

TANZANIA FOOD AND DRUGS AUTHORITY



***GUIDELINES FOR APPLICATION TO
CONDUCT CLINICAL TRIALS IN TANZANIA***

(Made under Section 63(1) of the Tanzania Food, Drugs and Cosmetics Act, Cap 219)

Third Edition

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Abbreviations

API	-	Active Pharmaceutical Ingredient
ADRs	-	Adverse Drug Reactions
AEs	-	Adverse Events
API	-	Active Pharmaceutical Ingredient
BSE	-	Bovine spongiform encephalopathy
BUCHS	-	Bugando University College of Health Sciences
CE	-	Conformité Européene
CEP	-	Certificate of Suitability to the monograph of European Pharmacopeia
CIOMS	-	Council for International Organizations of Medical Sciences
CoA	-	Certificate of Analysis
CRF	-	Case Report Form
CRO	-	Contract Research Organization
CSDT	-	Common Submission Template
CTA	-	Clinical Trial Application Form
CTC	-	Clinical Trial Model Certificate
CTD	-	Common Technical Document
DG	-	Director General
DMC	-	Data Monitoring Committee
DSMB	-	Data and Safety Monitoring Board
IEC	-	Independent Ethics Committee
FPP	-	Finished Pharmaceutical Product
GCLP	-	Good Clinical and Laboratory Practices
GCP	-	Good Clinical Practice
GHTF	-	Global Harmonization Task Force
GMP	-	Good Manufacturing Practice
IB	-	Investigator's Brochure
ICH	-	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	-	Independent Data Monitoring Committee
IHI	-	Ifakara Health Institute
IMP	-	Investigational Medicinal Product
IP	-	Investigational Product
IRB	-	Institutional Review Board
ISO	-	International Organization for Standardization
ITM	-	Institute of Traditional Medicine
JP	-	Japanese Pharmacopoeia
KCMC	-	Kilimanjaro Christian Medical Centre
MTA	-	Material Transfer Agreement
MUHAS	-	Muhimbili University of Health and Allied Sciences
NEC	-	National Ethics Committee
NF	-	National Formulary
NIMR	-	National Institute for Medical Research
PI	-	Principal Investigator
Ph.Eur	-	European Pharmacopoeia
QA	-	Quality Assurance
QC	-	Quality Control
REC	-	Research Ethics Committees (Independent /Institutional)

SADC	-	Southern Africa Development Community
SAE	-	Serious Adverse Event
SmPC	-	Summary of Product Characteristics
SUSARs	-	Suspected Unexpected Serious Adverse Reactions
SOPs	-	Standard Operating Procedures
SPC	-	Summary of Product Characteristics
TFDA	-	Tanzania Food and Drugs Authority
TSE	-	Transmissible Spongiform Encephalopathy
USP	-	United States Pharmacopoeia
WHO	-	World Health Organization
WMA	-	World Medical Assembly

Acknowledgements

This is the third edition of the *Guidelines for Application to Conduct Clinical Trials in Tanzania* to be developed by Tanzania Food and Drugs Authority (TFDA). The edition supersedes the first and second editions which were developed in years 2004 and 2009 respectively.

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The current edition of the guidelines also contains excerpts from other internationally recognized guidelines such as those prepared by ICH, TFDA, Health Canada, US-FDA, WHO, South African Medicines Control Council, ISO and EMA. We are utterly grateful to these institutions for making their documents easily available for adoption and/or adaption. The CTD format which has been included in this edition has been modified from the ICH guidelines of which we are specifically indebted.

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Adam Mitangu Fimbo
Director – Medicines and Complementary Products
Tanzania Food and Drugs Authority

Foreword

The Tanzania Food and Drugs Authority (TFDA) is the regulatory authority in Tanzania responsible for regulating clinical trials. Sponsors and Investigators who intend to conduct clinical trials in the country are required to obtain an authorization or permit from TFDA before enrolling participants into their studies. Such legal requirement has also been promulgated in Section 63(1) of the *Tanzania Food, Drugs and Cosmetics Act, Cap 219*. Apart from a permit from TFDA, Investigators are also required to obtain an ethical clearance issued by the National Institute for Medical Research (NIMR). The Tanzania Commission for Science and Technology (COSTECH) is also responsible for issuing research permits for foreign investigators intending to take part in trials conducted in the country.

This third edition of the *Guidelines for Application to Conduct Clinical Trials in Tanzania* has been revised to incorporate requirements which were not included in the previous editions developed in years 2004 and 2009 respectively. The revision has also taken into account the current state of affairs in as far as clinical trials are concerned and a mounting experience which has been accrued over the past years including issuance of permits from other institutions in the country.

In the above context therefore, the guidelines highlights requirements that needs to be followed by Investigators and Sponsors when submitting their applications for approval to conduct trials in Tanzania. Good Clinical Practice (GCP) principles and other ethical considerations are also detailed with the aim of ensuring that trial participants are protected and safeguarded against any harm that might arise as a result of participating in trials.

Specific requirements for studies involving animal species which were missing in the previous editions have also been added in this document. The aim here is to assist those who are engaged in animal research to comprehend existing procedures for securing permits for veterinary clinical studies. Much as the TFDA is also regulating medical devices and diagnostics and since the previous editions of these guidelines did not include requirements for studies involving these categories of products, specific requirements have also been summarized to guide Investigators and Sponsors.

The revised guidelines have been arranged in a modular format as adopted from the ICH guidelines to allow for consistent and uniform documentation of submissions. This will in-turn pave-a-way for speedy assessment of applications by TFDA and ultimately decisions on approval/non-approval based on clear and transparent criteria.

Investigators and Sponsors are therefore urged to read these guidelines together with those prepared by the International Conference on Harmonization of Technical Requirements for Registration of Human and Veterinary Medicinal Products (ICH and VICH) as well as WHO-GCLP guidelines when submitting documentation, planning for, carrying out and reporting clinical trials.

New ideas and inputs from stakeholders that might help in improving the current edition of the guidelines are still encouraged and welcomed by TFDA.



Hiiti B. Sillo

Director General

Tanzania Food and Drugs Authority

Definition of terms

In the context of these guidelines the following words/phrases are defined as follows.

Act

The Tanzania Food, Drugs and Cosmetics Act, Cap 219 and all regulations relating to clinical trials made under the Act.

Adverse Drug Reactions (ADRs)

All noxious and unintended responses to a clinical trial medicinal product related to any dose or all unintended noxious responses to a registered medicinal product which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event (AE)

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

Active pharmaceutical ingredient (API)

Means an active ingredient in any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

Applicant

A person applying to conduct a clinical trial which may include a sponsor, contract research organization (CRO) or in the case of investigator-initiated academic research studies, research institution or principal investigator.

Audit of a trial

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

Audit Certificate

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

Audit Report

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

Authority

Means Tanzania Food and Drugs Authority or its acronym TFDA.

Bioavailability: refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action. It may be useful to distinguish between the “absolute bioavailability” of a given dosage form as compared with that (100 %) following intravenous administration (e.g. oral solution *vs.* intravenous), and the “relative bioavailability” as compared with another form administered by the same or another non-intravenous route (e.g. tablets *vs.* oral solution).

Bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities in terms of peak (C_{max} and T_{max}) and total exposure (AUC) after administration of the same molar dose under the same conditions are similar to such a degree that their effects with respect to both efficacy and safety can be expected to be essentially the same. Bioequivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic circulation. Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the study participant(s) being unaware and double-blinding usually refers to the study participant(s), investigator(s), monitor, and in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF)

A document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

Clinical Trial/Study

A systematic study on medicinal product(s) in human participants (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

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

Phase I

These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary

evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans.

Phase II

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

Phase III

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

Phase IV

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

Clinical Trial/Study Report

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

Comparator (Product)

A medicinal or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Confidentiality

Maintenance of the privacy of trial participants including their personal identity and all personal medical information.

Contract

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

Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multi-centre trial.

Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multi-centre trial.

Contract Research Organization (CRO)

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

Clinical performance

behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s)

Control Product

Any approved product used according to label directions, or any placebo, used as a reference in a clinical study for comparison with the investigational veterinary product under evaluation.

Data and Safety Monitoring Board (DSMB)

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

Direct Access

Permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical trial. TFDA inspectors with direct access should take all reasonable precautions to maintain the confidentiality of study participants' identities and sponsor's proprietary information.

Disposal of Study Animals

The fate of the study animals or their edible products during or following completion of the study. For example, after complying with any restrictions to minimize public health concerns, animals may be slaughtered, returned to the herd, sold or returned to their owner.

