MINISTRY OF HEALTH **SOCIALIST REPUBLIC OF VIETNAM**

No: 799/QĐ-BYT **Independence - Freedom - Happiness**

Hanoi, date March 7th, 2008

DECISION

On the issuance of Guideline on "Good Clinical Practice"

MINISTER OF HEALTH

Pursuant to Decree No. 188/2003/NĐ-CP dated December 27, 2007 of the Government detailing functions, obligations, and authority and structural organization of Ministry of Health;

Pursuant to Decree No. 79/2006/NĐ-CP dated August 9, 2006 detailing on the implementation of provisions of Drug Law;

At proposal of Head of Department of Science and Training and Director of Vietnam Drug Administration,

DECIDES:

Article 1: To issue the "Guideline for Good Clinical Practice – GCP" (hereafter referred as Guideline for GCP) in conjunction with this Decision.

Article 2: Assign Head of Department of Science and Training to cooperate with related Departments to be responsible for propagating, instructing, monitoring, inspecting of the implementing and deploying of this Guidelines.

Article 3: This Decision takes effect since the issuing date.

Article 4: Chief of secretariat, Director of Health Inspector, Heads of Departments, Offices, and Entities attached to Ministry of Health, Manager of Health Departments of the provinces and centrally-run cities, Head of Health department of agencies shall implement this Decision.

Receipt:
- As in Article 4;
- Minister of Health;
- Deputy Minister of Health
- Vietnam Medical Association, Vietnam Pharmaceutical Association;
- Ministry of Health's Website;
- Keep as achieves at DST and DAV

FOR THE MINISTER

DEPUTY MINISTER

Signed

Nguyen Thi Kim Tien

MINISTRY OF HEALTH

GUIDELINE FOR GOOD CLINICAL PRACTICE

Abbreviated: Guideline for GCP

Issued in the conjunction with Decision No: 799 /2007/QĐ-BYT

Date 07 month March 2007 of Minister of Health.

Chapter I

GENERAL PROVISIONS

1. Scope

This document instructs on the preparation of dossier, protocol, review process, approval and carry out the implementation, monitoring, checking and inspection Clinical trials in Vietnam in order to satisfy requirements of Good Clinical Trial of World Health Organization and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human use and comply with current legislation in Vietnam.

2. Subject

This guideline applies to organization, person whose activities relate to clinical trial of pharmaceutical product in Vietnam.

3. Definition

The terms in this Guideline are understood as below:

Clinical trial of pharmaceutical products

Clinical trial of pharmaceutical product is a scientific practice in human in order to identify clinical effect, detect unexpected adverse reaction of pharmaceutical product, the absorption, distribution, metabolism and excretion of pharmaceutical product so that the safety and the effect of pharmaceutical products are demonstrated.

Terms of "clinical trial of pharmaceutical products", "Clinical trial" and/or "pharmaceutical products clinical trial" have the same meaning. Hereafter, only term of Clinical trial is used within this document.

Good clinical practice

Good clinical practice-GPC is an international standard guideline instructing the investigator, Head of Sponsor, researching staff, sponsor, aid agencies, competent authorities; reviewing committees (including scientific and ethnic committees) of assessing the ethics and science in designing, conducting, implementing, monitoring, and assessing, recording, analyzing and reporting clinical trials.

GCP assures the reliability, accuracy of reported data of clinical trial results and the international acceptance to clinical results together with simultaneously protects the safety and rights of trial subjects.

The term of Good Clinical Practice on pharmaceutical product is the same and translated from "Good Clinical Practice – GCP" in English. Within this document, it is unified to use term "Good Clinical Practice"

Investigator and research organization

Investigator (also known as researcher) is person responsible for conducting the clinical trial at the trial site. In case the clinical trial is conducted by cohort, group leader (also known as the principal investigator or the manager of the project) shall be essentially responsible for such clinical trial.

In addition to the principal investigator, there are also Investigators and collaborators including experts and local people who is under the instruction of principal investigator of project on assignment, management and monitoring in order to conduct researching process related to clinical trial.

Research organization (organization who conducts the clinical trial)

Research organization (organization who conducts the clinical trial) is medical unit which has functions in scientific research, has adequate man power and material facilities for the clinical trial which are reviewed and approved by MOH. Research organization is one to be responsible for legal matters concerning to the clinical trial.

Besides researching organization, there may be collaborative organization in addition to said stakeholder of the clinical trial if necessary. Such collaborative

organization assumes responsibility in several certain stages and/or parts of the clinical trial according to the allocation of researching organization.

Organization/person who have drug in clinical trial

Organization/person who have drug in clinical trial have function in researching, producing, importing, exporting or distributing drug which is in need of clinical trial.

Sponsor

The sponsor may be an individual, an enterprise or an entity or an organization. The sponsor assumes responsibility in proposal, management and/or financial supply of the clinical trial.

Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

Independent Ethics Committee-IEC (also known as Ethics Committee) which is an independent entity is established local or national level. IEC includes medical experts and non-medical members. IEC is responsible for reviewing the scientific aspects of protocol and matters related to subject's voluntarily so that the safety, rights, health of trial subjects and the publicity are assured and giving the approval or not to the clinical trial.

Investigator's brochures - IB

Investigator's brochures – IB is document recording clinical and pre-clinical data of investigational products, whose information needs to be brief, simple, clear and not to be advertisement in order to provide investigators needed information about investigational products and process to control safety – which allows clinical physician or investigator may understand and self-determine exactly the risk/benefit of the proposed clinical trial.

Standard Operation Practice

Standard of Practice (SOP) is document which is developed by related units to define activities and unified operations in order to get the agreements when implement.

Monitoring, audit

- Monitoring are those of clinical trial process to assure that the trial is conducted, recorded and reported in accordance with the research outline, standard operation process, GPC and other regulations being applied in the country.

- Monitor is a person entrusted by the sponsors or the investigators in an agreement, such person assume responsibility in monitoring and reporting clinical trial process and verifying the data.

- Audit

Audits are activities of competent authorities which base on the reviewing, evaluation of documents and report in order to checking the compliance to protocol.

- Inspection

Inspection is official inspection activity of related competent authorities to review the compliance to GCP.

Chapter II

TARGET AND PRINCIPLES OF GCP

1. Target of GCP

Target of the issuance of GCP as follows:

- To protect the trial subjects in clinical trial:

+ To assure the safety of the trial subject.

+ To assure rights or the trial subject including rights to be informed, to self-determine joining the research, to give up the research at the any time, to be protected individual information and other rights.

- To assure the quality of the research based on the scientific unity of the research process, research target, quality of the performance, monitoring made to the clinical trials.

- To assure the unity in the management process, monitoring, analysis and report made to the clinical trial, so that given out results are accepted under the international standard guidelines.

- To assure the reliability and the effective performance of the quality monitoring system.

2. Principles of GCP

GCP gives out 13 principles, each of them intends to obtain one ore more targets of GCP. The principles of GCP present the international recognition of ethic and quality target of clinical the trials.

There is no principle setting up the independent responsibility of each party joining the clinical trial (such as investigator, sponsor, IEC, IRB or competent authorities). However, all of 13 principles require for jointly liability of the related parties to the clinical trial. Principles of GCP include:

- ***Principle 1:*** The clinical trial should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki.

- ***Principle 2:*** Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society.

- ***Principle 3:*** The clinical trial should be conducted only if anticipated benefits clearly prevail over the foreseeable risks. Scientific and social benefit should be carefully considered so that the rights, the safety and health of trial subjects are assured.

- ***Principle 4:*** The clinical trial should be conducted in strict compliance with the protocol approved by IEC, IRB and competent authorities.

- ***Principle 5:*** The approval to clinical trial, clinical trial methods of a certain product shall be carefully considered, such action must be supported by non-clinical, clinical information and other available research results relating to the product.

- ***Principle 6:*** The clinical trial should be conducted in the compliance with scientific protocol as specified in the approved research process.

- ***Principle 7:*** The trial subjects optionally agree to participate in the trial and those should be fully provided with information of the clinical trial as well as other related one. Trial subjects are entitled to request for the explanation, clarification of the information relating to the clinical trial and their own culture,

custom should be respected. Participating in the clinical trial, the trial subjects are provided healthcare services for free and this matter should be pre-notified. In case, the trial subjects are not qualified by the awareness or the legal personality to make the agreement, such agreement should be obtained from their legal representatives.

- *Principle 8:* The medical care given to, and medical decisions made on subjects should be the responsibility of the qualified physician in the clinical trials.

- *Principle 9:* Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s) in the clinical trials.

- *Principle 10:* All clinical trial information should be recorded, handled and stored in such way that allows accurate reporting, interpretation, monitoring the reliability thereof.

- *Principle 11:* The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulation of each country.

- ***Principle 12:*** Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP) and they should be used in accordance with the approved protocol.

- ***Principle 13:*** Systems that assure the quality and method for assuring the quality of every aspect of the trial should be fully implemented in the compliance with the Guideline for GCP and regulation of each country.

It is required to approach the principles of GCP from the position of a manager, law maker, sponsor or investigator. Each of such position should approach and apply the principles of GCP in the suitable way.

