث والرقابة على المستحضرات الحيوية بطبع ونشر المدونة المصرية على الجهات المختصة .

مادة ٤ - ينشر هذا القرار فى الوقائع المصرية ، ويعمل به من اليوم التالى لتاريخ نشره .

تحريراً فى ٢٠٠٦/١١/٢٩

وزير الصحة والسكان

ا. د / حاتم الجبلى

N R A

National Guidelines and Regulations for GCP

INTRODUCTION

Goos Clinical Practice (GCP) is an interational ethical and scientific quality standard for designing conducting recording and reporting trials that involve the participation of human subjiects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this Guideline is to provide a standard to facilitate the mutual acceptance of clinical data by the regulatory authority.

The guideline was developed with consideration of the international current good clinical practices of the European Union. Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

The guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authority.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well being of human subjects.

GLOSSARY

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeuticdose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and adverse event is at least a reasonable possibility, ie. The relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding). Symptom, or disease temporally associated with the use of a medicinal (investigational) porduct, whether or not related to the medicinal (investigational) product.

Amendment (to the protocol)

See Protocol Amendment.

Applicable Regulatory Requirement (s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit

A systematic and independent examination of trial related activties and documents to determine whether the evaluated trial related activites were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, Sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate

A declaration of confirmation by the auditor that an audit. Has taken place.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

Audit trial

Documentation that allows reconstruction of the course of events.

Blinding / Masking

A procedure in which one or more parties to the trial arc kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and doubleplinding usually refers to the subject(s) being unaware of the treatment assignments(s).

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial / Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial / Study report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentation, and analysis are fully integrated into a single report.

Comparator (Product)

An investigational or marketed product (ie Active control), or palcebo, used as a reference in a clinical trial.

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct a multicentre trial.

Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to preform one or more of a sponsor's trial-related duties and functions.

Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e. g., domestic and foreign regulatory authorities, spinsor's minitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Documentation

All Pecords, in any from (Including, but not limited to, written, electronic, magnetic, and optical records, and scans, X-rays, and electrocardiograms) that describe of record the methods, conduct, and/or results of a trial the factors affecting a trial, and the actions taken.

Essential Documents

Documents whith individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Independent Data and Safety Monitoring Board

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptale representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), Constituted of medical / scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection by among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities and the methods and the material to be used in obtaining and documenting informed consent of the trial subjects.

Informed Consent

A process by which a subject voluntarily contirms his or her willingness to participate in a particular trial, after having been relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at site of the trial, at the sponsor's and/or contract reseaech organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority.

Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by reviewing, approving and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial / Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved from, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator

A person responsible for the conduct of the clinial trial at a trial site. If a trial is conducted by a team of individeuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure

A compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative

An individual or juridical or other body authorized under law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related Communication according to the sponsor's SOPs.

Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, therefore, carried out by more than one investigator.

Non-clinical Study

Biomedical studies not performed on human subjects.

Opinion (in relation to independent Ethics Committee)

The judgment and/or the advice provided by an independent Ethics Committee (IEC).

Original Medical Record

See Source Documents.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rational for the trial, but these could be provided in other protocol referenced documents. The term protocol refers to protocol and protocol amendments.

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR).

Any untoward medical occurrence that at any dose :

- results in death,

- is life-threatening,

- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.

Source Data

All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data, and records (eg. Hospital records, clinical and office charts, laboratory notes, memoranda, subjects, diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.

Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (eg. It does not include a corporation of an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs).

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Sub investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (eg. Associates residents, research fellows). See also investigator.

Subject / Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identify and used in live of the subject's name when the investigator reports adverse events and/or other trial related data.

Trial Site

The location(s) where trial-related activities are actually conducted.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

Chapter (1)

THE PRINCIPLES OF GCP

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that atr consistent with GCP and the applicable regulatory requirement(s).

- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

- The available non clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

- Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

- Freely given informed consent should be obtained from every subject prior to clinical trial participation.

- All clinical trial information should be rerecorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicaple regulatory requirement(s).

- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

- Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Chapter (2)

Protection of trial subjects and consultation of Ethics Committees

Protection of trial subjects

- The current revision of the Declaration of Helsinki is the accepted basis for clinical trial ethics, which must be fully known and followed by all engaged in research on human beings.
- The personal integrity and welfare of the trial subjects is the ultimate responsibility of the investigator in relation to the trial; but independent assurance that subjects are protected is provided by an Ethics Committee and freely obtained consent.

Ethics Committees

- The sponsor and/or investigator must request the opinion of relevant Ethics Committee(s) regarding suitability of clinical trial protocols (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 serious or unexpected AEs occurring during the trial, likely to affect the safety of the subjects or the conduct of the trial, and should be asked for its opinion if a reevaluation of the ethical aspects of the trial appears to be called for.

- Subjects must be entered into the trial until the relevant Ethics Committee(s) has issued its favourable opinion on the procedures and documentation. Sponsor/investigator should consider recommendations made by the Ethics Committee.

- In submitting clinical trial proposals to an Ethics Committee, they should be asked to consider the following :

  - The suitability of the investigator for the proposed trial in relation to his/her qualifications experience, supporting staff, and available facilities, on the basis of the information available to the committee.

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

  - The adequacy and completeness of the written information to be given to the subjects, their relatives, guardians and, if necessary, legal representatives.

  - The means by which initial recruitment is to be conducted and by which full information is to be given, and by which consent is to be obtained. All written information for the subject and/or legal representative must be submitted in its final form.

- Provision for compensation/treatment in the case of injury or death of a subject if attributable to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor.

- The extent to which investigators and subjects may be rewarded/compensated for participation.

- The Ethics Committee should give its opinion and advice in writing within a reasonable time limit, clearly identifying the trial, the documents studied and date of review.

Informed Consent

- In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/ favourable opinion of the written informed consent and any other written information to be provided to subjects.

- The written information consent form and any other written information should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written information consent form, and written information should receive the IRB/IEC's approval / favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

- Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in a trial.

- None of the oral and written information concerning the trial, including the written information consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the insitution, the sponsor, or their agents from liability for negligence.

- The investigator, or a person designated by the investigator should fully the subject or, if the subject is unable to provide legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favourable opinion by the IRB/IEC.

- The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

- Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

- Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

- If a subject is unable to read or if a legally acceptable representative is unable to read. An impartial witness be present during the entire informed consent discussion. After the written informed consent from and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative and that informed consent was freely given by the subject or legally acceptable representative .

- Both the informed consent discussion and the written informed consent form and any other written information to be provided to subject should include explanations of the following:

a) That the trial involves research.

b) The purpose of the trial.

c) The trial treatment (s) and the probability for random assignment to each treatment.

d) The trial procedures to be followed, including all invasive procedures.

e) The subject's responsibilities.

f) Those aspects of the trial that are experimental.

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable. to an embryo. fetus, or nursing infant.

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

i) The alternative, procedure (s) or course (s) of treatment that may be available to the subject, and their important potential benefits and risks.

j) The compensation and/or treatment available to the subject in the event of trial - related injury.

k) The anticipated prorated payment, if any, to the subject for participating in the trial.

l) The anticipated expenses, if any to the subject for participating in the trial.

m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

n) That the monitor(s), the auditor(s), the IRB/IEC., and the regulatory authority will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confindentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

o) That record identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations. will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial -related injury.

r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

s) The expected duration of the subject's participation in the trial.

t) The approximate number of subjects involved in the trial.

- Prior to participation in the trial, the subject or the subject legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed of any amendments to the written information provided to subjects.

- When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (eg. Minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and. if capable. the subject should sign and personally date the written informed consent.

- A non-therapeutic trial (i.e. A trial in which there is no anticipated direct clinicale benefit to the subject), should be conducted in subject who personally give consent and who sign and date the written informed consent form.

- Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled.

(a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

- In emergency situation, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatroy requirements. The subject or the subject's legally acceptable representative should be informed about the trial ans soon as possible and consent to continue and other consent as appropriate should be requested.

Chapter (3)

SPONSOR

- The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicenter trials, their organization and or selection are the sponsor's responsibility.

