الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidelines for Investigational New Drugs (IND) Requirements

Version 1.1

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Drug Sector

Saudi Food & Drug Authority

Kingdom of Saudi Arabia

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Contents

Introduction

This guideline (in conjunction with the SFDA clinical trials requirements guidelines) is intended to give the sponsor an idea about the requirements for the approval of an Investigational New Drug (IND). These requirements should be fulfilled before shipping and distributing the investigational drug to clinical investigators in Saudi Arabia.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

SFDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At this point, the sponsor should follow this guideline to begin the first introduction of the IND in humans.

There are three IND types:

A. Investigator IND: submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit this type of IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

B. Emergency IND: allows the SFDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used

for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

C. Treatment IND: Submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the SFDA review takes place.

Once the IND application is submitted, the sponsor must wait for SFDA approval before initiating any clinical trials or even shipping or distributing the IND (decision is expected within 60 days).

Definition

- **Investigational New Drug (IND)** means a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. The terms ‘‘investigational drug’’, ‘‘investigational new drug’’ and "investigational medicinal product" are considered to be synonymous.

Promotion and Commercial distribution of an IND

1. A sponsor or an investigator, or any person acting on behalf of a sponsor or investigator, must not represent or promote that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This does not intend to restrict the full exchange of scientific information concerning the drug. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

2. A sponsor or an investigator must not commercially distribute or test market an investigational new drug.

Charging for and commercialization of investigational drugs:

1. Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of SFDA. In this case, the sponsor should provide a full written explanation of why charging is necessary.
2. A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided:
    i. There is adequate enrollment in the ongoing clinical investigations under the authorized IND.
    ii. Charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved.

Labeling of an IND

1. The labeling must ensure protection of the trial subject, enable identification of the product and trial and assist proper use of the product. The package labeling should state ‘‘Caution: New Drug—for investigational purposes.’’
2. The label should not include any statement that is false or misleading and should not states that the IND is safe or effective for the purposes for which it is being investigated.

Pre-IND Meetings

These meetings may be requested by the sponsor to address any questions, concerns and scientific issues related to the IND that may arise.

The questions should be as specific, comprehensive, and precise as possible to identify the critical issues.

a) *Purpose of the meeting*

For pre-IND meetings, the purpose is to discuss Chemistry, Manufacturing and Controls (CMC) issues as they relate to the safety of an investigational new drug proposed for use in initial clinical studies.

b) *Meeting Request*

The sponsor should submit a meeting request at least one month in advance. The request should contain a list of the specific objectives of the meeting, including a list of CMC-related questions or any other concerns.

c) *Information Package*

Sponsors should prepare an information package that includes a brief summary of the relevant CMC information, the developmental status, and the plan and time line for future development of the drug. The CMC-related questions should be presented in the information package in final form, grouped together and identified. The questions should be as specific, comprehensive, and precise as possible to identify the critical issues. The questions should be presented in the same relative subject matter order as a typical CMC section of an application or as otherwise appropriate to aid in the review of the information. Sufficient CMC background information on the drug should be provided by the sponsor in the information package to allow the SFDA to address the specific questions. Sponsors should coordinate the agenda and the content of the information package to expedite review of the material and discussion at the meeting. Where data presentation is appropriate, sponsors should present a summary of the data (e.g. tables, charts and graphs).

The discussion of safety issues for conventional synthetic drugs is typically brief. For certain types of drugs, such as biotechnological drugs, biological drugs, natural products, complex dosage forms, and drug-device combinations, it may be appropriate to discuss the CMC information in more detail. Examples where detailed discussion may be appropriate include, but are not limited to:

a. Drugs from human sources (e.g., appropriate donor screening procedures for tissues, blood, or other fluids; removal or inactivation of adventitious agents (e.g., viruses, bacteria, fungi, mycoplasma))
b. Drugs from animal sources (e.g., removal or inactivation of adventitious agents, transmissible spongiform encephalopathy (TSE)-free certification)
c. Biotechnology drugs, particularly rDNA proteins from cell line sources (e.g., adequacy of characterization of cell banks, potential contamination of cell lines, removal or inactivation of adventitious agents, potential antigenicity of the product)
d. Botanical drugs (e.g., raw material source, absence of adulteration)
e. Reagents from animal or cell line sources (same considerations as for drugs derived from animal cell or cell line sources)
f. Novel excipients
g. Novel dosage forms (e.g., characteristics, potential for overly rapid release of dose, if applicable)
h. Drug-device delivery systems (e.g., demonstration of device and its characteristics, potential for overly rapid release of dose, particle size distribution considerations, where applicable)