Chapter III

RIGHTS AND RESPONSIBILITY OF IEC, THE SPONSORS, INVESTIGATOR AND RESEARCH ORGANIZATION

1. Right of Independent Ethics Committee (IEC)

Review and approve for ethnic aspect of research and specific scientific aspect of protocol in clinical trial in which subjects is human according to regulations and consult to Minister for the approval before implementing trials as well as for the changes in implementing process.

2. Responsibility of IEC

- IRB/IEC takes responsibility for scientific and ethnic aspects of trial in order to assure rights, the safety and health of the trial subject, especially clinical trials with sensitive subjects.

IRB/IEC should conduct the assessment and reply for proposal of the clinical trial in an appropriate time and their opinion should be in written documents.

- *IRB/IEC should consider the followings:*

+ The scientific aspects of protocol

+ Related ethnic aspects and the compliance of other legislation applied in the trial

+ The assurance of the right of subjects, even in case subject does not finish the trial

+ Qualification and ability of Manager of trial and investigator

+ The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

+ Composition, Functions and Operations of IRB/IEC is stipulated in current guideline " Regulation of constructional organization and operation or the ethic Committee in medical research"

+ The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3

years after completion of the trial and make them available upon request from the competent authorities.

The investigators, sponsors or regulatory authorities may ask the IRB/IEC to provide its written procedures and membership lists.

2. Rights of the sponsor (organization or individual have researching drug)

- The sponsor may transfer any or all trial-related duties to the investigators or the research organization as recorded in the agreement. However, the ultimate responsibility for quality and integrity of the trial data always resides with the sponsor.

- The sponsor may establish and conduct the irregular or regular monitoring; such protocol is independent with the daily and/or regular, and/or irregular monitoring of the investigators, the research organization, Ethics Committee and competent authorities.

- The sponsor may apply the emergency measures to suspend or terminate the investigators, research organization's participation upon identifying serious infringements, noncompliance with the trial protocol or unexpected adverse reaction that seriously impact on health of the trial subjects.

- The sponsor may reserve the ownership of investigation results, rights to publish the investigation results, register of copyright, intellectual property right (if it satisfies the requirement as stipulated by law), right to publish document relating to the clinical trial in accordance with the applicable regulation and after get the agreement with Head of organization or individual having researching drug.

3. Responsibility of the sponsor

- The sponsor should draft and provide the investigator's brochures introducing, assuring quality as well as stability of the investigational products. The sponsor should be responsible for reliability of information related to the investigational product recorded in the investigator's brochures.

- The sponsor should provide investigator's brochures to investigator and should jointly assume responsibility in designing the research, the clinical trial protocol, and products of the sponsor.

- Submit investigator's brochure to competent authorites

- After obtaining the approval of Ethics Committee, Science Committee and the management office, the sponsor should sign a pharmaceutical product's trial agreement with the principal investigator (chief of the trial) and research organization (the entity that holds the trial).

- The sponsor assumes responsibility in manufacture, package, labeling and encoding the investigational products. Such products should be manufactured in compliance with the applicable GMP issued by the competent authorities in order to assure its quality. As to the trial wherein the blinding is conducted, the investigational products should be labeled, encoded and blinded in compliance with the approved protocol, and the product's label should be designed in accordance with the applicable regulation.

- The sponsor only provides the investigators with the pharmaceutical product after it is approved by the ethics committee and the competent authorities. The sponsor should assume the responsibility in revoking and destroying the unused, ruined and remained products after completing the clinical trial.

- The sponsor should monitor and control trial's quality, trial subject's safety and the adverse effects or inconvenience occurred to the trial subject as well as trial data, the compliance with approved protocol.

- The sponsor is responsible for regular and irregular reports on rate of progress, safety of the trial subjects, the compliance with the approved protocol, the management of investigational products as well as the safety and unexpected adverse reaction of the investigational products to IEC and the management office.

- The sponsor is responsible for management, accession and the confidentiality of the trial subjects, in cooperating with the investigator to comply with the approved protocol.

- After publishing the trial result and manufacturing the products, the sponsor also assumes the ultimate responsibility for the safety, quality of products as well as the diagnostic or treatment or prevention's effect of the investigational products.

- The sponsor should supply the investigator with finance and other resources in accordance with the approved outline and investigation agreement signed between the sponsor and the investigator.

- The sponsor should provide the investigator and the research organization with the compensation including financial and legal coverage for damage arisen (if any) in accordance with the applicable regulation, except that such damages arisen from negligent of the investigators and the research organization.

- The sponsor should provide the trial subjects with compensation including property and spirit and legal coverage in case of unexpected adverse reaction that seriously impact on research subject's health (such as death or invalidity. etc…). However, the compensation should be made in case such damage involves products that provided by the sponsor.

4. Right and responsibility of the principal investigator (manager of the research)

- The principal investigator may select investigators and management office and cooperate with related offices to propose to the sponsor.

- The principal investigator may select the laboratory that meets GLP's requirements in accordance with the applicable regulation. In case the selected laboratory does not satisfy requirement of GLP, it must be approved by an assessment committee established by the management office.

- The principal investigator should be paid for clinical investigational products. They may share responsibility and rights with the sponsor in the trial. Rights or the investigator and the research organization should be recorded in written documents in the research design and the research contract.

- They may publish the trial results provided that such action is agreed by the sponsor and it is recorded in written documents in the research contract.

- Discoveries of products that are not recorded in the approved research design or the research agreement should be own by the investigator.

- Rights to conduct the clinical trial, to select the trial subjects, to audit and monitor the clinical trial according to the approved trial design and protocol.

- Investigator may suspend or terminate the clinical trial if the unexpected adverse reaction that seriously affect the trial subjects and the community.

- They may propose the amendment of the research protocol to IRB/IEC, the sponsors and the competent authorities if it is necessary. Such amendment should be performed if it is approved in written by IRB/IEC, sponsors and the management office.

- The principal investigator may sign the trial agreement with the sub-investigator and/or incorporating entity to conduct any stage of the clinical trial or the medical care for the trial subjects (if any) in accordance with the approved research protocol.

5. Responsibility of the principal investigator

- The principal investigator is responsible for selecting qualified investigators, medical expert that educated in the fields related to the clinical trial and proposing them to the sponsors for assessment and approval.

- The investigator takes responsibility in drafting the outline of the research, trial protocol, process and standards for selecting trial subjects, coordinating with the sponsor to complete science profile, ethics documents in accordance with current Vietnam's regulation.

- The investigator assume the responsibility on negotiating, drafting and signing the research agreement with the sponsor (including finance for the research, assessment, approval, monitoring and management of the trial) and settling the payment in accordance with the research agreement signed between the investigator and the sponsor.

- The investigator is responsible to coordinate with the sponsor in submitting the trial document to IEB/IEC and the competent authorities for the approval.

- After obtaining the approval of IRB/IEC and the competent authorities, the investigator is responsible for conducting the clinical trial in accordance with the approved trial design. It is also responsible for obtaining the agreement of the consent from the trial subject and selecting trial subject in order to assure that such selection is random.

- The investigator assumes the responsibility for the compliance with the approved trial protocol. Any amendment (if any) made to such protocol is

performed only after it is approved by IRB/IEC and the competent authorities in written document. Such amendment should be reported to the sponsor.

- The investigator should conduct the procedure of blinding the products (if any) in compliance with the design, and assure the confidentiality of the blinding procedure. It should be decoded after finishing the trial or it is required by the sponsor, IRB/IEC and the management office in case of involving to the safety of the trial subjects.

- The investigator takes responsibility in recording, reporting and storing data, original profiles of the clinical trial and handling, analyzing data, making judgment and regularly/irregularly reporting to the sponsor, management office, IRB/IEC on sub-reaction, adversity, safety and effect of the investigational products. It is also responsible for drafting the final report of the clinical trial to the sponsor, management office, IRB/IEC and drafting checking over report as required by the competent authorities.

- The investigator is responsible for providing the sponsor, IRB/IEC or the competent authorities with the profile, data and other documents relating to the clinical trial if it is required in accordance with the applicable regulation. It is required to assist the auditor, monitor designed by the sponsor, competent authorities, IRB/IEC to audit, monitor and inspect the clinical trial.

- It is responsible for monitoring, storing and providing the investigational product to the subjects according to the approved trial design, protocol. Beside, it is required to take responsibility in revoking, managing and delivering remained product to the sponsor after finishing the clinical trial.

- The investigator is responsible for paying allowance (if any) to the trial subjects, medical caring trial subjects in compliance with trial design and conducting medical care that relating to the clinical trial.

- The investigator should provide the trial subjects with compensation including property and spirit and legal coverage in case of unexpected adverse reaction that seriously impact on research subject’s health (such as death or invalidity. etc…) in such damage involves to incompliance to approved protocol.

6. Right of research organization

- Manage and control activities related to clinical trial

- Terminate or early finish if discovers any unexpected adverse effects of researching product which seriously impact to the health of subject or community.

7. Responsibility of research organization

- The research organization is responsible for assisting the investigators, sponsor, IRB/IEC and the management office in matters relating to resources (employment, properties including equipments, devices, etc.), legal basis and other condition of the clinical trial in accordance with the approved trial design and contract.

- Sign and liquidate the contract

- The research organization should coordinate with the investigator in monitoring, assuring the quality as well as effect and the safety of the clinical trial.

- The research organization should monitor regularly and report to sponsor, IEC and competent authorities according to regulation in protocol and contract.