- Before initiating the clinical trial(s), the sponsor (of the sponsor and the investigator, should submit any required application(s). to the appropriate authority for review, acceptance, and/or permission to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

- The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

The sponsor must establish detailed Standare Operating Procedures (SOP) to comply with Good Clinical Practice, and is responsible for conducting an internal audit of the trial The sponsor should agree with the investigator on 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. CRF). Any such agreement must be documented.

- Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

- A sponsor may transfer any or all of the sponsor's trial - related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

- The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, out side consultant(s) may be appointed for this purpose.

- The sponsor should utilize qualified individuals (eg. Biostatisticlians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical reports.

- The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

- The sponsor should obtain the investigator's agreement to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC.

- Prior to initiating a trial, the sponsor should define establish, and allocate all trial- related duties and functions.

- The sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the malpractice and/or negligence.

- The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

- The sponsor should obtain confirmation of review by IRB/IEC and documented approval/favourable opinion.

- When planning trials, the sponsor should ensure that sufficient safety and efficacy data from non clinical studies, and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

- The sponsor should update the/investigator's Brochure as significant new information becomes available.

- The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

- The sponsor is responsible for supplying the investigator (s) institution(s) with the investigational product(s).

- The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial.

- The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s) / institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

- The sponsor should expedite the reporting to all concerned investigator(s), to the IRB(s)/IEC(s) where required, and to the regulatory authority of all adverse drug reactions (ADRs) that are both serious and unexpected.

- The sponsor should submit to the regulatory authority all safety updates and periodic reports, as required by applicable regulatory requirement(s).

Monitoring

- The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial.

Monitor's Responsibilities

- The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site :

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adeguate throughout the trial period.

(c) Verifying that storage times and conditions are acceptable for the investigational products. And that supplies are sufficient through out the trial.

(d) Verifying that investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brachure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator / institution, and have not delegated these functions to unauthorized individals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, ant that these douments are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized initial CRF changes for the investigator. The authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriateley reported within the time periods required by GCP the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents.

(q) Communicating deviations from the protocol, SOPs GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Monitoring Report

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant finding/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

Auditing

- The sponsor is responsible for performing audits as part of implementing quality assurance. The purpose of a sponsor's audit, which is independent of and separate from routing monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

- The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

- The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

- The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit repots.

- The sponsor's audit plan and procedures for a trial audit should guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial. the level of risks to the trial subjects. and any identified problem(s).

- The observations and findings of the auditor(s) should be documented.

- If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority.

- If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator / institution, as specified by the applicable regulatory requirement(s).

- Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).

Multicentre Trials

- For multicentre trial, the sponsor should ensure that :

- All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, by the regulatory authority, and given approval/favourable opinion by the IRB/IEC.

- The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

- The responsibilities of coordinating investigator(s) and the other paritcipating investigators are documented prior to the start of the trial.

- All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

- Communication between investigators is facilitated.

Chapter (4)

INVESTIGATOR

- The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority.

- The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, and in the product information.

- The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

- The investigator / institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority.

- The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

- The investigator should be able to demonstrate (eg. Based on retrospective data) a potential for recruiting the required number of suitalbe subjects within the agreed recruitment period.

- The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

- A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

- During and following a subject's participation in a trial, the investigator / institution should ensure that adequate medical care is provided to a subject for any adverse events, in clinically significant laboratory values, related to the trial. The investigator / institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

- It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

- Before initiating a trial, the investigator / institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent from, subject recruitment procedures (eg. Advertisements), and any other written information to be provided to subjects.

- As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the investigator's Brochure. If the investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated investigator's Brochure to the IRB/IEC.

- The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

- The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, should be submitted:

(a) to the IRB/IEC for review and approval.

(b) to the sponsor for agreement.

(c) to the regulatory authority.

- The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

- The investigator / institution should maintain the trial documents as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.

- The investigator should submit written summaries of the trial status to the IRB/IEC and NRA annually , or more frequently, if requested.