Content & format of an IND application

A sponsor who intends to conduct a clinical investigation must submit an ‘‘Investigational New Drug Application’’ (INDA) including, in the following order:

1. Cover sheet

A cover sheet for the application containing the following information:

a) The name, the contact details (e.g. address and telephone number) of the sponsor, the date of the application, and the name of the investigational new drug.
b) Identification of the phase or phases of the clinical investigation to be conducted.
c) A commitment not to begin clinical investigations until the IND application is approved by SFDA.

d) A commitment that an Institutional Review Board (IRB) will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research.

e) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

f) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

g) The name(s) and title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug.

h) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization (CRO), a statement containing the name and address of the CRO, identification of the clinical study, and a listing of the obligations transferred. If all obligations have been transferred, a general statement of this transfer including a list of the specific obligations transferred must be submitted.

i) The signature of the sponsor or the sponsor's authorized representative.

2. A table of contents

All sections under the table of contents should be paginated.

3. Introductory statement and general investigational plan

a) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

b) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other

countries that may be relevant to the safety of the proposed clinical investigation(s).

c) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

d) A brief description of the overall plan for investigating the drug product. The plan should include the following:

   i. The rationale for the drug or the research study.

   ii. The indication(s) to be studied.

   iii. The general approach to be followed in evaluating the drug.

   iv. The kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate).

   v. The estimated number of patients to be given the drug in those studies.

   vi. Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

4. Investigator's brochure

A copy of the investigator's brochure, containing the following information:

a) A brief description of the drug substance and the formulation, including the structural formula, if known.

b) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

c) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

d) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be submitted when appropriate).

e) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

5. Protocols

a) A protocol for each planned study or for studies not submitted initially in the IND should be submitted. In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries.

b) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of non-responders to an alternative therapy.

c) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

    i. A statement of the objectives and purpose of the study.

    ii. The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each sub-investigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the

research facilities to be used; and the name and address of each reviewing Institutional Review Board (IRB).

iii. The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

iv. A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

v. The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

vi. A description of the observations and measurements to be made to fulfill the objectives of the study.

vii. A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

6. Chemistry, manufacturing, and control (CMC) information

IND should be produced in accordance with the principles and guidelines of current Good Manufacturing Practices (refer to the SFDA Guidelines for Good Manufacturing Practice for Pharmaceutical Products).

a) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of available information . SFDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are

likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

b) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

c) As drug development proceeds and as the scale or production is changed from the pilot-scale production (for the limited initial clinical investigations) to the larger scale production (for expanded clinical trials), the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

d) IND submission is required to contain the following:

I. <u>Drug Substance:</u>

SFDA expects sponsors to reference one of the most current pharmacopeias, if applicable. Information on the drug substance should be submitted in a summary report containing the following items:

a. A description of the drug substance, including its physical, chemical, or biological characteristics:

A brief description of the drug substance and some evidence to support its proposed chemical structure should be submitted. It is understood that the

amount of structure information will be limited in the early stage of drug development.

b. The name and address of its manufacturer:

The full address of the manufacturer of the investigational drug substance should be submitted.

c. The general method of preparation of the drug substance:

A brief description of the manufacturing process including a detailed flow diagram, a list of the reagents, solvents, and catalysts used, should be submitted. More information may be requested as needed. For example, assessment the safety of biotechnology-derived drugs or drugs extracted from human or animal sources.

d. The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance:

A brief description of the test methods used should be submitted. Proposed acceptable limits of the clinical trials material should be provided. Submission of a copy of the certificate of analysis is also required. Validation data and established specifications ordinarily may not be submitted at the initial stage of drug development. However, for some well characterized, therapeutic biotechnology-derived products, preliminary specifications and additional validation data may be needed in certain circumstances to ensure safety in Phase 1.

e. Information to support the stability of the drug substance during the toxicological studies and the proposed clinical study(ies):

A brief description of the stability study and the test methods used to monitor the stability of the drug substance should be submitted.