- The research organization should comply with the Guideline for GCP, applicable guideline on ethics in research and clinical trial of Vietnam.

CHAPTER V

REVIEWING PROCEDURE AND APPROVAL FOR CLINICAL TRIAL

(Attached with diagram in reviewing procedure of dossier for clinical trial and check list of minimised documents needed for implementing clinical trial)

1. Registration of clinical trial

- Sponsor prepare for registration dossier including: form for proposal of clinical trial, proposal for principal investigator and research organization attached with product's dossier (according to form in annex 1, 2a and 2b).

- Submit above dossier to MOH (Department of Science and Training). Withthin 15 working days since the day of receiving completed dossier, MOH will reply to sponsor for next steps.

2. Design of protocol

Base on approved document of MOH, Sponsor cooperate with principal investigator to develop protocol of clinical trial (according to forms in annex 3, 4 and 5), that includes:

- Sponsor provides investigation's brochure, legal dossier and proposal for protocol to the Principal Investigator and management office.
- Principal Investigator in co-operation with sponsor and investigator group to develop the design of protocol, prepare the completed dossier, protocol and related legal dossiers as requested in the list of needed document to conduct clinical trial.

3. Submission of clinical trial's dossier.

Dossier of clinical trial should be sent to MOH (DST) to review, consider and approve. Responsibilites is assumed under of each unit as the following:

- Sponsor is responsible for submission of investigation's brochure and proposal of clinical trial to competent authorities to review and consider as stipulated in Guideline for list of document.

- Principal investigator and Management Office are responsible for submitting protocol to IEC for reviewing and approving as stipulated in Guideline for list of document.

Permanent staff of IEC and competent authorities are located at Department of Science and Training (DST-MOH). Only dossier submitted to MOH before 20th monthly (based on receiving date of Administrative department – MOH) can be reviewed in such month. For dossier submitted after that day will be reviewed in the next month.

4. Reviewing and approving for clinical trial.

- Reviewing the investigation's brochure

Within 30 working days after receiving completed application dossier, MOH will conduct a reviewing board according to legal regulation

- Reviewing application dossier

Within 30 working days after receiving completed application dossier, parallel with reviewing the IB, MOH will conduct the IEC meeting in medical research according to legal regulation.

- Informing the result

Within 15 working days after getting reviewing result of IB's reviewing board and IEC, DST will summary, complete the dossier and minute (according the form in annex 7) and inform to sponsor and management office to supplement, complete application dossier for clinical trial (if needed).

- Approving for clinical trials

Within 15 working days, DST will summary. Complete dossier and protocol of clinical trial to submit to Minister for approval.

Only application dossier approved by both above reviewing procedures (including reviewing IB and researching dossier) will be considered to approved by MOH.

MOH will inform sponsor and management office in case application dossier is not approved by any of two above revewing procedures or both.

CHAPTER V

IMPLEMENTATION AND CONDUCTING CLINICAL TRIAL

1. Implementing clinical trial

since application dossier is accepted to be legitimate, Ministry of Health shall hold a meeting between Science and Ethics Board to assess the dsier.

For dossier of clinical trial approved and accepted to be put into trial by Science and Ethics Board, the Board shall send conclusion and/or notification of acceptance to Ministry of Health. For dossier of clinical trial need to be corrected, the correction, repair, supplement and completment of protocol according to conclusion of Board shall be completed by Sponsor and investigator within at least of ten days counted from the end of Board's meeting. For application dossier of clinical trial not accepted by Science and Ethics Board, Ministry of Health shall issue a notification for Investigator and Sponsor right after recieving Board's conclusion.

After 15 working days counted from the date of recieving conclusion and/or notification of acceptance of Science and Ethics Board, Minister of Health shall issue a Decision of approving clincial trial protocol.

Sponsor and Investigator shall be conducted trial only after recieving notification of acceptance of Ethics Board and approval Decision of approriate authorities.

During the implementation, Sponsor only signs a contract with investigator being principal one (project manager) and research organization shall preside at trial. Enclosure sub-contracts (if any) when signing with research co-operation organizations and investigator shall be directly signed by leader of trial and approved by research organization (management organization).

3. Implementing investigation

Investigator provides investigational information for trial subject or legal representative to vulnerable subjects who are incapble of giving consent.

Collect volunteer willingness in participation of subject into agreement.

Organize, implement the investigation in accordance with approved protocol and procedure.

Investigator holds the implementation, records and monitors investigation regularly, updates data, keeps and preserves original data, keep confidence of each subject and requires specific person directly access to original data.

Investigator periodically reports each three months to sponsor, IRP/IEC on the safety of investigational products, side effects, progress, unexpectedly reports if these adverse effects seriously impact on subject's health. In case, it is found that the said effects seriously impact on subject's health, the investigator has right of stopping the investigation and shall immediately report in written document to sponsor, IRB/IEC and research organization.

Sponsor periodically performs the monitor, audit six months at trial site and sends monitoring report, audit to IRB/IEC and management office. During the process of monitoring, if sponsor finds out that the investigator do not comply with progress with serious level, investigator has the right of stopping the trial and sending report to IRB/IEC and management office and inform investigator.

- IRB/IEC execute an/a unnotified or periodical report planned, audited and sent to sponsors and investigator by IRB/IEC. Audit and monitor should be performed one time in at least on year.

- Management office may hold the inspection or audit based on report of investigator, sponsor, IRB/IEC and build audit and inspection plan and simultaneously inform relevant parts.

4. Finishing investigation

- Clincial trial which has approved decision of Minister of Health can be conducted.

- Procedures of clinical trial only can conducted affter having written agreement of subject or legal representatives of subject.

- Principal investigator and management office are responsible for conducting the research according to approved protocol design and procedures.

- Request of dossier and document in implementing duration to principal investigator and sponsoer is regulated in Guideline of document list. All documents used in clinical trial must be available in checking of sponsor or investigating of competent authorities.

- Principal investigator reports every 03 months to sponsor and IEC about safety of investigating product, adverse effects and rate of progress; irregular reports if has any serious adverse effect which serioulsy impact to subject's health. In that case, principal investigator has right to stop the clinical trial and immediately inform to sponsor, IEC and competent authorites by written document.

- Sponsor delegates Clinical Research Associate (CRA) to regularly monitor at least 6 months in field and send the report to IEC and competent authorities. In monitoring process, if sponsor discovers any serious incompliance, sponsor has right to stop the clinical trial and send the report to IEC, competent authorities and inform to Principal investigator.

- IEC conduct irregular checking and irregular checking which is planned by committee and inform to sponsor or principal investigator.

- Competent can conduct the inspection or checking which bases on report of principal investigator, sponsor and IEC. The inspection or checking must be planned and inform to related unit.

2. Record, report and statistical analysia

a. Record and report

- Principal investigator must ensure the accuracy and completeness of entry data. If clinical data is directly entered into computer, the investigator should ensure the legibility and unity in saving in accordance with regulation. Any change in personal receipt and data should be clear, not obscure the original entry and inform unit of measurement. The final report of investigator should conform to investigation protocol signed by sponsors, monitors, investigators and statisticians. Investigator should submit the coded list, identify trial subjects to regulatory authorities after finishing clinical trial and keep confidential.

- When using electronic data systems, sponsor should use legitimate data handling programs and standard operating process for these systems should be available. Sponsor should ensure the legibility in handling data, identify entry data of each trial subject by non-sense coding method, maintain list of people accepted to amend the data.

- Monitor should propose suitable measures to avoid losing data or disuniting data.

b. Statistical analysis

- Sponsor and investigator should gain agreement of location, statistician as well as information relating to statistical analysis, even name of the assigned statistician should be written in protocol of clinical trial. Kind of statistical analysis will be used should be pre-identified and written down in protocol. Any change in comparison with protocol in practicing should be disclosed at the final report. Statistical analysis is planned and implemented, evaluated by experienced and competent statistician. Investigator and monitor should ensure the integrity of data when handling.

- The result of statistical analysis in presentation should show out the importance of clinical trial. It should be taken into account confidential, unused or

unidentified data in statistical analysis, therefore, the measures of protecting, verifying and monitoring are required.

3. Monitoring and check/audit

- *Monitoring*

Objectives of monitoring are to protect rights and health of trial subject, consider data report, the implementation of investigator to ensure the accuracy, completeness and reality of data resource. Consider whether the implementation complies with protocol or changes in comparison the first protocol conform to GCP and management requirement.

Monitor should be appointed by sponsor and is a communication between sponsor and investigator.

Monitor should have specific clinical knowledge needed to monitor clinical trial, be familar with investigational products, protocol, written informed consent form and other written information to be provided to subjects, the sponsor's SOPs, understand GBP and management requirements which are being applied in each country relating to clinical trial.

The scope and nature of monitoring is to consider based on objective, purpose, design, complexity, blinding technique, size, endpoint of trial. There is a need for on-site monitoring before, during, after clinical trial. The responsibility of monitor is to monitor the process of clinical trial and ensure the investigation is conducted in accordance with GCP, to record, report data true according to procedure, management requirement and investigational ethics, to be a main line of communication between the sponsor and investigator.

Particular responsibility of monitor:

- Evaluating the site of clinical trial before, during, after conducting clinical trial

- Verifying qualification and resources of investigator

- Verifying for investigational products (storage time, condition provided for trial subject).