Documentation

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

Drug/Device Combination Product

Means a product comprised of two or more regulated components i.e. drug/device, biological/device, drug/biologic/device that are physically, chemically or otherwise combined or mixed and produced as a single entity or

- Two or more separate products packaged together in a single package or as unit and comprised of drug and device products or device and biological product or
- An investigational device or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed e.g. to reflect a change of intended use, dosage form, strength, route of administration or significant change in dose and
- Any Investigational drug, device or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device or biological product where both are required to achieve the intended use, indication or effect.

Essential Documents

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

Ethical Clearance

An authorization to conduct a clinical trial issued by the National Ethics Committee based on ethical issues related to trials involving human participants in Tanzania.

Export

With its grammatical variations and cognate expression, means to take or cause to be taken out of Tanzania by land, sea or air.

Finished pharmaceutical product (FPP)

Means a finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

Generic product

Means a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Good Clinical Practice (GCP)

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

Good Clinical Laboratory Practice (GCLP)

Applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity of data generated by analytical laboratories.

Good Manufacturing Practice (GMP)

That part of quality assurance which ensures that investigational products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current TFDA GMP Guidelines.

Impartial Witness

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

Indemnity

legal exemption from liability for damages

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of participants in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

Informed Consent

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

Informed Consent (veterinary study)

A documented process by which an owner, or owner's agent, voluntarily confirms the owner's willingness to allow their animal(s) to participate in a particular study, after having been informed of all aspects of the study that are relevant to the decision to participate.

Import

With its grammatical variations and cognate expressions, means to bring or cause to be brought into Tanzania by land, sea or air.

Inspection

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

Insurance

The act, system, or business of insuring property, life, one's person, etc., against loss or harm arising in specified contingencies, as fire, accident, death, disablement, or the like, in consideration of a payment proportionate to the risk involved.

Intended use/purpose

Means the use for which the device is intended according to the data supplied by the Manufacturer on the labeling, in the instructions and/or in promotional materials.

Interim Clinical Trial/Study Report

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

Investigational medicinal Product

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

Investigational medical device

Medical device being assessed for safety or performance in a clinical investigation
Note 1 to entry: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.
Note 2 to entry: In this International Standard, the terms “investigational medical device” and “investigational device” are used interchangeably.

Investigational Products

For the purpose of these guidelines it means human medicines, herbal medicines, biologicals, veterinary medicines, medical devices and diagnostics.

Investigator

A person responsible for the conduct of the clinical trial at a trial site.

Investigator's Brochure (IB)

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

In Vitro diagnostics

Means a device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.

Legally Acceptable Representative

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

Manufacture

Includes all operations involved in the production, fabricating, processing, refining, transformation, packing, packaging, re-packaging and labeling of Investigational Products.

Manufacturer

Means a natural or legal person with responsibility for manufacturing of a medicinal product or active pharmaceutical ingredient. It involves operations such as production, packaging, repackaging, labelling and relabeling of pharmaceuticals.

Medical device

Means, an instrument, apparatus, implement, medical equipment, machine, contrivance, implant, in vitro reagent, laboratory reagent, laboratory equipment or other similar or related article, including any component, part or accessory, which is –

- i. Recognized in the Official National Formulary, or Pharmacopoeia or any supplement to them;
- ii. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals or;
- iii. Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its principal intended purposes through chemical action within the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principle intended purposes;

Material Transfer Agreement (MTA)

A written agreement entered into by a *provider* and a *recipient* of research material. The purpose of the MTA is to protect the intellectual and other property rights of the provider while permitting research with the material to proceed.

Mock-up

Means a copy of the flat artwork design in full colour, providing a replica of both the outer

and immediate packaging, providing a two-dimensional presentation of the packaging/labelling of the medicine. It is also referred to as a paper copy or computer generated version.

Monitor

A person appointed by, and responsible to, the sponsor or Contract Research Organization (CRO) for the monitoring and reporting of progress of the trial and for verification of data.

Monitoring Report

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

Multi-centre Trial

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

On-going stability study

Means the study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

Pilot-scale batch

Means a batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

Primary batch

Means a batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life.

Pre-clinical Studies

Biomedical studies not performed on human study participants.

Principal Investigator (PI)

A person responsible for the conduct of the clinical trial at a trial site. A pharmacist, physician, dentist, veterinarian or other qualified person, resident in Tanzania Mainland and member of good standing of a professional body, responsible for the conduct of clinical trial at a clinical trial site. If a trial is conducted by a team of individuals at a trial site, the principal investigator is the responsible leader of the team. See also Sub-investigator.

Production batch

Means a batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

Protocol

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

Protocol Amendment

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

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCLP and TFDA requirement(s).

Quality Control (QC)

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

Randomization

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

Risk

Means the possibility of loss, damage or any other undesirable event.

Risk assessment

Means identifying and characterizing the nature, frequency, and severity of the risks associated with the use of a product conducted throughout the product's lifecycle, from the early identification of a product as a candidate, through the pre-marketing development process, and after marketing.

Serious Adverse Event (SAE) or Serious Adverse Drug Reactions (Serious ADR)

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Source Data

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

certified copies).

Source Documents

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

Sponsor

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

Sponsor-Investigator

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

Standard Operating Procedures (SOPs)

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

Study Animal

Any animal that participates in a clinical study, either as a recipient of the investigational veterinary product or as a control.

Sub-investigator

Any individual member of the clinical trial team designated and supervised by the Principal Investigator at a trial site to perform critical trial-related procedures and/or make important trial-related decisions (e.g. associates, residents, research fellows).

Target Animal

The specific animal by species, class and breed identified as the animal for which the investigational veterinary product is intended for use.

Trial participant

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

Study participant Identification Code

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

Trial Site

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

Unexpected Adverse Drug Reaction

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

Veterinary Product

Any product with approved claims to having a protective, therapeutic or diagnostic effect or to affect physiological functions when administered to or applied to an animal. The term applies to therapeutics, biologicals, diagnostics and modifiers of physiological function.

Vulnerable Study participants

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

Well-being (of the trial subjects)

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

1. INTRODUCTION

Clinical trials are planned scientific investigations conducted in humans and animals to gather information on the safety and efficacy of medical products and health technologies. Such experiments involve the administration of investigational products in patients, healthy volunteers or animal species to generate data which can later on be used for marketing authorization of a product.

The Tanzania Food and Drugs Authority (TFDA) is the regulatory authority in Tanzania mandated to approve clinical trials for conduct as well as for marketing authorization of medicines, medical devices, diagnostics and other products. New application to conduct a clinical trial is required for the following categories of products/circumstances:

- a) Medicines, biologicals, cosmetics, medical devices and diagnostics unregistered in Tanzania.
- b) A clinical investigation of a non-CE-marked medical device in the following circumstances;
 - (i) The introduction of a completely new concept of device into clinical practice where components features and/or methods of action, are previously unknown;
 - (ii) Where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body, in which case compatibility and biological safety will need to be considered;
 - (iii) Where a device, either CE-marked or non-CE-marked, is proposed for a new purpose or function;
 - (iv) Where in vitro and/or animal testing of the device cannot mimic the clinical situation
 - (v) Where there is a new manufacturer especially of a high-risk device
- c) Registered medicines, biologicals, cosmetics, medical devices and diagnostics where the proposed clinical trials are outside the conditions of approval. These may include changes to:
 - (i) Indications and clinical use
 - (ii) Target patient or animal population(s)
 - (iii) Routes of administration
 - (iv) Dosage
 - (v) The intended use of a device(s)
- d) Research on a drug/device combination product if the combination is unregistered or if one of the components is unregistered.

These guidelines have been developed to assist applicants to prepare applications for authorization of their clinical trials in Tanzania. The document is divided into different modules as follows:

- Module 1: Administrative and General Information
- Module 2: Overview and Summaries-
- Module 3: Data on Quality
- Module 4: Non-Clinical Study Reports
- Module 5: Clinical Study Reports
- Module 6: Veterinary Clinical Trials
- Module 7: Medical Devices and Diagnostics Clinical Trials

Applicants should submit their applications as per the Modules and the Common Technical Document (CTD) highlighted in these guidelines. Information in these Modules should be present in relevant sections. The overall organization of the CTD format should not be modified.

If not contained in the bulk of the documentation, any additional data should be included as addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview.