- The investigator should promptly provide written reports to the sponsor, the IRB/IEC and Regulatory Authority, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

- The investigator should notify (with documentation) sponsor, the Ethics Committee and NRA immediately in the case of the serious AEs and to take appropriate measure to safeguard subjects.

- The investigator should make all data available to the sponsor, monitor and authority for verification. audit and inspection purposes.

- The investigator should agree and sign the final report of the trial. For mutlicentre trials the signature of the coordinating investigator may suffice if a great in the protocol.

- The investigator should ensure that the confidentiality of all information about subject is respected by all persons involved as well as the information supplied by the sponsors.

Chapter (5)

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT (S)

- The contents of a trial protocol should generally include the following topics.

General Information

- Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

- Name and address of the sponsor and monitor (if other than the sponsor).

- Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

- Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

- Name, title address, and telephone number(s) of the qualified physician who is responsible for all trial-site related medical decisions (if other than investigator).

- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information

- Name and description of the investigational product(s).

- A summary of findings from non clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

- Summary of the known and potential risks and benefits, if any, to human subjects.

- Description of and justification for the route of administration, dosage, dosage regimn, and treatment period(s).

- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

- Description of the population to be studied.

- Refernces to literature and data that are relevant to the trial, and that provide background for the trial.

- A detailed description of the objectives and the purpose of the trial.

- The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design, A description of the trial design, should include :

- A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

- A description of the type/design of trial to be conducted (eg. Double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

- A description of the measures taken to minimize/avoid bias, including:

(a) Randomization.

(b) Blinding.

- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up. if any.

- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

- Maintenance of trial treatment randomization codes and procedures for breaking codes.

- The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

Selection and Withdrawal of Subjects

- Subject inclusion criteria.

- Subject exclusion criteria.

- Subject withdrawal criteria.

Treatment of Subjects

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment / trial treatment group/arm of the trial.

- Medication(s) treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

- Procedures for monitoring subject compliance.

Assessment of Efficacy

- Specification of the efficacy parameters.

- Methods and timing for assessing, recording, and analysing of efficacy parameters.

Assessment of Safety

- Specification of safety parameters.

- The methods and timing for assessing, recording, and analysing safety parameters.

- Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

- The type and duration of the follow-up of subjects after adverse events.

Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

- Access to biostatistical expertise is necessary before and throughout the entire trial procedure, commencing with designing of the protocol and ending with completion of the final report.

- Where and by whom the statistical work shall be carried out should be agreed upon by both the sponsor and the investigator.

Experimental Design

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

a) An 'a priori' rationale for the target 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 judgment on the clinical significance of statistical differences;

b) Measures taken to avoid bias, particularly methods of randomization when relevant.

Randomisation 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 at the site of the investigation and with the sponsor.

- In case of a blinded trial the protocol must state the conditions for which the code may/must be broken. A system is required enabling access to the treatment of individual subjects in case of an emergency. The system must only permit access to the treatment key of one subject at a time. If the code is broken it must be justified in the CRF.

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 high quality at the point of collection and the statistician must ensure the integrity of the data during their processing.

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

- An account must be made of missing and unused and spurious data during statistical analyses. All omissions of this type must be documented to enable review to be performed.

Data Handling

- The investigator undertakes to ensure that the observations and findings are recorded correctly and completely in the CRFs and signed.

- Entry to a computerized system is acceptable when controlled as recommended in the EEC guide to GMP.

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

- 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 initialed by the investigator. 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 changed and deletions.

- If data are altered during processing, the alteration must be documented and the system validated.

- Laboratory values with normal refernce ranges should always be recorded on CRF or attached to it. Values outside a clinically accepted reference renge or values that differ importantly from previous values must be evaluated and commented upon by the invertigator.

- Data enter than those requested by the protocol may appear on the CFR clearly marked as additional findings, and their significances should be described by the investigator.

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

- The investigator should always make a confidential record to allow the unambiguous identification of each patient.

- The sponsor must use validated, error-free data processing programmes with adequate user documentation.

- Appropriate measures should be taken by the monitor to avoid over-looking missing data or including logical inconsistencies. If a computer assigns missing values automatically, this should be made clear.

- When electronic data handling systems or remote electronic data entry are employed, SOPs for such systems must be available. Such systems should be disigned to allow correction after loading, and the correction must appear in an audit file.