- Verifying that investigator follows the approved protocol and all approved amendment(s).

- Reverifying the consent of subject's participation in the trial and the compliance with procedure of selecting subject of investigator.

- Monitoring should be in accordance with standard operating procedures and sponsor's requirements. Monitor has responsibility of completing monitoring report according to sponsor's requirement.

- *Check/ Audit*

The objectivies of audit is to evaluate the compliance of investigator to protocol, of procedure, management of SOPs and GCP.

Sponsor appoints auditor in independence with clinial trial. Auditor should have qualification and experience in indepently auditing clinical trials.

Auditing procedure and plan and formality should be submitted to regulatory authorities. In case, there is a serious infringement of GCP, the audit report should be submitted to regulatory authorities, in general, the report should be submitted to the sponsor.

Audit is separated from monitor

4. Finish the clinical trial

Requirements of dossir and documents when finish the clinical trial of Principal Investigator and sponsor are included in Guideline of document list.

- When complete the clinial trial, even in case of stop or early finish for any reason, principal investigator must inventory researching drugs, payment and send reports to sponsor, competent authorities and IEC.
- Principal investigator is responsible for stored the original dossier for at least 15 years till the time sponsors inform that they want to take back the original dossier or inform that principal does not need to store this one.
- Principal write the clinical trial result according to stipulated forms, then send to sponsor, IEC and competent authorities to review.
- Competent authorities are responsible for setting up Committee and checking/evalutating the clinical trial result.
- Sponsor and Principal investigator set up the checking/evaluating document to liquidate contract after the trial is checked/evaluated.

- Sponsor takes back the products and conduct to destroy drugs togerther with destroying document sent to principal investigator and competent authorites.
- Sponsor pay the fee and handle all existing issues with principal investigaror before investigator submits the final report to sponsor.

5. Report and publication of clinical trial results

There are many kinds of reports and each kind has specific objective and conforms to a required form of each one according to guideline for GCP and of each countries with particular requirement.

- Monitoring report means a written report of monitor sent to sponsor after each trial site visit and/or clinical trial relating communication acccording sponsor's SOPs.

- Check/audit report is a written evaluation by the sponsor's auditor of the results of the audit, the report is independent of monitoring report.

- Clinical trial report is a written description of a trial report of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects.

- The clinical and statistical description, presentations, and analyses are fully integrated into a single report and comply with the guideline for structure and content of GCP.

- Unscheduled and/or interim report is a written report of intermediate results and their evaluation based on analyses performed during the course of a trial.

In addition to above mentioned reports, there also include other ones such as: investigational report, drug adverse report, sponsor's report, investigator's report, early finished report, final report.

- Final report is a complete description of clinical trial after finishing comprising description of clinical trial method (including statistic method) and relevant documents. The report is a presentation and evaluation of result, statistical analysis, ethics of clinical trial.

- The final report shall be written in a required form of each countries.

- Publication should be agreed by sponsor and written in investigation protocol and/or investigation contract. Publication and writing in press of trial results also depend on regulation of each publisher and scientific evaluation.

6. Finance in clinical trial

- Expenditure for clinical trial includes the fee paid for professional staff, lost material, support to the volunteer, insurance which principal investigator and management office cooperating with sponsor dicuss, develop and sign in a contract.

- Management expenditure for clinical trial (including: reviewing the dossier, holding the meeting of Committee, approving, conducting GCP training for investigator, monitoring, checking, investigating at site) is defined in contract which is agreed by sponsor and principal investigator.

- The payment for activities is responsibilities of sponsor, principal investigator and managing office which is stipulated in regulation and signed/approved contract.

FOR THE MINISTER

DEPUTY MINISTER

Signed

Nguyen Thi Kim Tien

1 – GUIDELINES FOR NEEDED DOCUMENT LIST BEFORE CONDUCTING THE CLINICAL TRIAL

No	Document name	Objectives	Responsibility of		Form
			Investigator/ Management office	Sponsor	
1.1	Application form for clinical trial	Provide summary product information about drug proposed for clinical trial and proposed principal investigator		√	Annex 1
1.2	Investigator's brochure	To improve for scientific information provided to principal investigator, which is available and related to researching product	√		Annex 2a, 2b
1.3	Application for approval of protocol		√		Annex 3
1.4	Protocol & CRF	Protocol provide detailed SOP, checking/audit, evaluation and CRF	√	√	Annex 4
1.5	Contract for clinical trial between sponsor and principal investigator/ management office	To prove for the agreement about finance aspect between sponsor and principal investigator/ management office	√	√	Annex 5
1.6	The agreement for participating which is signed between related unit, for example: - Investigator – investigator of sub entities between sponsor - Investigator /management office and authorities at site (if needed)	To confirm for the agreement to participate in clinical according to current regulation	√	√	

1.7	Information provided to subject + Information card and consent form (including suitable information to communicate to subject) + Any other information in written	To confirm for the voluntary to participate in clinical trial To prove that subject will be provided suitable information in written (including content and communication way) to assist for the handling the voluntary form To prove that selecting method is suitable and not forced – to ensure for the ethnic aspect in clinical trial	√ √	√ √	Annex 6
1.8	Insurance contract	To improve that the subject will have compensation if has damage in the trial	√	√	
1.9	Form for approval of IEC	Prove for the approval of IEC/MOH in clinical trial			Annex 7
1.10	Date of approval for dossier/ approval of basic reviewing committee/ independent IEC for the followings: + Protocol any any	To confirm the approval for clinial trial of of basic reviewing committee/ independent IEC. To confirm the version and approved	√	√	Minute of IEC

	admendement + Report for any disease case + Consent form + Any information in written to provide subject + Notice for selection of subject (if applicable) +Compensation for suject + Any documents represented for agreement	date of documents			
1.11	Members of IEC/MOH	To prove that IEC is established according to requirement of GCP	√	√	Decision in estb. of committee
1.12	Approval of competent authorities to protocol	To confirm the approval of competent authorities before conducting clinical trial according to current regulations	√	√	Decision for MOH's approval of protocol
1.13	CV and GCP certificate issued by MOH of investigators (including management officers of clinical trial, pharmacist	To prove for unified qualifications and abilities to conduct clinical trial and monitor/medically check to	√	√	
1.14	Institution obtained GCP requirement (site, document storage, monitoring, discussion area, official equipments...) and GLP requirements (standard lab, standard technical procedures...) or approval for instution by MoH.	To document ability of the institution, equipments for in-vitro testes of the trial.	√	√	
1.15	Sample of label (s) attached to investigational product container (s).	To document compliance with applicable labelling regulations and appropriateness of		√	

		instruction provived to the subjects.			
1.16	Instructions for handling of investigational products ans trial-related materials (if not included in protocol or Investigatior's Brochure).	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials.	√	√	
1.17	Shipping records for investigational products and trial –related materials.	To document shipment dates, batch numbers, and method of shipment of investigational products and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	√	√	
1.18	Certificate (s) of analysis of investigational products shippded.	To document indentity, purity, and strengthen of investigational products to be used in the trial.		√	
1.19	Decoding procedures for blinded trials.	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subject'treatment.	√	√	
1.20	Standard Operating Procedure (SOP) of techniques in the trial.	To document and ensure techniques used in the trial be consolidated, scientific, objective and accurate.			
1.21	Random list	To document that the method of subject selection is random.		√	

2- ESSENTIAL DOCUMENT FOR THE CONDUCT OF A CLINICAL TRIAL DURING THE CLINICAL CONDUCT OF THE TRIAL

	Tittle of Document	Purpose	Located in Files of		Sample
			Investigator /Institution	Sponsor	
2.1	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available.	√	√	
2.2	Any revison to: • Protocol/amendment(s) and CRF • Informed consent form • Any other written information provided to subjects. • Advertisement for subject recruitment (if used)	To document revisions of these trial-related documents that take effect during trial.	√	√	
2.3	Dated, documented approval/favourable opinion of Competent Authority/Independent Ethics Committee (IEC) of the following : • Protocol amendment (s) • Revision (s) of: - Inform Consent Form. - Any other written information to be provided to the subject. - Advertisement for subject recruitment (if used). - Any other documents given approval/favourable opinion. - Continuing review of trial (where required)	To document that the amendment (s) and/or revision (s) have been subject to Competent Authority/IEC review and were given approval/farourable opinion. To identify the version number and date of the document (s).	√	√	
2.4	Regulatory authority (ies) authorizations/approvals/notifi cations where required for: • Protocol (amendments) and other documents	To document compliance with applicable regulatory requirements.	√	√	
2.5	Curriculum vitae, GCP certificated for new investigators (s) or sub-investigators which issued by MoH	To document ability and feasibility to conduct the trial and/or medical mornitor the subjects.	√	√	
2.6	Updates to normal value (s)/range (s) for	To document normal values and ranges that	√		√

	medical/laboratory/technical procedure (s)/test (s) included in the protocol.	are revised during the trial.			
2.7	Medical centers/laboratory/technical procedures/testes: • Certificate or • Established quality control and/or esternal quality assessment or • Other validation (where required)	To document that tests remain adequate throughout the trial period.	√	√	
2.8	Documentation of investigational products and trial-related materals shipment.		√	√	
2.9	Certificate (s) of analysis for new batches of investigational products.			√	
2.10	Monotoring visit reports	To document site visits by, and findings of the monitor.		√	
2.11	Relevant communications other than site visits: • Letters • Meeting notes • Notes of telephone calls.	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event reporting.	√	√	
2.12	Signed informed consent forms.	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission.	√		
2.13	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject.			
2.14	Signed; dated and completed case report forms (CRF).	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded.	√ (copy)		√ (original)
2.15	Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	√ (copy)		√ (original)