All clinical trials involving new investigational products should fulfill the requirements of module 1 to 5. Veterinary clinical trials will be required to adhere to module 1 and 6 and Medical Devices and Diagnostics Clinical Trials will be required to adhere to module 1 and 7. For clinical trials involving well established generic medicines submission of non-clinical and clinical data in module 2, 4 and 5 will be exempted unless there are changes in indication.

MODULE1: ADMINISTRATIVE AND GENERAL INFORMATION

This section describes administrative and application procedures applicants. Applicants are therefore advised to read carefully this section before compiling dossiers and assemble applications ready for submission to TFDA. Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondences) as needed. Documents should be organized in the order listed below. Generally, all of the documents in Module 1, other than the es, can be provided in a single volume. The es to the module should be submitted in separate volumes.

All applications and supporting documents shall be in English. Participants' information sheets and Informed Consent Forms (ICFs) shall be in both Kiswahili and English.

Data shall be presented in both A4 papers and in electronic format in Compact Discs (CDs). The Paper documents shall be arranged in spring file folders while electronic documents should be in word format, bookman old style, font 11. Extension sheets, tables, diagrams and other supporting documents shall as far as possible be of the same size, well annotated, numbered and appropriately cross-referenced.

The information must be compiled in accordance with these guidelines. Where information is required in the application forms its location shall be cross referenced in the submission.

1.1 Comprehensive table of contents for all modules

1.2 Cover letter

Applicants should include a cover Letter with all applications. A copy of the letter should be placed at the beginning of Module 1. The cover letter shall be signed by the Principal Investigator or sponsor.

1.3 Comprehensive table of content

Module 1 should include a comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application by module. In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document.

1.4 Application information

The application may be delivered physically or by courier to TFDA head office located at Mabibo External along Mandela Express way, P. O. Box 77150, Dar es Salaam, Tanzania. An application to conduct a clinical trial shall include:

- 1.4.1 An application to register a clinical trial must be accompanied by a completed Application Form (**Annex I**). The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately.
- 1.4.2 General investigational plan.
- 1.4.3 Capacity building plans including training and updating of staff involved in the trial.
- 1.4.4 Overall Summary of the clinical trial Protocol as prescribed in **Annex 2**.
This document must be submitted in both hard copy and electronic format. Note that electronic copies must be submitted on CD-ROM, in either MS Word or Word Perfect format (PDF format of the overall Summaries of the protocol and Quality Overall Summary (QOS) is not acceptable). This document in electronic files should be placed with the protocol at the beginning of the Module 1 after the application form.
- 1.4.5 Signed and approved protocol with data compiled as prescribed in **Annex 3** and current ICH guidelines.
- 1.4.6 Participant Information Leaflet (PIL), Informed Consent Forms (English and Swahili versions) and any other information to be given to participants. Details regarding the informed Consent forms should be as prescribed in **Annex 4**.
- 1.4.7 Declarations by Principal investigator, Co/Sub investigators and Monitor(s) in prescribed format (**Annex 5-7**).
- 1.4.8 Joint declaration by Sponsor (or representative) and National Principal Investigator in prescribed format (**Annex 8**).
- 1.4.9 Certified copy of insurance policy cover of study participants (See current TFDA Guidelines for Insurance and Indemnity in Clinical Trials).
- 1.4.10 Ethical clearance or a copy of acknowledgement of submission of study protocol from the National Ethics Committee in case of parallel submission.
- 1.4.11 Curriculum vitae (CVs) of investigator(s) (see **Annex 9** for recommended format)
- 1.4.12 Nonclinical Overall Summary as prescribed in **Annex 10**, up to date Investigator's Brochure (IB) and prescribing information if applicable. Details on the summaries and IB should be as described in **Module 2** of these guidelines.
- 1.4.13 Blank Case Report Forms (CRFs) and Serious Adverse Events reporting form to be used in the study.
- 1.4.14 Certificate of Good Manufacturing Practice (GMP) for manufacture of the trial medicine or other evidence of manufacture quality, safety and consistency.
- 1.4.15 Certificate of GMP manufacture of the placebo - if applicable.

- 1.4.16 Trial product labels and package Insert/s for other trial medicines.
- 1.4.17 Mock up labels for the Investigational products.
- 1.4.18 Evidence of accreditation/certifications of the designated Laboratories or other evidence of Good Laboratory Practice (GLP) and assay validation.
- 1.4.19 Letters of Access (if applicable) authorizing TFDA to access related files (Drug master Files, Site Reference Files) must be submitted.
- 1.4.20 Full, legible copies of key, peer-reviewed published articles supporting the application.
- 1.4.21 Filled in Quality Overall Summary – Chemical Entities Template (**Annex 11**).
- 1.4.22 Investigational Medicinal Product Dossier as prescribed in **module 3**.

There shall be no cross reference of particulars or documentation between one clinical trial and another.

- 1.5** An application to conduct a clinical trial may be made by a sponsor or the sponsor's agent who must also submit a power of attorney attesting that he is a duly appointed agent.
- 1.6** A statement by the applicant must be provided indicating that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading.
- 1.7** In the case of multi-centre trials, a coordinating investigator must also sign the application form.
- 1.8** If the trial is part of an international study, information regarding the other participating countries must be provided including the part of the trial that will be carried out locally.
- 1.9** TFDA will only process an application upon receiving a completed application together with the prescribed fees.
- 1.10** No approval shall be granted until when the applicant submits ethical clearance from the National Ethics Committee.

1.11 Application-Clinical Trial Amendments

- 1.11.1 Application for amendment(s) to a previously authorized clinical trial shall be made in forms **(Annex 12 and 13)**, whichever is applicable, and shall be accompanied with amendment fees as prescribed in the Fees and Charges Regulations in force at the time of application.
- 1.11.2 The applicant must submit the description of the proposed amendment including reasons thereof.
- 1.11.3 Original wording, revised wording and rationale for the change(s) including a copy of complete protocol incorporating all amendments should also be submitted, where applicable.
- 1.11.4 The applicant must also submit supporting data for the amendment, including as possible;
 - a. Updated overall risk-benefit assessment
 - b. Possible consequences for participants already in the trial
 - c. Possible consequences for the assessment of trial results
 - d. Summaries of data
- 1.11.5 TFDA approval must be obtained for the following amendments:
 - (i) Changes that affect patient selection and monitoring
 - (ii) Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc)
 - (iii) Changes that affect patient discontinuation
 - (iv) Addition/deletion of an investigational site
 - (v) Change of principal investigator
 - (vi) Changes that result in the extension of duration of a trial
 - (vii) Changes that relate to the chemistry and manufacturing information that may affect drug safety and quality (For example: specifications for the IMP where limits of the test are relaxed or deleted; where a new impurity or degradation product has been identified; and addition of new raw materials, solvents, reagents, catalysts or any other materials used in the manufacture of the API).
- 1.11.6 The application for amendment(s) shall be accompanied by Ethical Clearance or authorization from the NEC.

1.12 Payment of fees

New clinical trial applications and amendments shall be accompanied by an application fees as prescribed in the Fees and Charges Regulations in force at the time of application. Any application that will not be accompanied by appropriate fees will not be accepted.

Fees shall be paid in favour of the Tanzania Food and Drugs Authority directly to the bank through account No. 2041100069 NMB for local currency or Account Nos. 100380013 Citibank (T) and 02J1021399100 CRDB for foreign currency or by banker's draft. All bank

charges shall be borne by the applicant, who shall also make sure he sends an advice note giving details of the payment in particular the name of the applicant, the product or products paid for and amount of fees paid.

1.13 Clinical Trial Application (CTA) and Clinical Trial Application-Amendments

(CTA-A) Review Process

1. Assessment

TFDA reviews the documents submitted in Clinical trial applications and amendments to assess the quality of the products and determine that the use of the Investigational Medicinal product for the purposes of the clinical trial does not endanger the health of clinical trial participants or other persons, the clinical trial is not contrary to the best interests of a clinical trial subject, and the objectives of the clinical trial may be achieved.

Evaluation of applications shall be done on a first in first out (FIFO) basis unless the product meets the fast track criteria as set out in these guidelines.

Assessment of clinical trials applications shall involve evaluators from within or outside TFDA.

The Authority may during evaluation, request for clarification, certificates and/or samples through a query letter. Once a query has been raised and issued to the applicant, the evaluation process will stop until when TFDA receives a written response to the query. The response should be submitted within 6 months after being issued with a query letter. All queries issued in the same letter must be submitted together in one transaction.

Non-compliance to the requirements prescribed in these guidelines in content and format shall lead to rejection of the clinical trial.