*II. **Drug Product:***

SFDA expects sponsors to reference one of the most current pharmacopeias, if applicable. Information on the drug product should be submitted in a summary report containing the following items:

a. *A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear, but which are used in the manufacturing process:*

   A list of usually no more than one or two pages of written information should be submitted. The quality grade (e.g., NF, ACS) of the inactive ingredients should be cited. For novel excipients, additional manufacturing information may be necessary.

b. *Where applicable, the quantitative composition of the investigational new drug product, including any reasonable variations that may be expected during the investigational stage:*

   A brief summary of the composition of the investigational new drug product should be submitted.

c. *The name and address of the drug product manufacturer:*

   The full address(es) of the manufacturer(s) of the investigational drug product should be submitted.

d. *A brief, general description of the method of manufacturing and packaging procedures as appropriate for the product:*

   A flow diagram and a brief written description of the manufacturing process should be submitted, including sterilization process for sterile products.

e. The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product:

A brief description of the proposed acceptable limits and the test methods used should be submitted. Tests that should be submitted will vary according to the dosage form. For example, for sterile products, sterility and pyrogen tests should be submitted. Submission of a copy of the certificate of analysis of the clinical batch is also required. Validation data and established specifications are not required at the initial stage of drug development. For well-characterized, therapeutic, biotechnology-derived products, adequate assessment of bioactivity and preliminary specifications should be available.

f. Information to support the stability of the drug substance during the toxicological studies and the proposed clinical study(ies):

A brief description of the stability study and the test methods used to monitor the stability of the drug product packaged in the proposed container/closure system and storage conditions should be submitted.

(1) A brief general description of the composition, manufacture, and control of any placebo to be used in the proposed clinical trial(s):

Diagrammatic, tabular, and brief written information should be submitted.

(2) A copy of all labels and labeling to be provided to each investigator:

A sample of the proposed labeling that will be provided to investigator(s) in the proposed clinical trial should be submitted.

7. Pharmacology and toxicology information

Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or *in vitro*, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.

The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.

As drug development proceeds, the sponsor is required to update the informational amendments, as appropriate.

I. Pharmacology and drug disposition:

This section should contain, if known:

a) A description of the pharmacological effects and mechanism(s) of action(s) of the drug in animals.

b) Information on the absorption, distribution, metabolism, and excretions of the drug.

A summary report, without individual animal records or individual study results, usually suffices. In most circumstances, five pages or less should suffice for this summary. If this information is not known, it should simply be so stated.

II. Toxicology

A. Summary:

A summary of the toxicological effects of the drug in animals and *in vitro*. The particular studies needed depend on the nature of the drug and the phase of human investigation. When species specificity, immunogenicity, or other considerations appear to make many or all toxicological models irrelevant, sponsors are encouraged to indicate so.

Any new finding discovered that could affect subject safety must be reported to SFDA. Usually, 10 to 15 pages of text with additional tables (as needed) should suffice for the summary. It should represent the sponsor's perspective

on the completed animal studies at the time the sponsor decided human trials were appropriate. Use of visual data displays (e.g., box plots, stem and leaf displays, histograms or distributions of lab results over time) will facilitate description of the findings of these trials.

The summary document should be accurate and updated as new information or findings from the completed animal studies have become known.

The summary of the toxicological findings should ordinarily contain the following information:

i. A brief description of the design of the trials and any deviations from the design in the conduct of the trials. In addition, the dates of the performance of the trials should be included. Reference to the study protocol and protocol amendments may suffice for some of this information.

ii. A systematic presentation of the findings from the animal toxicology and toxicokinetic studies. Those findings that are considered as possible signals of human risk should be highlighted. The format of this part of the summary may be approached from a "systems review" perspective (*e.g.*, CNS, cardiovascular, pulmonary, gastrointestinal, renal, hepatic, genitourinary, hematopoietic, immunologic, and dermal). If a product's effects on a particular body system have not been assessed, that should be so noted. If any well documented toxicological "signal" is not considered evidence of human risk, the reason should be given.

iii. Identification and qualifications of the individual(s) who evaluated the animal safety data and concluded that it is reasonably safe to begin the proposed human study. This person(s) should sign the summary attesting that the summary accurately reflects the animal toxicology data from the completed studies.

iv. A statement of where the animal studies were conducted and where the records of the studies are available for inspection, should an inspection occur.