2.16	Notification by origination investigator to sponsor of serious adverse events and related reports.	Notification by origination investigator to sponsor of serious adverse events and proper related reports.	√		√
2.17	Notification by sponsor and/or investigator, where applicable, to regulatory authority (ies), IEC of unexpected serious adverse drug reaction.	Notification by sponsor and/or investigator, where applicable, to regulatory authority (ies), IEC of unexpected serious adverse drug reaction.	√		√
2.18	Notification by sponsor to investigator of safety information.	Notification by sponsor to investigator of safety information.	√	√ (where required)	
2.19	Interim and annual reports of IRB/IEC and authority (ies).	Interim and annual reports of IRB/IEC and authority (ies).	√	√ (where required)	
2.20	Subject identification code list	To document that investigator/institution keep confidential list of names of all subjects allocated to trial number on enrolling in the trial.	√		
2.21	Subject code log	To document the participation of the subjects by trial code.	√		
2.22	Investigatinal product (s) accountability at the site.	To document the investigational products have been used according to the protocol.	√	√	
2.23	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.	√	√	
2.24	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated.	√	√	

3- **ESSENTIAL DOCUMENT FOR THE CONDUCT OF A CLINICAL TRIAL**

AFTER COMPLETION OR TERMINATION OF THE TRIAL

After completion or termination of the trial, all of the documents identified in section 1 and 2 should be in the file together with the following:

	Tittle of Document	Purpose	Located in Files of		Sample
			Investigator/Institution	Sponsor	
3.1	Investigational product (s) accountability at the site.	To document that the investigational product (s) have been used according to the protocol. To document the final accounting of investigational product (s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor.	√	√	
3.2	Documentation of investigational product destruction	To document destruction of unused investigational products by sponsor or at site.	√ (if destroy at site)	√	
3.3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow up is required. List should be kept in a confidential manner and for agreed upon time.	√		
3.4	Final trial close-out monitoring report.	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files.		√	
3.5	Treatment allocation and decoding documentation.	Return to sponsor to document any decoding that may have occurred.		√	
3.6	Final report by investigator to IRB/IEC and regulatory authority (ies).	To document completion of the trial.	√		
3.7	Clinical study report	To document results and interpretation of trial.	√ (if applicable)	√	Annex 8

Annex 2a

INVESTIGATOR'S BROCHURE

(Apply to pharmaceutical products and traditional medicines)

1. Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product (s) that are relevant to the study of the product (s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such ad the dose, dise frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-bevefit assessment of the appropriateness of the proposed trial. Fof this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineated the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatoty authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternativem provided that it inclides current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a vew indication), an IB specific to that vew use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More requent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Board (IRB)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revesed IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator (s) and the investigators are responsible for providing the up-to-date IB to the responsible IRB/IECs. In the case of an

investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, the he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol, as a the minimum current information described in this guideline.

2. General Considerations

The IB should include:

2.1. Title Page

This should provide the sponsor's name, the identify of each investigational product (i.e., research number, chemical or approved generic name , and trade name (s) where legally persissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

2.2. Confidentiality Statement

The sponsor may wish to include a statement instruction the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

3. Contents of the IB

The IB should contain the following sections, each with literature references where appropriate:

3.1.Table of contents

An example of the table of contents is given in Appendix 2.

3.2. Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmakinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

3.3. Introduction

A brief introductory statement should be provided that contains the chemicals name (and generic and trade name (s) when approved) of the investigational product (s), all active ingredients, the investigational products (s) pharmacological classd and its expected position within this class (e.g. advantages), the anticipated prophylactic, therapeutic, or diagnostic indication (s). Finally, the introductory statement should provide the general approach to the followed in evaluating the investigational product.

3.4. Physical, chemical, and pharmaceutical properties and formulation.

A description should be provided of the investigational product substance (s) (including the chemical and/or structural formulae, and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation (s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form (s) should also be given.

Any structural similarities to other known compounds should be mentioned.

3.5. Nonclinical studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram)
- Dose interval
- Route of administration
- Duration of post-exposure follow-up
- Results, including the following aspects:

- Nature and frequency of pharmacological or toxic effects
- Severity or intensity of pharmacological or toxic effects.
- Time to onset of effects
- Reversibility of effects
- Duration of effects
- Dose response

Tabular format/listing should be used whenever possible to enhance the clarity of the presentation.

The following sections should discussion the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

a) Nonclincal Pharmacology:
A summary of the pharmacological of the investigational product and, where appropriate, its significant metabolites stidied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect (s)).

b) Pharmacokinetics and Product Metabolism in animals:
A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the lical and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c) Toxicology
A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:
- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g., irritancy and sensitization)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

3.6. Effects in Humans

Introduction:
A thorough discussion of the known effects of the investigational product (s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacidynamics, dise response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should be provided regarding results of any use of the investigational product (s) other than from in clinical trials, such as from experience during marketing.

a) Pharmacikinetics and Product Metabolisn in Humans
- A summary of information on the pharmacokineticsd if the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food)

- Other phamarcokinetic data (e.g., results of population studies performed within clinical trial (s).

b) Safety and efficacy

A summary of information should be provided about the investigational products, (including metabolites, where appropriate), safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) should be usefull. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the products.

c) Marketing experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summaried (e.g., formulation, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

3.7. Summary of data and guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), whenever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on trlated products should be discussed. This could help the investigator to anticipate adverse drug reaction or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical

investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

Annex 2b

INVESTIGATOR'S BROCHURE

(Apply to vaccine and medical biological products)

1. Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product (s) that are relevant to the study of the product (s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such ad the dose, dise frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-bevefit assessment of the appropriateness of the proposed trial. Fof this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineated the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatoty authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternativem provided that it inclides current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a vew indication), an IB specific to that vew use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More requent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Board (IRB)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revesed IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator (s) and the investigators are responsible for providing the up-to-date IB to the responsible IRB/IECs. In the case of an

investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, the he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol, as a the minimum current information described in this guideline.

2. General Considerations

The IB should include:

- Title Page

This should provide the sponsor's name, the identify of each investigational product (i.e., research number, chemical or approved generic name , and trade name (s) where legally persissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

- Confidentiality Statement

The sponsor may wish to include a statement instruction the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

3. Contents of the IB

The IB should contain the following sections, each with literature references where appropriate:

3.1. Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmakinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

3.2. Introduction

A brief introductory statement should be provided that contains:

- Investigational product name (generic and trade name (s) when approved)
- Physical property
- Component in a human single dose:

+ Active ingredients.
+ Excipients (if used)
+ Preservative (if used)
+ Stabilizer (if used)

- Indications
- Considering indications (if any)

- Contra-indication (if any)
- Interactions (if any)
- Presentation
- Storage and delivery
- Shelf life

Finally, the introductory statement should provide the general approach to the followed in evaluating the investigational product.

3.3. Nonclinical studies

The results of all relevant nonclinical studies as specific safety, general safety, potency, immunogenicity, pyrogen … should be provided in summary form. However, application of nonclinical trial should be depended on substance of each vaccine.

This summary should provide used method, result and their comparison with permitted specifications (if available).

- General requirements for all clinical trials:
  + Species tested
  + Species of animal
  + Number, sex, old, weight of animals in each group
  + Unit dose: immunological dose, route.
  + Total immunological dose
  + Dose interval (if vaccine with schedule of more than 2 doses)
  + Route of administration
  + Duration of post-exposure follow-up
  + Results, including the following aspects:
    - Method of result assessment: the specifications of assessment will be different basing on each trial, e.g., health status, weight, temperature, specific symptoms…
    - Time to onset and duration of symtoms
    - Specific result of investigational products
      - Substance and frequency of pharmacology or toxic effects.
      - Severity or sensitivity of pharmaxological and toxic effects.
      - Time to onset of effects
      - Reversibility of effects
      - Duration of effects
      - Dose response

The following sections should discussion the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed.

a) Nonclincal Pharmacology:

A summary of the pharmacological of the investigational product and, where appropriate, its significant metabolites stidied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect (s)).

b) Pharmacokinetics and Product Metabolism in animals:

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the lical and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c) Specific safety

- Determine reviving ability of vaccine attenuated strains.
- Detemine inactivation of inactivated vaccines.
- Determine inactivation and reviving ability of toxoid.

If investigational vaccine is proposed to trial on different administrations, safety and toxic studies in proper animal are required.

c) General safety

General safety trial should conduct following with WHO requirement for each vaccine which orgines from bacteria and virus.

d) Potency and immunogenicity

- Potency: summary of toxicology in relavant studies should be described as following titles:

+ Single dose
+ Booster dose
+ Oncology
+ Specific studies (e.g., anaphylactic, allergic…)
+ Toxic on reproduction
+ Genetic change

- Effects in Humans:

Introduction:

A thorough discussion of the known effects of the investigational product (s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacidynamics, dise response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should be provided regarding results of any use of the investigational product (s) other than from in clinical trials, such as from experience during marketing.