The Authority reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Authority to adequately assess the safety, efficacy or quality of the investigational medicinal product.

2. Good Manufacturing Practices (GMP) Certification

Certification of GMP compliance of manufacturing sites of the Investigational Medicinal Products, adjuvants, comparators and placebos shall be provided.

3. Timelines

The Authority will implement the following timelines in processing applications for clinical trials applications.

3.1 Evaluation of new applications

Complete applications will be evaluated within 60 working days of receiving the application.

3.2 Fast-track evaluation

A new clinical trial application may be fast tracked and be assessed within 30 working days of its submission if the applicant has requested and paid twice the prescribed clinical trials application fees.

4. Validity of clinical trials authorization

The clinical trials certification will be valid up to the proposed duration of the study indicated in the application. However, the validity will not extend beyond five (5) years. For the trial proposed to be conducted for more than 5 years, the applicant shall be required to request an extension. TFDA will issue an updated certificate.

5. Refusal of authorization

The authority shall not authorize a clinical trial where it is satisfied that-

- (a) The information and documents as set out in the guidelines have not been provided;
- (b) The application contains false or misleading information;
- (c) The information provided is insufficient to enable the Authority assess the safety and risks of the investigational medicinal product or clinical trial;
- (d) Queries raised by the Authority in relation to the application made to it were not adequately responded to;
- (e) The applicant has not submitted an ethical clearance from any approved institute for medical research;
- (f) The use of the drug, medical device or herbal drug for the purposes of the clinical trial endangers the health of a clinical trial participant or any other person;
- (g) The objectives of the clinical trial will not be achieved;
- (h) It is not in the public interest to authorize the clinical trial; and
- (i) Any other reasonable grounds as may be determined by the Authority.

Following regulatory authorization of a new clinical trial or ammendment, information regarding refusals by other regulatory authorities or REBs should be submitted as a notification. This information will be added to the file.

6. Clinical Trial Registration

Applicants shall be required to register their clinical trials in the National Registry as provided for in section 7 of the clinical trials control regulations, 2013, Pan African Clinical Trial Registry (PACTR) or any other publicly accessible registries accepting international clinical trial information and recognized by the World Health Organization (WHO). The trial registration number should be availed to the Authority.

7. Qualifications of Investigators

- 7.1 The principal investigator engaged in clinical trials must have a university degree in medicine or pharmacy or pharmacology or toxicology or biochemistry and related fields and must be competent with practical experience within the relevant professional area and must be a resident of Tanzania. The principal investigator must have had previous experience as a co-investigator in at least two trials in the relevant professional area and shall be responsible for the conduct of the clinical trial at a clinical trial site.
- 7.2 In case of veterinary trials the Principal Investigator must have a degree in veterinary medicine.
- 7.3 In case of multi-centre studies where the PI is not a resident of Tanzania, the appointed national principal investigator must be the resident and should assume full responsibilities for all local clinical trial sites.
- 7.4 All investigators in a clinical trial as well as the trial monitor must have had formal training in Good Clinical Practices (GCP) within the last three years. Evidence of attending GCP course should also be submitted.
- 7.5 The investigator should ensure that he or she has sufficient time to conduct and complete the trial, and those other commitments or trials do not divert essential subjects, resources or facilities away from the trial in hand. The maximum number of clinical trials that a Principal Investigator shall be allowed to supervise at the same time shall be five (5).

7.6 Capacity of the clinical trial site

Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial and to deal with all reasonable foreseeable emergencies. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed.

7.7 Requirements concerning Data and Safety Monitoring Board (DSMB)/Data

Monitoring Committee (DMC)

7.7.1 The clinical trial shall be required to establish a data safety monitoring board or committee to enhance the safety of trial participants in situations in which safety concerns may be unusually high. DMCs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity. The DSMB/DMC shall be considered in the following situations;

- i. The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
- ii. There are a priori reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- iii. There is prior information suggesting the possibility of serious toxicity with the study treatment;
- iv. The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
- v. The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
- vi. The study is large, of long duration, and multi-center.

7.7.2 The sponsor shall appoint members of a DSMB/DMC by considering selection of individuals with relevant expertise, experience in clinical trials and in serving on other DMCs, and absence of serious conflicts of interest. The objectives and design of the trial and the scope of the responsibilities given to the DMC determine the types of expertise needed for a particular DMC. At least one member should be a local expert.

7.7.3 The applicants shall submit a DSMB/DMC charter with following details:

- (a) A broad statement of the aims and objectives of the DSMB/DMC
- (b) Terms of Reference
- (c) Composition of the DSMB/DMC
- (d) Qualifications of the DSMB/DMC members.
- (e) One member should be a local member.
- (f) Specific roles including responsibilities of statisticians
- (g) The role of statistical stopping rules
- (h) Relationship with the principal investigators and trial management team
- (i) Clarification of the decision-making powers
- (j) How DSMB/DMC meetings will be organized
- (k) Whether the DSMB/DMC will be blinded to treatment
- (l) What options a DSMB/DMC can recommend
- (m) In what form and to whom decisions will be conveyed

- (n) Who the DSMB/DMC will report to
- (o) The role of the DSMB/DMC in the publication of results
- (p) Disclosure of competing interests of DSMB/DMC members

7.7.4 The Sponsor may appoint an Independent Safety Monitor (ISM) for low risk smaller phase 1 or II trials that do not require a full DSMB or DMC. The ISM shall be a physician with an expertise in the relevant study area who will be reviewing all adverse events that may occur from the study.

7.8 Requirements concerning clinical trial involving special populations

7.8.1 Vulnerable Persons and Groups

These are groups and individuals that “may have an increased likelihood of being wronged or of incurring additional harm” during clinical trials. This includes for example persons who are illiterate, marginalized by virtue of their social status or behaviour, or living in an authoritarian environment, may have multiple factors that make them vulnerable. Vulnerable groups include Individuals in hierarchical relationships, Institutionalized persons, poor people and the unemployed, some ethnic and racial minorities, homeless persons, nomads, refugees or displaced persons, people living with disabilities, people with incurable or stigmatized conditions or diseases and people faced with physical frailty. Declaration of Helsinki and CIOMS guidelines should be considered when conducting clinical trials in vulnerable groups or individuals.

7.8.2 Women

Clinical trials should enroll subjects that are representative of the population(s) expected to use the therapeutic product. Specifically:

- 7.8.2.1 It is recommended that a representative number of women be included in clinical trials for therapeutic products that are intended to be used specifically by women or by heterogeneous populations that include women.
- 7.8.2.2 It is recommended that women, including those of child-bearing potential and postmenopausal women, be included at the earliest possible stages of clinical trial research so that potential sex-related differences are identified and taken into consideration when planning Phase III pivotal trials.
- 7.8.2.3 Although it may be reasonable to exclude certain potential subjects at early stages due to characteristics that may render evaluation of therapy more difficult (e.g. women and/or men on concomitant therapies), inclusion of such subjects is encouraged as early as possible in phases of clinical development so that therapeutic product interactions (e.g. drug-drug; natural health product-drug; natural health product- natural health product and product-disease) can be identified and assessed.

7.8.2.4 ICH M3 guidelines should be followed when women are to be included in clinical trials. Further details regarding designing and conducting clinical trials involving women are explained in **Annex 14**.

7.8.3 Paediatric population

Data on the appropriate use of medicinal products in the paediatric population should be generated unless the use of a specific medicinal product in paediatric patients is clearly inappropriate. The pediatric development programme should not delay completion of adult studies and availability of a medicinal product for adults.

The decision to proceed with a paediatric development programme for a medicinal product, and the nature of that programme, involve consideration of many factors.

In case of trials involving pediatric populations, ICH-E11 guidelines for Clinical investigations trials in pediatric population should be followed.

7.8.4 Geriatric population

Drugs should be studied in all age groups, including the elderly, for which they will have significant utility. Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug. The ICH guidelines for studies in support of special populations: geriatrics E7 should be followed for clinical trials that involve;

- New Investigational products that that are likely to have significant use in the elderly, either because the disease intended to be treated is characteristically a disease of aging (e.g., Alzheimer's disease) or because the population to be treated is known to include substantial numbers of geriatric patients (e.g., hypertension).
- New formulations and new combinations of established medicinal products when there is specific reason to expect that conditions common in the elderly (e.g., renal or hepatic impairment, impaired cardiac function, concomitant illnesses or concomitant medications) are likely to be encountered and are not already dealt with in current labelling.
- New formulation or new combination is likely to alter the geriatric patient's response (with regard to safety/ tolerability or efficacy) compared with that of the non-geriatric patient in a way different from previous formulations.
- New uses that have significant potential applicability to the elderly.