B. <u>Full Data Tabulation</u>:

The sponsor should submit a full tabulation of the data. This should consist of line listings of the individual data points, including laboratory data points, for each animal in these trials along with summary tabulations of these data points. To allow interpretation of the line listings, accompanying the line listings should be either:

1) a brief (usually a few pages) description (i.e., a technical report or abstract including a methods description section) of the study.

2) a copy of the study protocol and amendments.

III. Compliance with the good laboratory practice regulations:

For each nonclinical laboratory study subject to the good laboratory practice regulations, a statement that the study was conducted in compliance with the good laboratory practice regulations, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance and the sponsor's view on how such non-compliance might affect the interpretations of the findings.

8. Previous human experience with the investigational drug

A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

i. *If the investigational drug has been investigated or marketed previously, either in Saudi Arabia or other countries:* detailed information about such

experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. *If the drug has been the subject of controlled trials:* detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided.

Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

ii. If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (i) should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in Saudi Arabia, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

iii. If the drug has been marketed outside Saudi Arabia, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing.

Additional information

In certain applications, as described below, information on special topics may be needed.

a. *Drug dependence and abuse potential:* If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

b. *Radioactive drugs:* Sufficient data from animal or human studies should be submitted to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

c. *Pediatric studies:* Plans for assessing pediatric safety and effectiveness should be submitted.

d. *Other information:* A brief statement of any other information that would aid evaluation of the proposed clinical investigations.

Relevant information.

Any other relevant information needed for review of the application may be requested. The following points will be considered:

a. *Information previously submitted.* The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the SFDA by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

b. *Material in a foreign language.* The sponsor must submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor must also submit a copy of each original literature publication for which an English translation is submitted.

c. *Number of copies.* The sponsor must submit two hardcopies and one softcopy of all IND submissions.

d. *Numbering of IND submissions.* Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The

initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

Phases of an investigation

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. In general the phases are conducted sequentially, they may overlap. These three phases of an investigation are:

- *Phase 1 studies:*

Are the initial introduction of an investigational new drug into humans. It may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

- *Phase 2 studies :*

Includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication(s) in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

- *Phase 3 studies:*

Are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

Protocol amendments

- *New protocol:*

Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor must submit to SFDA a protocol amendment containing the protocol for the study.

Such study may begin provided that both the IRB and SFDA have approved the protocol.

- *Changes in a protocol*

1. A sponsor must submit a protocol amendment describing any change in Phase 1, 2, or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment include:
    i. Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.
    ii. Any significant change in the design of a protocol (such as the addition or dropping of a control group).
    iii. The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

2. No protocol changes to be made until the approval of both the IRB and SFDA is granted.
3. If a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided SFDA is subsequently notified by protocol amendment and the reviewing IRB is notified.

IND safety reporting

- *Review of safety information*

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the SFDA by the sponsor.

- *IND safety reports*

1. Written reports
    i. The sponsor should notify SFDA and all participating investigators in a written IND safety report of:
        a. Any adverse experience associated with the use of the drug that is both serious and unexpected; or
        b. Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

    Each notification must be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on SFDA adverse drug reaction (ADR) reporting form for health care

professionals (form no. ADR-1, available on the National Pharmacovigilance Center website);

ii. In each written IND safety report, the sponsor must identify all safety reports previously filed with the IND concerning a similar adverse experience, and must analyze the significance of the adverse experience in light of the previous, similar reports.

2. Transmission of safety reports. The sponsor must also notify SFDA by telephone, E-mail, or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information.

3. Reporting format and frequency. SFDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required in this guideline. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the SFDA.

- *Follow-up*

a) The sponsor must promptly investigate all safety information received by it.

b) Follow-up information to a safety report must be submitted as soon as the relevant information is available.

c) If the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable under the previous section (IND safety reports) is so reportable, the sponsor must report such experience in a written safety report as soon as possible, but no later than 15 calendar days after the determination is made.

d) Results of a sponsor's investigation of other safety information must be submitted, as appropriate, in an information amendment or annual report.