The potency trial can conduct during time of vaccine development. There are many different method to conduct the potency trial. The best is challenge method (e.g., rabid vaccine, pertussis vaccine..). An other method can be

used is seroconversion determination. However, chemical property assessment can be acceptable with vaccine which their antigen is polysaccharide.

Nowaday, potency trial in living organism intends to be replaced by in-vitro testes when the knowledge of immunogenicity and protection of vaccine is increasing.

- Immunogenicity:

Data of immugenicity studies on animal model can support to select dose, schedule, route which will assess in the clinical trial. Nonclinical trial should be designed to assess relevant immuno respond, e.g., seroconverion rate, GMT, cell-mediated immuno respond in the animals. In case vaccine contains many antigents, the trial of immunogenicity should be conducted in each kind of antigen. Although immunogenicity is necessary during time of vaccine development, it is always not a specification for release (e.g., conjugated Hib vaccine).

- Pyrogen: This trial is conducted following WHO requirement
- Some other remarkable aspects:

+ Adjuvant: Adjuvant used in vaccine must be obtained with national pharmacopie requirement and do not have unexpected reaction. The evidence of interaction between adjuvant and antigen should be provide (can use result of studies which were conducted in the past). In case of adjuvant is new without toxic studied data, it must study toxicology for such adjuvant firstly. Nonclinical study should assess the combination between adjuvant and antigen when they are formulated and became vaccine.

+ Excipient and preservative: If these material are new for use, the toxicology study of each material is required.

+ Some vaccine should be notified:

Combined vaccine: The combination of antigen or sero type should be studied about immunogenicity in animal model before its clinical trial is conducted. Combination assessment by comparing between separated antigens in animal to determine immuno respond is the best way.

The interfere between the live vaccine strains should be studied on immunogenicity in animals.

- ADN vaccine: base on guildance of WHO on assessment the quality of ADN vaccine to conduct the pre-clinical assessment

- recombinant vaccine: Base on guildance of WHO on assessment the quality of recombinant vaccine to conduct the pre-clinical assessment

- peptit synthetic vaccine: Base on guildance of WHO on assessment the quality of peptit synthetic vaccine to conduct the pre-clinical assessment.

- Live attenuated vaccine: The major concerns for this type of vaccine is the ability to recover the toxic, transmit and exchange the genetic information which apply on wild strains or other biological strains. Results to recongnise the attenuated strains should be indicated (genetic order). It can be continue to use in the clinical study to monitor the results of eliminated agents and duration of all stages of clinical assessment. OPV vaccine (Oral Polio Vaccine) is a typical example for attenuated vaccine.

a) Pharmacokinetic and metabolism agents in animals.

It is necessary to summary the information on pharmacokinetic of investigations drug (s) including the below information, if any:

Pharmacokinetic (include metabolism, aborbtion, binding ability with plasma protein, distribution and eliminate)

Bioavailibility of investigational drug (abolutely, relatively) which use other dosage form to control.

The sub population (for example sex, age, function of organization will be impaired)

Interation (for example the interaction between the products and affects by food)

Other pharmacokinetic (for example the results from population which conducts in the frame of clinical studies).

b) Safety and Efficacy

It is necessary to provide the summary of information of safety of investigational drug (include the metabolized agents if have), pharmacokinetic, efficacy, dosage respond which had in previous studies in human (in healthy volunteer and/or patients). The raising matters from this information should be exchanged. In case when several clinical studies were completed, the usage of summary information on safety many times through the indications in sub-population also brings the benefit to make data clearly. Summary by tables about adverse events in clincal studies (include the indications which were studied)

The major differences between forms/hypersensivity in these indications or in sub-group should be exchanged.

IB need to provide the description about risks and anaphylactic shock that can be occured in order to estimate which base on the previous experiences of investigational drug and relevant product. It is necessary to provide the

description about precautions or special follow up as a part of investigational vaccine.

c) Advertisement

IB should be clearly state the countries which investigational vaccine were advertised or approved. Any significant information which arise from usage of vaccine in market should be summary (for example the way to prepare the vaccine, dosage and route of administration and adverse events of investigational vaccine). IB should be clearly state the list of countries which not approve for investigational vaccine or withdraw from market/registration.

- *Summary the data and instructions for investigators.*

This section should provide, exchange the pre-clinical data and clinical data and summary the information from different sources on different aspects of investigational drug (s). Follow this way, investigator should be provided the explainations which consistent with available data and the treatment with information arise from future clinical study.

If can, the document which public for relevant product should be exchanged. It will help the investigator to know the anaphylactic shock or other matters in the clinical study.

The overall objectives of this section will provide the investigators more clear about risks and anaphylactic shock can be occured, and for detail experiments, obsevations and precautions that needed in the clinical study for investigational drug. It is necessary to have guildance for clinician investigator about the way to recognize and treatment when overdosage and adverse events can be occured on human base on experiences and characteristic of investigational drugs.

Annex 3

(Form of Application for clinical trial)

SOCIALIST REPUBLIC OF VIETNAM
Indepence – Freedom - Happiness

……., date … month … year …

APPLICATION FOR CLINICAL TRIAL

To: Ministry of Health
(Department of Science and Training)

Full name of Principal Investigator:

ID or Passport number:

Presidential organization:

Office address:

Tel: Fax:

Email:

Account number:

Would like to request Ministry of Health to consider and approval for conducting the clinical trial:

◊ Name of drug

◊ Batch Number

◊ Strength

◊ Content

◊ Dosage form

◊ Route of admistration

◊ Shelf life

Classification:

◊ Western Medicine

◊ Oriental Medicine

◊ Vaccine

◊ Bio-pharmaceutical product

Request to conduct of clinical trial on the stage

Or propose to conduct of clinical trial from stage... to stage

The clinical trial for said drug was finished on the stage

Accompanied documents

Request the Ministry of Health considers and permit the above drug to be conducted clinical trial.

Principal Investigator and Presidential agency (The organization accept to conduct the clinical trial) commit to implement the ethics principles which stated in the protocol endorsed by Ministry of Health in right way.

Principal Investigator

Head of Presidential Agency (Organization accept to conduct the clinical trial)

Signed and sealed.

Annex 4

Ministry of Health
THESIS OF THE CLINICAL TRIAL

I. General information of clinical trial

1. *Title*	**2**. *Code*
3. *Time of conducting* (From..../200.. to ..../200..)	**4**. *Under management of* State leve ☐ Ministry/ Local ☐. Province
5. *Expense* Total: In which, from SNKH national budget: From other sources: please indicate resource's name	
6	The study applying for conducting the clinical trial on state (please indicate) ☐ Or proposing to conduct clinical trial on the stages (please indicate) ☐
7	*Principal Investigator*

Full name:

Academic tilte/Diplomas:

Scientific title:

Tel: (Office)/ (Home phone) Fax:

Mobile:

E-mail:

Office address:

Home address:

8	*Presidential entity (Agency, organization accept to conduct the clinical trial)*

Name of agency, organization:

Tel: Fax: E-mail:

Address:

9	*Agency or individual who order the clinical trial (the agency that is permitted to use the copyright of the products to be subjected to clincal trial and the clinical trial result in order to manufacture or to use such products or to conduct the trial on the next stage)*

Name of organization:

Tel: Fax: E-mail:

Office Address:

Name (in case the individual orders):

Academic title/Diplomas:

Scientific title:

Tel: (Office)/ (Home) Fax:

Mobile:

E-mail:

Office address:

Home address:

Note:

In case the organization and individual need to interpret or supplement some section in this thesis, it may be longer, number of pages is not limited

II. Content of clinical trial

(To clarify the sections in accordance with the regulation on Clinical trial Regulations and the content of Experimental stages)

10	***Objective of the study***

11	***Background of the domestic/foreignes studies***

- Overview of the studied products

- Overview of the study of clinical trial

Foreign:

Domestic:

12	***Method of approaching, studying contend and technology to be used: indicate the method of approaching, study's design, method for selecting sample, size of samples, standard for selecting trial object, method of studying, technology to be used, standard operating procedures (SOPs) for each of technology that will be used in study – compre those with similar methods, quota of the study, the unique, the inventive step of the study design and method of studying)***

12.1 Place of study

12.2 Duration of study:

12.3 Method of study: Describing the type of study (random, blind, open), study's design (parallel group, capture technique), blind technique (single blind and double blind), and method and procedure to choose randomly.

12.4 Study's objects: Describing the objects of study (selected standards and exclusion of potential subjects), standards operating procedures (SOPs) applying for selection the objects who participate in the study: method, standards and time to indicate the subjects in studying groups.

12.5 Sample size: The quantity of subjects need to meet the objective of the study, which base on statistical mathemetic.

12.6 Schedule to use the investigational products: Build up the standard operating procedures (SOPs): Describing and detail the route for use, dosage, interval and treatment duration applying for investigational products and compared products. Person who has responsibility for technology, procedure for use the drugs. The criteria for monitor and assessment. The relationship of responded dosage should be intersted.