8. Conduct of clinical trials (Post registration requirements)

Clinical trials should be conducted according to the Tanzania Food Drugs and Cosmetics Act, Cap 219, clinical trials control regulations 2013, ICH-Good Clinical Practice guidelines. The study design, statistical considerations, choice of control groups, reporting of data and conduct of the trial should be as detailed in ICH guidelines E3-E16. Analysis of samples at the clinical laboratory shall follow WHO-Good Clinical Laboratory Practice guidelines.

8.1 Advertisement of clinical trials

Clinical trials may be advertised in order to promote the trial to the public and recruit participants.

Advertisements may be done using IEC materials such as brochures, posters, banners or through televisions, radio programs, newspapers and any other media. Before such advertisements are made public, approval must be obtained from TFDA and ethics committees and must follow existing local rules and regulations.

8.2 Importation and exportation of Investigational Products

Applicants are required to obtain an import permit for importation of Investigational products after authorization of the trial.

In case of exportation of the Investigational Products the applicant should obtain export permit from TFDA.

Further guidance can be accessed from the Tanzania Food, Drugs, and Cosmetics (clinical trial control) regulations, 2013 and TFDA guidelines for importation and exportation of pharmaceutical products and raw materials.

8.3 Reporting of Serious Adverse Events (SAEs)/Suspected Unexpected Serious Adverse Reactions (SUSARs)

8.3.1 All serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening should be reported to TFDA within 24 hours by telephone, facsimile transmission, or e-mail followed by a complete report within 7 additional calendar days of their occurrence. The report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

8.3.2 All other SAEs and SUSARs that are not fatal or life-threatening must be filed as soon as possible but no later than 14 calendar days after first knowledge by the sponsor. Details regarding safety reporting are found in the guidelines for reporting safety data in clinical trials.

8.3.3 The applicant should develop a trial specific form or use the reporting form attached as **Annex 15** followed by detailed written reports. When completing the CIOMS form, trial specific details such as the participants ID numbers and/or protocol number should be included.

8.3.4 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should also be reported.

8.3.5 For reported deaths, additional information (e.g., autopsy reports and terminal medical reports) should be submitted.

8.3.6 The relationship between SAE(s)/SUSARs and the IMP must be established, evaluated, clarified and submitted to TFDA for further assessment.

8.3.7 The expedited reporting is applicable for clinical trials of investigational products, comparator products and for products used in bioavailability (BA) and bioequivalence (BE) studies.

8.4 Submission of Progress Reports

The sponsor and/or PI must submit progress reports to TFDA on a six monthly basis from the date of initiation of the clinical trial. The content should be as prescribed in the ICH-E3 guidelines structure and content of clinical study reports.

8.5 Termination of Clinical Trial

8.5.1 Premature termination

If a clinical trial is terminated by the principal investigator or sponsor in its entirety, the principal investigator or sponsor must inform TFDA not later than 15 days after the date of the termination; and must:

8.5.1.1 Provide TFDA with the reason(s) for the termination and its impact on the proposed or ongoing clinical trials in respect of the investigational medicinal product including issues related to accountability and disposal of investigational products as well as maintenance of records.

8.5.1.2 As soon as possible, inform all co-investigators of the termination and of the reasons for the termination and advise them in writing of potential risks to the health of clinical study participants or other persons including ensuring that patients continue to receive medical care.

8.5.1.3 Submit confirmation that the dispensing or importation of the drug to the discontinued sites has been stopped.

8.5.1.4 Submit Confirmation that reasonable measures to ensure the return of all unused quantities of the drug will be taken.

8.5.2 Suspension, termination or withdrawal of a clinical trial by the Authority

The Authority may suspend, terminate or withdraw authorization of a clinical trial if satisfied that:

- a) The conditions of authorization of a trial have been violated.

- b) There is information raising doubts about the safety or scientific validity of the trial, or the conduct of the trial at a particular trial site

Section 17 of the clinical trials control regulations, 2013, can be referred to for further guidance.

8.5.3 End of trial (Study close-out)

8.5.3.1 After the trial has been conducted and closed, the sponsor and/or principal investigator shall submit a closing report within 60 days. This should be followed by a final study report within six months after trial closure unless otherwise justified. The structure and content of the final study report should be as provided in the ICH guidelines for Structure and Content of Clinical Study Reports.

8.5.3.2 Any unexpected safety issue that changes the risks-benefit analysis and is likely to have an impact on trial participants should be reported together with proposed actions to be taken.

8.6 Disposal of Investigational products

8.6.1 The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorisation by the Sponsor.

8.6.2 The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period.

8.6.3 Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted.

8.6.4 Request to dispose investigational products shall be made to TFDA as prescribed in the Regulations for Recall, Handling & Disposal of Unfit Medicines & Cosmetics of 2015.

8.6.5 The destruction process shall be authenticated by a TFDA Inspector and destruction certificate will be issued. The destruction shall be done in accordance to applicable environmental regulations provided by the local Government Authorities, Environment Management Council (NEMC) or any other institution responsible for environment management on the proposed mode of destruction and issuance of disposal permit.

8.6.6 Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.

8.6.7 When destruction of investigational medicinal products takes place a dated certificate of destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

8.7 Publication of clinical trial results

The sponsor/Principal Investigator must publish the results of a clinical trial after completion. The publication may be done in peer reviewed journals, books or any other materials to allow for a wider community including study participants, to access the data/evidence generated from the trial.

Sponsors and principal Investigators must publish trial outcomes as they were originally registered in the registry.

A copy of the publication must be submitted to TFDA for review.

8.8 Appeals

As provided in Section 64 (3) and (4), of Tanzania Food, Drugs and Cosmetics Act, 2003, any person who is aggrieved by a decision of the Authority of not granting authorization for the conduct of clinical trial may make his representation within sixty days to the Authority. If no such representation is submitted by the applicant within the said period or if after consideration of any comments so submitted the Authority is still not satisfied it shall reject the application.

The applicant shall do so by giving grounds for review for each reason given for the rejection of a clinical trial. The grounds for the request shall be based on the information that was submitted in the application. Any additional or new information that was not earlier submitted will only be considered upon submission of a new application. The Authority may review, reject or vary its own decision.

MODULE 2: SUMMARIES OF NON-CLINICAL, CLINICAL DATA AND QUALITY DATA

This Module is applicable to phase I, II and III clinical trials that involve new Investigational Products. Clinical trials using well established Investigational products that have been registered and marketed in Tanzania are exempted to submit details on this part. Updated Investigator's brochure and prescribing information will suffice. The summaries shall be submitted in both hard and electronic formats. Note that the electronic copies must be submitted on CD-ROM, in either **MS Word or Word Perfect** format (PDF format of the QOS is not acceptable).

The organization of these summaries is described in ICH Guidelines for M4Q, M4S, and M4E.

Module 2 should contain 7 sections in the following order:

- (i) CTD Table of Contents
- (ii) CTD Introduction
- (iii) Quality Overall Summary
- (iv) Nonclinical Overview
- (v) Clinical Overview
- (vi) Nonclinical Written and Tabulated Summaries
- (vii) Clinical Summary

2.1 CTD Table of contents

A listing of the contents of module 3 and 4

2.2 CTD Introduction

This sub-section is not applicable to Clinical Trials Applications (CTAs). This section is reserved for use during the preparation of application at later stages of development of the New Investigational Product (e.g., New Applications) and maintained to ensure consistent numbering of subsequent sections.

2.3 Investigational Product Quality Overall Summary (IP-QOS)

This document must be submitted in both hard copy and electronic format. Note that electronic copies must be submitted on CD-ROM, in either MS Word or Word Perfect format (PDF format of the QOS is not acceptable). This document in electronic files should be placed at the beginning of **Module 3**.

The applicant shall fill in the summary of the quality of the Investigational product in the Quality Overall Summary – Chemical Entities template (**Annex 11**) as well as additional Quality information as outlined in the template, should be completed as stipulated in the guidelines. The template shall be used for clinical trials involving human and veterinary medicinal products, biologicals, medical devices and diagnostics.

For placebo-controlled studies, a qualitative list of the ingredients in the placebo should be submitted.

2.4 Non-Clinical overview

Nonclinical overall Summary overview as prescribed in **Annex 10** should be submitted. This document must be submitted in both hard copy and electronic format. This document in electronic files should be placed at the beginning of **Module 4**.