IND annual report

A sponsor must within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(A) Individual study information. A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

1. The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.
2. The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study with mentioning of the reasons for the drop out.
3. If the study has been completed, or if interim results are known, a brief description of any available study results.

(B) Summary information. Information obtained during the previous year's clinical and nonclinical investigations, including:

1. A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.
2. A summary of all IND safety reports submitted during the past year.
3. A list of subjects who died during participation in the investigation, with the cause of death for each subject.
4. A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.
5. A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trails, and information about bioavailability.

6. A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.
7. A summary of any significant manufacturing or microbiological changes made during the past year.

(C) A description of the general investigational plan for the coming year to replace that submitted one year earlier.

(D) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(E) A description of any significant protocol modifications made during the previous year.

(F) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

IND Exemptions

A. The clinical investigation of a drug product that is lawfully marketed in Saudi Arabia is exempt from the requirements of IND regulations if all the following apply:
    1. The study is not intended to support an approval of a new indication or a significant change in the product labeling.
    2. The study is not intended to support a significant change in the advertising for the product.
    3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
    4. The study is conducted in compliance with institutional review board (IRB) and informed consent regulations.
    5. The study is conducted in compliance with promotion and charging for investigational drugs regulations.

B. A drug intended solely for tests *in vitro* or in laboratory research animals.

C. A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

Clinical holds and requests for modification

- *General*

A clinical hold is an order issued by SFDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by SFDA in the interest of patient safety.

- *Grounds for imposition of clinical hold*

Clinical hold of Phase 1,2 or 3 study under an IND.

SFDA may place a proposed or ongoing Phase *1,2 or 3* investigation on clinical hold if it finds that:

i. Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

ii. The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

iii. The investigator brochure is misleading, erroneous, or materially incomplete; or

iv. The IND does not contain sufficient information required to assess the risks to subjects of the proposed studies.

v. The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring). The clinical hold would not apply under this paragraph to clinical studies conducted:

   a. Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

   b. Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

   c. Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

vi. The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

vii. SFDA may place an ongoing treatment protocol or treatment IND on clinical hold if it is determined that:

   a. The investigational drug is not under investigation in a controlled clinical trial under an IND in effect for the trial and not all controlled clinical trials necessary to support a marketing application have been completed, or a clinical study under the IND has been placed on clinical hold:

   b. The sponsor of the controlled clinical trial is not pursuing marketing approval with due diligence;

c. If the treatment IND or treatment protocol is intended for a serious disease, there is insufficient evidence of safety and effectiveness to support such use; or

d. If the treatment protocol or treatment IND was based on an immediately life-threatening disease, the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

- May be effective for its intended use in its intended population; or
- Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

e. There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

f. Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well controlled and the investigations that are designed to be adequate and well controlled; or

g. The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

h. Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

i. The drug has received marketing approval for the same indication in the same patient population; or

j. The SFDA determines that it would not be in the public interest for the study to be conducted or continued.

- *Discussion of deficiency*

Whenever SFDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold SFDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

- *Imposition of clinical hold*

The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The SFDA will then provide the sponsor a written explanation of the basis for the hold.

- *Resumption of clinical investigations*

An investigation may only resume after SFDA has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the SFDA that the investigation(s) can proceed. SFDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, SFDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. the sponsor may not proceed with a clinical trial until the sponsor has been notified by SFDA that the hold has been lifted.

- *Appeal*

If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the clinical hold decision.

- *Conversion of IND on clinical hold to inactive status*

If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by SFDA.

Inactive status

1. If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by SFDA on inactive status. This action may be taken by SFDA either on request of the sponsor or on SFDA's own initiative. If SFDA seeks to act on its own initiative, it must first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor have 30 days to respond as to why the IND should continue to remain active.
2. If an IND is placed on inactive status, all investigators must be notified and all stocks of the drug must be returned or otherwise disposed of.
3. A sponsor is not required to submit annual reports to an IND on inactive status.
4. A sponsor who intends to resume clinical investigation under an IND placed on inactive status must submit a protocol amendment containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan must reference such information. Clinical investigations under an IND on inactive status may only resume after a notification by SFDA that the clinical investigations described in the protocol amendment may begin.
5. An IND that remains on inactive status for 5 years or more may be terminated.