12.7 Spontaneous treatment: Any other treatments were identified and allowed to use spontaneously.

12.8 Usage testing: Develop the Standard Operating Procedures (SOPs): The clinical and

laboratory testing, pharmacological analysis,... testing will be implemented. Responsible people, procedure to take samples, storage, technical. The criteria for assessment, compare the results.
12.9 Assessment the side effects level: Describe the procedure how is a respond will be recorded (describe and assess the method and frequent of measure), process to monitor and measure to identify the compliance with treatment among the subjects.

12.10 Exclusived criteria of subjects in the process of study: Exclusived criteria for subjects and instructions on complete the whole study or a part of a study.

12.11 Record and report the adverse events: The method to record and report the cases of adverse events, relevant provisions relate to compliance.

12.12 Technical of blind and protect the identification of participated subjects: The procedures to maintain the list of identificated subjects, treated dossier, randomized list of subjects and/or case report forms (CRFs). The dossier must allow to identify the patients or parcipated subjects seperately as well as check and restructure the data.

12.13 Rules for open the code: Information on set up the code of the study, place to storage the list and who, when and how open the code in urgent cases.

12.14 Storage the investigational drug: Method will be implemented to ensure the safety of packaging and storage of investigational drugs and comparable products if use, and speed up and identify the compliance with the treatment and other guildance.

12.15 Method for assess the results: Describe the method which used to assess the results, (include the statistical method) and report of patients or subjects who will withdraw from study.

12.16 Method for handle the adverse events

12.17 The way to provide information for subjects: Information should be described for participated subjects, including how they will be provided information about the study, how and when collect their agreement.

12.18 Training for group of study: Training for group of study who participate in the clinical study (include Principal Investigator, Branch Principal Investigator, coordinate investigators, investigators, Pharmacist, nurse, technician): Basic content on the study, information of the way to conduct the study, standard operating procedures (SOPs) and procedures to manage and use the drugs.

12.19 Ethical matters: Precautions and methods of ethics relate to the study.

12.20 Caring the health of subjects after participate in the study: Caring the health of subjects after participate in the study should be provided, scheme of treatment after complete the study.

12.21 Plan of implementation

12.22 Plan of monitor, audit, inspection:
- Monitor the Principal Investigator and group of study
- Monitor of sponsor
- Monitor and audit of inspectors from competent authorities, Ethics Committee.

Contents of ethics in bio-pharmaceutical research:

(Include: Information about the study, informed consent form, agreement to implement the instructions on ethics in study)

13	***International co-operation***

Content of co-operation	Name of partners

14	***Implementation speed***			
No	Main works to be conducted (main milestones for the assessment)	Products to obtain	Duration (Start-End)	Performer
1	*2*	*3*	*4*	*5*

III. Study results

15	***Expected forms of study results***

I	**II**	**III**
♦	♦	♦ Diagram
♦	♦	♦ Data table
♦	♦	♦ Analytical report
♦	♦	♦ Foreseeing document
♦		♦ Process of treatment
♦		♦
♦		♦

IV. Organizations/individuals joining the study

16	***Activities of organization co-operating to conduct the study (recording all organizations joining the study and their work within such study)***		
No	Name of organization	Address	Activity/contribution to the study
1			
2			
3			

17	***Team of investigators***		
No	Full name	Scientific title – place of work	Certificate of GCP training
A	Principal Investigator		
B	Investigators		
1			
2			
3...			

V. Budget for conducting study and source of budgets (see the enclosed appendix for detailed explaination)

Unit: million VND

18	***Budgets for conducting the study assigned to expenses***						
No	Source of budget	Total	Wherein				
			Specialized rentals	Materials, energy	Equipment, specialized devices	Small construction, repairment	Other expense
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
	Total Budgets Wherein:						
1	SNKH Budgets						
2	Other sources (details) Sponsor, purchase order of organizations, individuals - Other (mobilized capital, incidental capital....)						

....., date month year 200..

Head of Presidential (Full name, signature and stamp)

Principal investigator (full name and signature)

....., date month year 200..

For the Minister of Health
Head of Department of Science and Training

ESTIMATE OF EXPENDITURE FOR THE STUDY

Unit: Million VND

No	***Description***	***Total***		***Source***		
		Expenditures	***Percent (%)***	***SNKH Budget***	***Sponsor***	***Other***
1.	Specialized rentals					
2.	Materials, Energy					
3.	Equipment, specialized devices					
4.	Small construction, repairment					
5.	Other expense					

Explanation of expenditures
(million VND)

Item 1: Specialized rentals

No	***Details of rentals***	Total expenditure	***Source***		
			SNKH Budget	***Sponsor***	***Other***

Item 2: Materials, Energy

No	***Description***	***Unit of measurement***	***Quantity***	***Unit price***	***Amount***	***Source***		
						SNKH Budget	***Sponsor***	***Other***
2.1	*Materials*							
2.2	*Equioments, accessories*							
2.3	*Energy, fuels*							
	- Coal							
	- Electricity	kW/h						
	- Petrol, kerosene							
	- Other fuels							
2.4	*Water*	m^3						
2.5	*Purchasing book, reference documents, data*							

Item 3: Equipments, specilized devices

No	***Description***	***Unit of measurement***	***Quantity***	***Unit price***	***Amount***	***Source***		
						SNKH Budget		
3.1	*Purchasing technical device*							
3.2	*Purchasing testing means, measuring devices*							
3.3	*Equipment depreciation*							
3.4	*Facility rental*							
3.5	*Transportation and installation*							

Item 4: Small construction, repairment

No	*Description*	*Expenditures*	*Sources*		
			SNKH Budget	*Sponsor*	*Other*
4.1	Expenses for building m^2 facility, laboratory				
4.2	Expenses for repairing m^2 m^2 facility, laboratory				
4.3	Expenses for installation of water and electricity system				
4.4	Other expense				
	Total:				

Item 5: Other expense

No	*Description*	*Expenditures*	*Sources*		
			SNKH Budget	*Sponsor*	*Other*
5.1	*Expenditure for business trips*				
5.2	*Management of the entities*				
5.3	*Cost for assessments, checking and finalization*				
	- Validation fee				
	- Fee for approval the dossier				
	- Fee for audit				
	- Fee for monitor, intermediate finalization				
	- Fee for internal finalization				
	- Fee for official finalization				
5.4	*Other expense*				
	- Training				
	- Meeting				
	- Printing and stationery				
	- Translation				
	.....				
5.5	*Allowance paid for the principal investigator*				

Annex 5

(Form of Clinical trial agreement)

SOCIALIST REPUBLIC OF VIETNAM

Independence – Freedom - Happiness

…….,date.....month.....year

CLINICAL TRIAL AGREEMENT

Legal basis: .....

Base on demand and capability of relevant parties:....

Representative of party A (Agency, organization, individual) who have drus to be subjected to clinical trial:

Full name: (Individual or Representative of Organization, who register for clinical trial:

Position:

Address: Office or private house (as to individual)

Tel:

Fax:

Email:

ID number or Passport number:

Representative of the party B (Agency, Organization who accept to conduct the clinical trial)

Full name: Individual and Representative of organization who accept to conduct the clinical trial:

Position:

Address (as to agency and Organization):

Tel:

Fax:

Email:

Together wish to enter into this clinical trial agreement for the drug product (product's name, concentration, content, formulation, route of administration, classification, indication, treatment, dosage and usage)

Request to conduct of clinical trial on the stage:

Or request to conduct of clinical trial from the stage.....to stage

Or request to conduct the assessment the tolerbility on Vietnamese people

With the following content:

1- Content of Agreement

2- Time and Schedule

3- Expenditure

4- Obligations of the Parties

5- Right of Parties

6- Common Regulations

Representative of the Party A	**Representative of the Party B**
(Signed. Stamped or certified by Local People's Committee where the invidual resides (in case of individual)	*(Signed and sealed)*

Annex 6

INFORMED CONSENT FORM

(including the provided information form and informed consent form)

Name of study:

Version: ICF Date …../…../……...

Name of sponsor:

Subject's code: ……

This document was informed to all participated subjects adequately, not omit any pages or any items. This content of the document should be explained clearly by oral to participated subjects.

1. Describle all matters related to the study

   Objectives of the study

   Estimated time

   Method of conducting (detail all contents will be conducted)

2. Inclusion criteria the subjects into the clinical trial
3. Exclusion criteria the subjects in clinical trial
4. Who will be person to assess the private information and medical information to select the subjects to participate the study?
5. Number of subjects will participate the study
6. Describe the risk and disadvantages
7. Describe the advantages of subjects or other people
8. Expenditures will be paid in the study
9. Publication the methods and alternative treatments
10. Describe the filing dossier confidentially but can regconise the title

11. Clearly point out the competent authorities that can check the dossier of subjects

12. Compensation / medical treatment if occurs the injuries (Where can have other information)

13. Person to contact when have the questions relate to

- The study
- The rights of subjects
- In case of having injuries relate to study

It is necessary to state that participation in the study is volunteer, not to be punish if refuse to continue to participate in the study at any time without lacking the rights.

Signature of volunteer subjects

Date of signing the consent form

Informed consent form

I,

_____

verified that

- I have read the information provided for the field trial.....
  .....at....., ICF version.....date...../...../....., page).....and I have been explained by investigators about this study as well as the procedures to volunteer the study.
- I have chances to ask all questions relate to this study and I satisfy with answers and explainations.
- I have time and chance to consider the ability to participate the study.
- I understood that I have rights to access the data provided in information sheet by responsible people
- I understood that I can withdrawn the study at any point with any reasons.