The non-clinical overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed 30 pages.

The non-clinical overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics

- Toxicology
- Integrated overview and conclusions
- List of literature references

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise. The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labelling).

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

2.5. Clinical overview

This section is generally applicable to clinical trials that are in late phase of development. Available data and details will mainly be on safety studies conducted for the same Investigational product in other populations. First in human (FIH) clinical trials with no data on the effect of the Investigational product in humans are exempted to submit details on this part.

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information.

The clinical Overview should be presented in the following sequence

- Product Development Rationale
- Overview of Biopharmaceutics (If applicable)
- Overview of Clinical Pharmacology
- Overview of Efficacy (If applicable)
- Overview of Safety
- Benefits and Risks Conclusions
- Literature References

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the format and the content of this part.

2.6 Nonclinical Written and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

This section is applicable to phase I, II and III clinical trials that involve new Investigational Products. Clinical trials using well established Investigational products marketed in Tanzania are exempted to submit details on this part. Clinical trials that were conducted in Tanzania in previous phases are also exempted on this part. Updated Investigator's brochure will suffice.

2.7 Clinical Summary

This is a summary of the Investigational product experience in humans. The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5. This section is not applicable for first in human (FIH) clinical trials whose Investigational products have not been tested in humans.

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy for guidance on the content of this section.

MODULE 3: QUALITY OF THE INVESTIGATIONAL PRODUCTS

Introduction to the module

This module shall describe details regarding the chemistry, manufacturing and control of the Investigational Product. Data to demonstrate quality of the investigational product including relevant batch analyses results should be attached. The data should be presented as provided in the sections below.

If a comparator medicinal product is used, the proprietary name of the medicinal product, non-proprietary name or common name of the Active Pharmaceutical Ingredient, company name, country from which the clinical supplies were obtained (as well as the market status in that country), dosage form(s) and strength(s) should be listed. Preferably, the comparator product should be obtained from the market with stringent authorities. For comparator FPPs not obtained from the market with stringent authorities, where the results of the clinical trial are intended to be used in support of a new investigational application for market authorization, the applicant should be aware that additional information may be requested at the registration stage (e.g., comparative *in vivo* or *in vitro* studies).

If the comparator medicinal product is modified in any way in order to blind the trial (e.g., grinding of tablets, encapsulation of tablets), results of an *in vitro* study (e.g., comparative dissolution profiles for solid dosage forms) comparing the unchanged and the modified product should be submitted. For sterile products that are repackaged for blinding purposes, it should be demonstrated that sterility is maintained.

3.1 Table of contents of Module 3

A Table of Contents should be provided that lists all of the reports and gives the location of each study report in the Common Technical Document.

3.2 Body of data

3.2.S ACTIVE PHARMACEUTICAL INGREDIENT

Some of the information included under the “S Active Pharmaceutical Ingredient” section may not be available to the applicant of the Clinical Trial Application. If such is the case, the manufacturer of the Active Pharmaceutical Ingredient can file a Drug Master File directly to TFDA. The API manufacturer would then be considered the DMF Holder. This DMF will be held in strict confidence and will be used in support of the application only upon receipt of written authorization from the supplier/DMF Holder of the Active Pharmaceutical Ingredient (i.e., via a Letter of Access).

The sponsor should be able to provide most of the information on the Active

Pharmaceutical Ingredient, except possibly the proprietary information found in the closed part of the Drug Master File (e.g. sections S.2.2, S.2.4 and S.2.6 (see below)). It is the responsibility of the sponsor to obtain all other information from the supplier of the Active Pharmaceutical Ingredient and include this in the application. The information from the Open part of the DMF should be included in the Quality Overall Summary.

Regardless of the information provided by the supplier of the Active Pharmaceutical Ingredient, the manufacturer of the dosage form is responsible for ensuring that acceptable specifications and properly validated analytical procedures for the Active Pharmaceutical Ingredient are developed by the manufacturer's facilities and for providing the results of batch analyses performed at the manufacturer's facilities.

For further information on the requirements for DMFs, see TFDA's guidelines on submission of documentation for marketing authorization of human medicinal products.

3.2. S.1 General Information

3.2. S.1.1 Nomenclature

Information on the nomenclature of the Active Pharmaceutical Ingredient should be provided. For example:

- (a) Recommended International Non-proprietary Name (INN);
- (b) Compendial name, if relevant;
- (c) Chemical name(s);
- (d) Company or laboratory code;
- (e) Other non-proprietary name(s) (e.g., national name, United States Adopted Name (USAN), British Approved Name (BAN)); and
- (f) Chemical Abstracts Service (CAS) registry number.

3.2. S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section S 1.1. For Active Pharmaceutical Ingredients existing as salts, the molecular mass of the free base should also be provided.

3.2. S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the Active Pharmaceutical Ingredient. Give the physical and chemical properties of the Active Pharmaceutical Ingredient such as the physical description, solubilities (e.g. aqueous/nonaqueous solubility profile, pH-dependent solubility profile), polymorphism, particle size distribution, pH and pKa values. Other characteristics could include UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc.. This list is by no means exhaustive, but provides an indication as to the type of information that could be included.

Physical Description:

The description should include appearance, colour, and physical state.

Solubilities:

The solubility should be provided in a number of common solvents (e.g. water, alcohols, etc.) as well as the solubilities over the physiological pH range (pH 1 to 8) in at least 3 buffered media. Phrases such as “sparingly soluble” or “freely soluble” should be quantitatively defined or a literature reference can be provided (e.g., “as per USP”). If this information is not readily available, it should be generated in-house.

3.2.S.2 Manufacture

If a Drug Master File from the manufacturer should be submitted to TFDA.

3.2.S.2.1 Description of Manufacturing Process and Process controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. Sponsors are expected to provide a flow diagram, accompanied by a narrative description (Phase II and Phase III only), summarizing the synthetic process of the Active Pharmaceutical Ingredient. Active Pharmaceutical Ingredients which are milled/micronized should be indicated as such. A summary of the expectations at each phase is provided below.

For Active Pharmaceutical Ingredients which are manufactured as sterile substances, a complete description of the method of sterilization should be provided. Controls in place to maintain sterility during transportation and storage should also be summarized.

Phase I Clinical Trial Applications

A flow diagram of the synthetic process(es) should be provided that includes chemical structures and configurations of starting materials, intermediates and the Active Pharmaceutical Ingredient. In addition, all reagents (including chemical formulae), solvents and catalysts should be specified in the flow diagram.

Phase II Clinical Trial Applications

In addition to the flow chart, a stepwise narrative description of the Active Pharmaceutical Ingredient manufacturing process should be provided. The use of all reagents, solvents, catalysts and auxiliary materials should be summarized in the manufacturing process description. Relevant process controls should be indicated where critical steps in the synthesis have been identified.

The description of the manufacturing process at Phase II should be sufficiently detailed to address quality and safety concerns without being overly restrictive to process optimization.

For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description, addressing critical process controls and safety concerns, should be provided at Phase II.

Phase III Clinical Trial Applications

A detailed flow chart and narrative process description should be provided. The detailed description provided at Phase III should include critical steps identified in the process and relevant process controls (e.g. reaction times, pH, temperatures, etc.), including all purification steps.

In addition to the above information, the data provided for a Active Pharmaceutical Ingredient produced by fermentation should include:

- Source and type of micro-organism used; composition of media;
- precursors;
- additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration, etc.); and
- Name and composition of preservatives.

For Active Pharmaceutical Ingredients of plant origin, include a description of the botanical species and the part of plant used, the geographical origin and, where relevant, the time of year harvested. The nature of chemical fertilizers, pesticides, fungicides, etc. should be recorded, if these have been employed during cultivation. It may be necessary to include limits for residues resulting from such treatments in the Active Pharmaceutical Ingredient specification. Absence of toxic metals and radioactivity may also have to be confirmed.

3.2.S 2.3 Control of Materials

Active Pharmaceutical Ingredients or materials used in the synthesis which are of animal origin should be free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE) and an attestation confirming this should be provided either as an Attachment or directly within the QOS, if applicable.