Withdrawal of an IND

1. At any time a sponsor may withdraw an effective IND. SFDA must be notified, all clinical investigations conducted under the IND must be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor. The sponsor must maintain written records of any disposition of the drug.
2. If an IND is withdrawn because of a safety reason, the sponsor must promptly so inform SFDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

Termination of IND

If an IND is terminated, the sponsor must end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. The termination must be preceded by a proposal to terminate by SFDA and an opportunity for the sponsor to respond.

- *Reasons for termination*

  i. Human subjects would be exposed to an unreasonable and significant risk of illness or injury.

  ii. The IND does not contain sufficient information required to assess the safety to subjects of the clinical investigations.

  iii. The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.

  iv. The clinical investigations are being conducted in a manner substantially different than that described in the protocols submitted in the IND.

  v. The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation.

vi. The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information.

vii. The sponsor fails promptly to investigate and inform the SFDA and all investigators of serious and unexpected adverse experiences or fails to submit any other required documents .

viii. The sponsor fails to submit an accurate annual report of the investigations.

ix. The sponsor fails to comply with any other applicable requirement.

x. The IND has remained on inactive status for 5 years or more.

xi. The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold.

xii. The investigational plan or protocol(s) is not scientifically planed to determine whether or not the drug is safe and effective for use; or

xiii. There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

- *Opportunity for sponsor response*

1. If SFDA proposes to terminate an IND, SFDA will notify the sponsor in writing. The sponsor may provide a written explanation or correction or may request a conference with SFDA to provide the requested explanation or correction within 30 days. Otherwise, the IND will be terminated.
2. If the sponsor responds but SFDA does not accept the explanation or correction submitted, SFDA must inform the sponsor in writing of the reason for the non-acceptance and provide the sponsor with an opportunity for a meeting with the SFDA on the question of whether the IND should be terminated. This request must be made within 10 days of the receipt of non-acceptance.

- *Immediate termination of IND*

If at any time SFDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the SFDA must immediately, by written notice to the sponsor, terminate the IND. If an IND is

terminated, the SFDA will afford the sponsor an opportunity for a meeting (within 30 days) on the question of whether the IND should be reinstated.

Responsibilities of Sponsors and Investigators

The sponsors and investigators should comply with this guideline together with other related guidelines such as SFDA clinical trials requirements guidelines.

I. Responsibilities of Sponsors:

Sponsors are responsible for the following:

- *Selecting investigators and monitors*
  a. A sponsor must select only investigators qualified by training and experience as appropriate experts to investigate the drug.
  b. A sponsor must select a monitor qualified by training and experience to monitor the progress of the investigation.
  c. A sponsor must ship investigational new drugs only to investigators participating in the investigation.
  d. Before permitting an investigator to begin participation in an investigation, the sponsor must obtain the following:
     1. A signed investigator statement containing:
        a) The name and address of the investigator;
        b) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;
        c) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;
        d) The name and address of any clinical laboratory facilities to be used in the study;
        e) The name and address of the IRB that is responsible for review and approval of the study(ies);
        f) A commitment by the investigator that he or she:

a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

b) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

c) Will personally conduct or supervise the described investigation(s);

d) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and institutional review board review and approval are met;

e) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) ;

f) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

g) A commitment by the investigator that, for an investigation subject to an institutional review requirement, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all

unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

h) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

2. A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

3. Clinical protocol

a) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

b) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

4. Financial disclosure information

For any clinical investigator, the sponsor must submit the following:

a) Any financial arrangement between the sponsor and the clinical investigator involved in the conduct of a covered clinical trial;

b) Any significant payments of other sorts from the sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

c) Any proprietary interest in the tested product held by any clinical investigator involved in a study;

d) Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and

e) Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

The sponsor must obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

- *Informing investigators*

1. Before the investigation begins, a sponsor (other than a sponsor-investigator) must give each participating clinical investigator an investigator brochure.
2. The sponsor must, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means.