I agreed that our main doctors who take care my health will be informed the participation of myself in this study.

Tick in appropriate place (this decision will not affect on ability of yourself to participate in the study):

Yes	**No**

I agree to participate in this study:

Signature of subject …….….	Date/month/year …….……
If needed,	
* Signature of witness …….….	Date/month/year …….……
* Full name of witness …….….	
Signature of guildance person …….….	Date/month/year …….……
Full name of guildance person …….….	

Annex 7

FORM OF APPROVAL FOR CLINICAL TRIAL OF ETHIC COMMITTEE

Ministry of Health SOCIALIST REPUBLIC OF VIETNAM

Independence – Freedom - Happiness

No: …….. /HĐĐĐ ---------o0o--------

Regarding: Approval for DDNCYSH

Hanoi, date……month……..year

APPROVING CERTIFICATE OF ETHICS COMMITTEE IN BIO-PHARMACEUTICAL RESEARCH

Base on Decision No ……., date….month…year of Minister of Health on establish the Ethics Committee in bio-pharmaceutical research.

Base on the meeting minute of Ethics Committess in bio-pharmaceutical research of Ministry of Health date…month….year (please enclosed the meeting minute)

Ethics Committee in bio-pharmaceutical research approve on ethics aspect for the study:

1. Name of study:……...……...…….....…….…

2. Principal Investigator:

…….…….....……..

3. Presidential organizations (Organizations to accept the clinical trial): …….....

4. Place of implementation.....……..

5. Studying time: ……

Approving date: Date…….month……year

Director of Committee

(Sign, full name)

ANNEX 8

Form of report on result of the study

Cover page 1

MINISTRY OF HEALTH

REPORT ON RESULT OF THE CLINICAL TRIAL

Title:

Principal Investigator:

Presidential organization (entities):

Management level: Ministry of Health

Implementation time: from month.....year..... to month.....year.....

Total expenses to implemen the studt.....million VND

Wherein: SNKH budget.....million VND

Other sources (if have).....million VND

Year 200..

Title page

REPORT
ON RESULTS OF THE CLINICAL TRIAL

1. Title of study
2. Name of investigational products
3. Content of the study (if not describe in the title of study, brief introduction (1-2 sentences) about design, comparative method, duration, dosage and populations)
4. Name of sponsor
5. Study code
6. Stage of the study.
7. Date of starting the study
8. Data of ending the study
9. Name and title of main investigator
10. Name of supervisor of sponsor.
11. Commiment to comply with Good Clinical Practice (GCP).
12. Reported date

Cover page 3

TABLE OF STUDYING SUMMARY

Cover page 4

ABBREVIATED WORDS

Cover page 5

CONTENT

THE NEEDED CONTENT IN THE SUMMARY REPORT

1) **Rationale**
2) **Objective of the study**
3) **Plan of the study**

3.1- Plan and design of study

3.2- Discussion on design of the study, slection of placebo

3.3- Selection the subjects of study (population) (inclusion, exclusion criteria, criteria to remove the participation of subjects or assessment)

3.4 Investigational products

3.5 Ensure the quality of data

3.6 Statistical method which is mentioned in the protocol and identification the sample size

3.7 Changes when conduct the study and analysis follow the plan.

4) **Subjects who participate in the study (patients/volunteer)**
   a) The situation of patients who participate in the study
   b) Errors compare with the protocol

5) **Assessment the efficacy**

5.1- Data is analized

It is necessary to identify these patients who will be used in the analysis for efficacy correctly, and these cases will be eliminated, reasons.

5.2- Characteristic of anthropology and the other basic features

Establish the summary table the characteristic of anthropology of each patient.

5.3- Identify the suitable of investigational drug

Summary and analysize any result which assess the suitable of each patient with dosage scheme in the study such as concentration of drug in biological solution according to the time

5.4- Treatment efficacy and data table for each patient

i) Efficient analysis
ii) Analysis/statistic
iii) Set up the data table of responde for each patient
iv) Dosage, concentration and relationship with respond
v) Interactions drugs-drugs, drugs-patients
vi) Describe the data of each patient
vii) Conclusion about the efficacy
viii)

6. Safety Assessment

Analysis the data relate to the safety which was mentioned on 3 levels:

- Exposed level (dosage, duration of usage, quantity of patients) will be checked in order to identify the safy level of investigational drug.
- Adverse events will be occurred in more common frequent or testings or changes will be identified, as well as the factors affect to frequent of ADR and undersirable effects.
- Serious undersirable effects, significant undersirable effects which common occurs in patients which withdraw from study before term or death patients although these advents relate or not to the investigational drugs.

7. Exposed level

Exposed level with investigational drugs (and controlled drugs or placebo) will be needed to assess according to the quantity of used patients, usage interval and dosage level.

8. Adverse events (AE)

Summary about AE
Describe the AE
Analysis the AE
List the AE for each patient

9. Deadth and other serious AE

List of deadth and other serious AE
Report the cases of deadth, serious AE and symptoms of the other AE
Analysis and discussion on deadth and other serious AE

10. Testing assessment

List down the testing value of each patient (annex) and abnormal value
Assessment each of testing parameter

11. Survival signals, physiological symptoms and other observations relate to the safety.

Analysis the survival signals, physiological symptoms and other observations

12. Safety conclusion

Summary about the safety of investigational drugs, especially focus on the changes of dosage, AEs lead to stop using, interfere of medical method or deadth….

13. Discussion and Conclusion

General assessment on the efficacy and safety of investigational drugs, relationship between the risks and benefits.

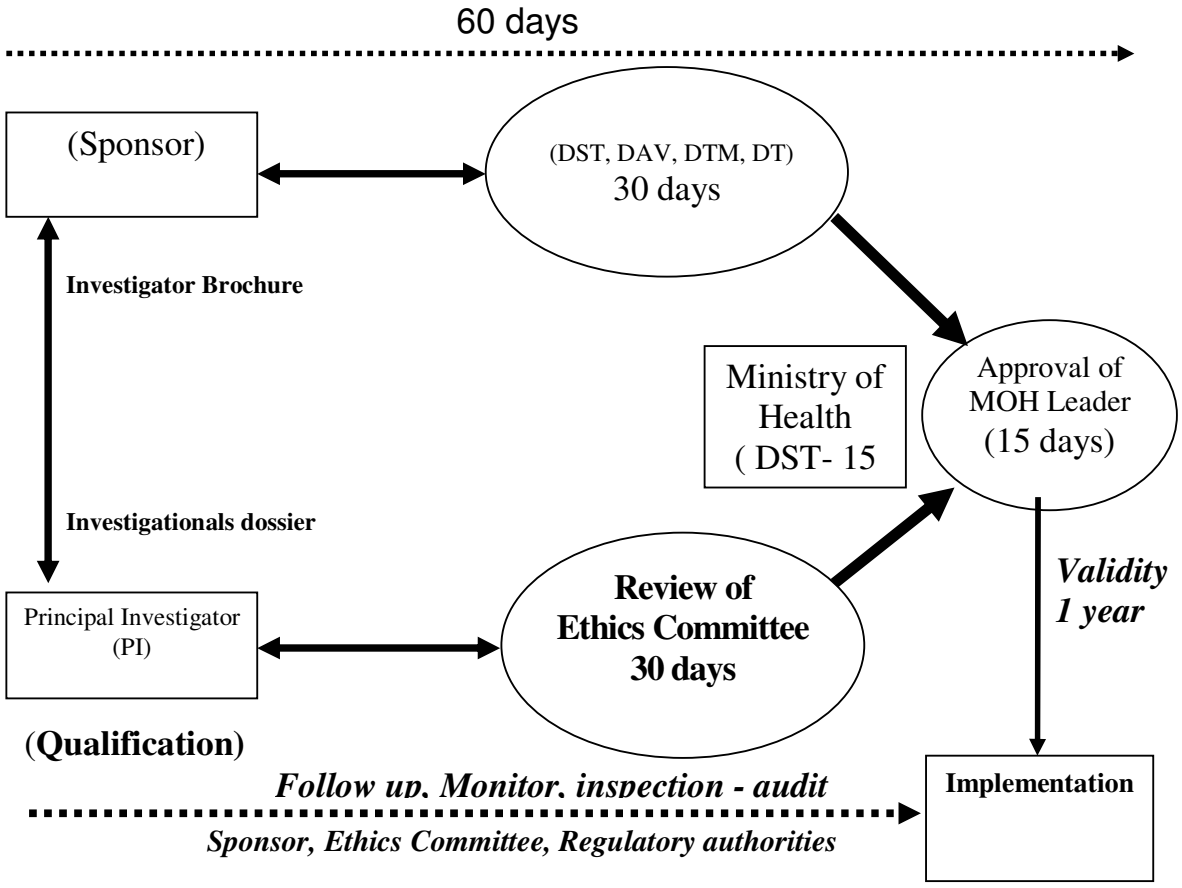
14. Table, diagram and related graph

15. List of reference document

16. Annex

List down the annex which have in the report

PROCESS OF APPROVAL, REVIEW DOSSIER FOR CLINICAL TRIAL



DST: Department of Science and Training

DAV: Drug Administration of Vietnam

DTM: Department of Traditional Medicines

DT: Department of Treatment