Phase II and Phase III Clinical Trial Applications

Sponsors should provide details of the starting materials for the synthesis of the Active Pharmaceutical Ingredient. The level of detail expected concerning controls on starting materials for synthesis increases as synthetic steps get closer to the final Active Pharmaceutical Ingredient. Generally, the “starting material for synthesis” is:

- A synthetic precursor one or more synthetic steps prior to the final intermediate
- A well-characterized, isolated and purified substance with the structure fully elucidated
- controlled by well-defined specifications which include one or more specific identity tests, and tests and limits for potency, specified and unspecified impurities and total impurities

Acids, bases, salts and esters (or similar derivatives) of the Active Pharmaceutical Ingredient, and the racemate of a single enantiomeric Active Pharmaceutical Ingredient, are not considered final intermediates.

For starting materials which are commercially purchased, the source and a copy of the provisional specifications is typically considered acceptable. For “starting materials for synthesis” which are manufactured in-house, a copy of the flow chart and provisional specifications for the starting material should be provided.

3.2.S 2.4 Controls of Critical Steps and Intermediates

[Information in this section not required for Phase I or Phase II Clinical Trial Applications]

Phase III Clinical Trial Applications

Provide a summary of critical steps identified in the synthesis and the tests and tentative acceptance criteria for their control. In-process controls or provisional specifications for isolated intermediates may be summarized here.

3.2. S.3 Characterizations

3.2. S.3.1 Elucidation of Structure and other Characteristics

For all Clinical Trial Applications

Confirmation of structure based on synthetic route and spectral analyses should be provided. Copies of the actual spectra are not required for Clinical Trial Applications, but should be available upon request.

The Quality Overall Summary should include a list of the studies performed and a conclusion from the studies (e.g., if the results support the proposed structure, spectral interpretations).

The studies carried out to elucidate and/or confirm the chemical structure of New Chemical Entities normally includes elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), X-ray diffraction (XRD) and Mass Spectra (MS) studies.

When a Active Pharmaceutical Ingredient is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the clinical studies.

A discussion should be included of the possible isomers that can result from the manufacturing process, the steps where they were introduced, and a summary of the results of the studies carried out to investigate the physical, chemical, and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, the Active Pharmaceutical Ingredient specification should include a test to ensure isomeric identity and purity.

If the Active Pharmaceutical Ingredient is a single isomer or a fixed ratio of isomers, provide the rationale for this decision. For existing drugs (e.g., generics), include a summary of any comparative studies performed.

For Active Pharmaceutical Ingredients that contain an asymmetric centre, where there has not been any information provided regarding the manufacture of the starting material through which it has been introduced, a summary of results of a study should be submitted demonstrating that the material exists as a racemic mixture (e.g., specific optical rotation).

It is recognized that some drugs (e.g., certain antibiotics, enzymes, and peptides) present difficulties with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the Active Pharmaceutical Ingredient. If a Active Pharmaceutical Ingredient consists of more than one component, the physicochemical characterization of the components and their ratio should be submitted.

If, based on the structure of the Active Pharmaceutical Ingredient, there is not a potential for isomerism, it may be sufficient to include a statement to this effect.

Polymorphism:

If the potential for polymorphism is a concern, sponsors are expected to provide a summary of investigations of the Active Pharmaceutical Ingredient, recrystallized from several solvents, to determine if the Active Pharmaceutical Ingredient exists in more than one crystalline form. If the results of studies conducted on the physical and chemical properties of the various crystalline forms indicate that there is a preferred polymorph, criteria should be incorporated into the Active Pharmaceutical Ingredient specification to ensure that the desired polymorph is the one obtained.

Particle size distribution:

For poorly soluble Active Pharmaceutical Ingredients, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behaviour of the FPP. Particle size can also be important in dosage form performance (such as inhalation products), achieving uniformity of content in low-dose tablets, desired smoothness in ophthalmic preparations, and stability of suspensions.

If particle size is deemed relevant to the performance of the FPP, results from several development batches should be provided, and appropriate controls on particle size distribution included in the specifications.

3.2.S.3.2 Impurities

The tables in the Quality Overall Summary template can be used to summarize the names, structures, and origin of the impurities. The origin refers to how the impurity was introduced (e.g., “Synthetic intermediate from Step 4 of the synthesis”, “Potential by-product due to rearrangement from Step 6 of the synthesis”, etc.). It should also be

indicated if the impurity is a metabolite of the Active Pharmaceutical Ingredient.

Results of the impurity investigation should be provided. For quantitative tests, it should be ensured that *actual numerical results* are provided rather than vague statements such as “within limits” or “conforms”. In the cases where a large number of batches have been tested, it is acceptable to summarize the total number of batches tested with a range of analytical results.

For Phase I Clinical Trial Applications

The structure (or other identifier, if not structurally characterized) as well as the origin should be included in the Active Pharmaceutical Ingredient impurity table.

For Phase II and III Clinical Trial Applications

The impurity name (or identifier), structure (if characterized) and origin should be provided in the table for all specified impurities.

Impurity levels for previously manufactured nonclinical and clinical batches may also be summarized within this section.

3.2. S.4 Control of the Active Pharmaceutical Ingredient

3.2.S.4.1 Specification

[Information in this section not required for Phase I Clinical Trial Applications]

A summary of the specification for the Active Pharmaceutical Ingredient should be provided. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the Active Pharmaceutical Ingredient.

The specification can be summarized according to the table in the Quality Overall Summary template including the Tests, Method Types (including Source), and Acceptance Criteria. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction, etc.) and Source refers to the origin of the analytical procedure (e.g., USP, Ph.Eur., BP, House, etc.).

Phase II Clinical Trial Applications

Specifications are considered interim as they are based on a limited number of development batches. A higher degree of flexibility will be allowed in specifications with sufficient scientific justification (refer to Section S.4.5 - *Justification of Specification*).

Phase III Clinical Trial Applications

Specifications are expected to be re-assessed prior to the Phase III application and reflect those intended for the marketing application, based on additional manufacturing

experience and stability information.

3.2.S.4.2 Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications]

For Phase II and III Clinical Trial Applications the applicant is required to submit information

A brief description of the analytical methods used for the Active Pharmaceutical Ingredient should be provided for all tests included in the Active Pharmaceutical Ingredient specifications (e.g. method type, column size, etc.). Detailed descriptions of the step-by-step analytical procedures should not be submitted for Clinical Trial Applications, but should be available upon request.

3.2.S.4.3 Validations of Analytical Procedures

[Information in this section not required for Phase I Clinical Trial Applications]

Phase II and III Clinical Trial Applications

The suitability of the analytical methods and a tabulated summary of the validation carried out should be provided (e.g. results or values for specificity, linearity, range, accuracy, precision, intermediate precision, limit of detection and limit of quantitation, where applicable). Complete validation reports should not be provided for Clinical Trial Applications.

3.2. S.4.4 Batch Analyses

Description of batches and results of batch analyses should be provided.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total impurity tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as “within limits” or “conforms”. When reporting the analytical results it is important that the method used for each test be identified (including Type and Source).

Batch analysis results for the Active Pharmaceutical Ingredient may be provided in either the Quality Overall Summary or by providing a copy of the Certificate of Analysis. The batch number, batch sizes, and dates and sites of production should be stated for all batches.

For Phase I Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided.

For Phase II Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of Active Pharmaceutical Ingredient may be provided as supporting data, with a commitment that the batch analysis for the specific lot to be used in that protocol will be submitted prior to dosing.

For Phase III Clinical Trial Applications

Analytical results from the batch (es) to be used in the proposed clinical trial, or batches representative thereof, should be provided.

Note: For the purpose of this guidance document, a “representative batch” is defined as a batch of Active Pharmaceutical Ingredient or FPP that is manufactured using the same formulation (for the FPP), method of manufacture and equipment, specifications and the same container closure system as the proposed clinical batch, with a similar batch size. All subsequent references in this guidance document to “representative batch” should be interpreted per this definition.

3.2.S.4.5 Justification of Specification

[Information in this section is not required for Phase I Clinical Trial Applications]

The sponsor should ensure the specification includes all the tests and acceptance criteria appropriate for the Active Pharmaceutical Ingredient, and that reasonable limits for impurities and residual solvents have been established. Acceptance criteria should be based on manufacturing experience, stability data and safety considerations.

3.2.S 6 Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized.

The tables in the Quality Overall Summary template can be used to summarize the

information on the batches used in the stability studies. Full long term stability data is not required at the time of filing, provided some preliminary stability data is available on representative batches together with a commitment that the stability of the clinical trial samples or representative batches will be monitored according to the stability protocol until the re-test period has been established.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as “within limits” or “conforms”.

Available long-term and accelerated stability data for the Active Pharmaceutical Ingredient should be provided at each stage of development to support its storage (conditions and re-test period) and use in the manufacture of the FPP.