- *Review of ongoing investigations*

a. The sponsor must monitor the progress of all clinical investigations being conducted under its IND.

b. A sponsor who discovers that an investigator is not complying with the signed agreement, the general investigational plan, or any requirements that is related to the investigation must promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor must require the investigator to dispose of or return the investigational drug and notify SFDA.

c. The sponsor must review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors must make such reports to SFDA regarding information relevant to the safety of the drug. The sponsor must make annual reports on the progress of the investigation.

d. A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects must discontinue those investigations that present the risk, notify SFDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding, and send a full report of the sponsor's actions to the SFDA. The sponsor must discontinue the investigation as soon as possible, and no later than 5 working days after making the determination that the investigation should be discontinued. Upon request, SFDA will confer with a sponsor on the need to discontinue an investigation.

- *Record keeping and retention*

a. A sponsor must maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required

to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

b. A sponsor must maintain complete and accurate records showing any financial interest paid to clinical investigators by the sponsor of the covered study. A sponsor must also maintain complete and accurate records concerning all other financial interests of investigators.

c. A sponsor must retain the records and reports for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and SFDA has been so notified.

d. A sponsor must retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies and release the reserve samples to SFDA upon request.

- *Inspection of sponsor's records and reports*

A sponsor must upon request from any properly authorized employee of the SFDA, at reasonable times, permit such employee to have access to and copy and verify any records and reports relating to the clinical investigation. Upon written request by SFDA, the sponsor must submit the records or reports (or copies of them) to SFDA. The sponsor must discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation.

- *Disposition of unused supply of investigational drug*

The sponsor must assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided

this alternative disposition does not expose humans to risks from the drug. The sponsor must maintain written records of any disposition of the drug.

- *Transfer of obligations to a contract research organization (CRO)*

  A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization (must be approved by SFDA). Any such transfer must be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description must be deemed not to have been transferred.

II. Responsibilities of Investigators

An investigator is responsible for the following:

- *Control of the investigational drug*

  An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.

- *Investigator record keeping and retention:*

  a. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug.

  b. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the

investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

c. An investigator must retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and SFDA is notified.

- *Investigator reports*

  a. *Progress reports.* The investigator must send all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required to submit annual reports to SFDA on the progress of the clinical investigations.

  b. *Safety reports*. An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.

  c. *Final report.* An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

  d. *Financial disclosure reports.* The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required. The clinical investigator must promptly update

this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

- *Assurance of IRB review*

  An investigator must assure that an IRB that complies with the requirements will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

- *Inspection of investigator's records and reports*

  An investigator must upon request from any properly authorized employee of SFDA, at reasonable times, permit such employee to have access to, and copy and verify any records or reports made by the investigator. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

- *Handling of controlled substances*

  If the investigational drug is a controlled substance, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution (refer to the guideline of controlled substances).

- *Disqualification of a clinical investigator*

  If SFDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements or has submitted false information in any required report, the SFDA will request a clarification from the investigator. If an explanation is offered but not accepted by the SFDA, the SFDA will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

Import and export requirements

- *Imports*

An investigational new drug can be imported into Saudi Arabia if it complies with the following:

1. The IND application has been approved by SFDA or if the sponsor received an import permit from SFDA.
2. The importer in Saudi Arabia is the sponsor of the IND;
3. The importer is a qualified investigator named in the IND; or
4. The importer is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the importer and describes what, if any, actions the importer will take with respect to the investigational drug.

- *Exports*

An investigational new drug may be exported from Saudi Arabia for use in a clinical investigation under any of the following conditions:

1. The sponsor has Pre-approval letter from the SFDA.

2. The IND complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator in a study submitted to and allowed to proceed under the IND;
3. Any other applicable regulations for exportation.

References

- Clinical Trials Requirements Guideline.
- FDA Guidance for Industry CGMP for Phase 1 Investigational Drugs.
- FDA Guideline for Drug Master Files.
- Good Laboratory Practice for National Pharmaceutical Control Laboratories.
- Guidelines for Good Manufacturing Practice for Pharmaceutical Products.
- Guidelines for Good Manufacturing Practice of Radiopharmaceuticals.
- Immunotoxicology Evaluation of Investigational New Drugs, Guidance for Industry, FDA.
- INDs for Phase 2 and Phase 3, Studies Chemistry, Manufacturing, and Controls Information, FDA.
- The GCC Guidelines for Stability Testing of Drug Substances and Pharmaceutical Products.