- The sponsor must ensure the greatest possible accuracy when transforming data. It should always be possible to compare the data print-out with the original observations and findings.

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

- If data are transformed during processing, the transformation must be documented and the method validated.

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

Archiving of Data

- The investigator must arrange for the retention of the subject identification codes for at least 5 years after the completion or discontinuation of the trial. Subject files and other source data must be kept for the maximum period of time but not less than 5 years. The sponsor, or subsequent owner, must retain all other documentation pertaining to the trial for the lifetime of the product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that hard copy be obtained from it if required.

- The protocol, documentation, approval and all other documents related to the trial, including certificates that satisfactory audit and procedures have been carried out, must be retained by the sponsor in the Trial Master File.

- The final report must be retained by the sponsor, or subsequent owner, for five years beyond the lifetime of his product. Any change of ownership of the data should be documented.

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

Language

- All written information and other material to be used by patients and Para clinical staff must use language which is clearly understood.

Chapter (6)

Definition of Clinical Trials

- In this context, a clinical trial of medicinal product(s) means any systematic study 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 the investigational products, and/or to study their absoption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products.

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

Phase I

- First trials of a new active substance in man, often healthy volunteers. The purpose is to establish a preliminary evaluation of safety and a first outline of the pharmacokinetic/-dynamic profile of the active substance in humans;

Phase II

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

Phase III

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

Phase IV

- Studies performed after marketing of the final medicinal product(s), although definition of this phase is not completely agreed upon. Trials in phase IV are carried out on the basis of information in the summary of product characteristics of the marketing authorization, e.g.

post-marketing survellance, assessment of therapeutic value or strategies. According to the circumstances. Phase IV studies require trial conditions (including at least a protocol) such as described above for pre-marketing studies. After a product has been placed on the market, clinical trials exploring e.g. new indications new methods of administration or new combinations, are considered as trials for new medicinal products.

Financial the Trial

- All finacial problems involved in conducting and reporting a trial should be clearly arranged and a budget made out. Information should be available about the sources of economical support (e.g. foundations, private or public funds, sponsor/manufacturer). Likewise it should be clearly apparent how the expenditures are distributed, e.g. payment of volunteers, refunding expenses of the patiests, payment for special tests, technical assistance, purchase of apparatus, possible fees to or reimbursement of the members of the research team, payment of the University/Clinic, etc.

- Competent authorities may require detailed knowledge about the connection (economic etc.) between the individual researcher and the manufacturer of the product(s) involved, in cases where such information is not obvious.

Insurance and Liability

- Patients/healthy volunteers taking part in a clinical trial should be satisfactorily insured against any injury caused by the trial. The liability of the involved patients (investigators, sponsor/manufacturer, hospital/clinics, etc.) must be clearly undrstood before the start of a trial of a medicinal product containing an active substance.

Systems of Notification/Approval of clinical Trials

- In Member States where regulation of medicinal products requires a notification or an application for approval before a trial is commenced the national rules must be consulted and complied with. In some countries a special form must be used. The notification/application must be signed by the investigator, the sponsor and the head of the institution or department, where the trial is to take place. The person(s) signing will be held responsible for the performance of the trial, including all deviations form the protocol, in accordance with the national regulations. The notification/application usually should comprise the information specified in the present document, but the requirements may vary among the Member States. For a product already authorized as a medicinal product, a reference to information previously submitted will usually be sufficient.

- In general, notifications/applications should be field with the competent authority in the following situations :

a) Non authorized products : all clinical trials;

b) Authorized medicinal products, if the trial is :

1 - Planned to explore new indications,

2 - Carried out in patient groups not previously studied adequately,

3 - Done with considerably higher dosage than previously approved.

4 - Phase IV studies.

Pre-Trial Data

- Chemical, pharmacutical, animal pharmacological and toxicological data on the substance and/or the pharmaceutical form in question must be available and professionally evaluated before a new product is subjected to clinical trials. The sponsor's responsibility for providing exhaustive, complete and relevant material, e.g. by means of an investigator's Brochure, is emplasized.