The proposed storage conditions and re-test period (or shelf life, as appropriate) for the Active Pharmaceutical Ingredient should be reported.

Stress testing:

Stress testing of the Active Pharmaceutical Ingredient can help identify the likely degradation products, which can in turn help establish the degradation pathways, the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual Active Pharmaceutical Ingredient and the type of FPP being developed.

3.2.S.7.2 Stability Protocol and Stability Commitment

If full long-term stability data supporting the re-test period is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or batches considered representative thereof, will be monitored according to the stability protocol. A summary of the stability protocol (in tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

3.2.S.7.3 Stability Data

Results of the stability studies (e.g., long-term studies, accelerated studies, stress conditions, etc.) should be presented in an appropriate format.

The actual stability results (i.e., raw data) used to support the clinical trial should be provided as a separate Attachment. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as “within limits” or “conforms”.

For Phase II and III Clinical Trial Applications

In cases where analytical procedures are only used in stability studies (i.e. stability-indicating assay method) and were not summarized in 2.3.S.4, a brief description of the analytical procedure as well as a tabulated summary of validation information should be provided per the instructions in Sections S.4.2 and S.4.3.

3.2. P FINISHED PHARMACEUTICAL PRODUCT (FPP)

3.2. P.1 Description and Composition of the FPP

A description of the FPP and its composition should be provided. The information provided should include:

- (a) Description of the dosage form;

The description of the dosage form should include the physical description, available strengths, release mechanism, as well as any other distinguishable characteristics (e.g., “The proposed FPP is available as oval, round, immediate-release, aqueous film-coated tablet in three strengths (5 mg, 10 mg, and 20 mg).”).

- (b) Composition, i.e., list of all components of the dosage form, their amount on a per unit basis (including overages, if any) and a reference to their quality standards (e.g., compendial monographs or manufacturer’s specifications);

The composition should express the quantity of each component on a per unit basis (e.g., mg per tablet, mg per mL, mg per vial, etc.) and percentage basis including a statement of the total weight or measure of the dosage unit. This should include all components used in the manufacturing process, regardless if they appear in the final FPP. If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., “1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride”). All overages should be clearly indicated (e.g., “Contains 2% overage of the active pharmaceutical ingredient to compensate for manufacturing losses.”).

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., “Microcrystalline Cellulose NF (PH 102)”). The function of each component (e.g., diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative, etc.) should also be stated.

The qualitative composition should be provided for all proprietary components or blends (e.g., capsule shells, colouring blends, imprinting inks, etc.). (c)Description of reconstitution diluent(s), if applicable;

List all reconstitution solvents/diluents to be used in the proposed clinical study.

If the reconstitution solvent/diluent is manufactured in-house, a separate FPP section (e.g. Sections P.1-P.8) should be completed for the chemistry and manufacturing information for the reconstitution solvent/diluent.

- (d) Type of container closure system used for accompanying reconstitution diluent, if applicable:

A brief description of the container closure system(s) used for the accompanying reconstitution diluent should be provided, if applicable (for commercially-purchased diluents, provide information only if the primary packaging has been changed);

- (e) Qualitative list of the components of the placebo samples used in the clinical trials, if different from the components listed in P.1 (b)

3.2.P.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that may influence batch reproducibility, product performance and FPP quality.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all potential diluents over the range of dilution. These studies, including tests for purity, potency, sub-visible particulate matter, pH, etc., should preferably be conducted on aged samples. Where the type of container is not specified, compatibility should be demonstrated in suitable containers. If one or more containers are identified, compatibility of admixtures should be demonstrated only in the specified containers.

For Phase I Clinical Trial Applications

This section should only be completed for sterile products. Summaries of compatibility studies with diluents and containers should be included in this section.

For Phase II and III Clinical Trial Applications

To the extent possible, information pertaining to the following aspects of pharmaceutical development should be submitted:

- (a) The compatibility of the Active Pharmaceutical Ingredient with excipients listed in P.1 should be discussed.
For combination products, a summary of investigations of the compatibility of the Active Pharmaceutical Ingredients with each other should be provided.
- (b) A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between earlier clinical formulations and the formulation (i.e., composition) described in P.1 should be discussed, if applicable.

- (c) The selection of the manufacturing process described in P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.
- (d) The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of Active Pharmaceutical Ingredient in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for labelling.

3.2.P 3 Manufacture

3.2.P 3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the FPP for the batches used in the clinical studies. If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate), this should be indicated. The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative office(s).

An attestation should be provided in the Quality Overall Summary or as an Attachment confirming that the FPP to be used in the Local study was manufactured according to Good Manufacturing Practices.

3.2.P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The batch formula should express the quantity of each component on a per batch basis including a statement of the total weight or measure of the batch. This should include all components used in the manufacturing process, regardless if they appear in the final FPP. If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., “1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride”). All overages should be clearly indicated (e.g., “Contains 5 kg overage of the active pharmaceutical ingredient to compensate for manufacturing losses.”). Batch formula tables should be representative of the lots intended for use in the proposed clinical trial.

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., “Microcrystalline Cellulose NF (PH 102)”).

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. Sponsors are expected to provide a flow diagram, accompanied by a narrative description (Phase II and Phase III only), summarizing the manufacturing process of the FPP. The level of detail expected at each phase of Clinical Trial Application is outlined below.

For sterile products, a complete narrative description of the manufacturing process should also be submitted *regardless of the clinical trial phase*. Furthermore, details of sterilization and lyophilization (if applicable) procedures should be provided for all Clinical Trial Applications.

For Phase I Clinical Trial Applications

A flow chart of the manufacturing process should be provided clearly indicating the order of addition of components and a summary of unit operations (e.g. blending, screening, etc.).

For Phase II Clinical Trial Applications

A flow chart and narrative description of the manufacturing process should be provided. Detailed summaries of process controls (e.g. blending times, end-points for drying operations, etc.) are not required, with the exception of the sieve/screen size for immediate-release solid oral dosage forms.

The description of the manufacturing process at Phase II should be sufficient to fully describe the process without being restrictive to continuing process development and optimisation.

For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description which addresses critical process controls, and safety and bioavailability concerns, should be provided at Phase II.

For Phase III Clinical Trial Applications

A flow chart and a detailed narrative description of the process should be provided. A summary of in-process controls and process parameters (e.g. mixing/blending time, temperature, pH for preparations of solutions) should be provided. The critical steps, process controls, intermediate tests and final product controls should be identified and described in additional detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

3.2.P.3.4 Controls of Critical Steps and Intermediates

[Information in this section not required for Phase I or Phase II Clinical Trial Applications]

Phase III Clinical Trial Applications

To the extent possible at the time of submission, sponsors should provide information on the following:

Critical Steps: Tests and tentative acceptance criteria for controls on the critical steps in the FPP manufacturing process, where identified.

Intermediates: Information on the quality and provisional controls on intermediates isolated during the process, where relevant.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

This includes the specifications for all excipients, including those that do not appear in the final FPP (e.g., solvents). If the standard claimed for an excipient is a Schedule B compendial monograph, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the compendial monograph.

Confirmation should be provided that none of the excipients which appear in the FPP are prohibited for use in drugs.

3.2.P.4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data).

This information should include biological source, country of origin, manufacturer, and a brief description of the suitability of use based on the proposed controls.

For gelatin for use in pharmaceuticals, supporting data should be provided which confirms that the gelatin is free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE). If the supplier of the gelatin has a DMF registered with TFDA, a Letter of Access should be provided.

Supporting information for excipients of human or animal origin should be provided as a separate Attachment.

3.2.P.4.6 Novel Excipients

For excipient(s) used for the first time in a FPP or by a new route of administration, full details of manufacture, characterisation and controls should be provided, with cross-references to supporting safety data (nonclinical and/or clinical) using the relevant sections of the Quality Overall Summary according to the Active Pharmaceutical Ingredient and/or FPP format.

3.2.P. 5 Control of FPP

3.2.P.5.1 Specification(s)

[Information in this section is not required for Phase I Clinical Trial Applications]

A summary of the specification(s) for the FPP should be provided. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the dosage form.

The specification(s) can be summarized according to TFDA's Quality Overall Summary template including the Tests, Method Types, Sources, and Acceptance Criteria. The Method

Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, etc.) and the Source refers to the origin of the analytical procedure (e.g., USP, BP, House, etc.).

For phase II Clinical Trial Applications

Specifications are considered interim as they are based on a limited number of development batches. A higher degree of flexibility will be allowed in specifications with sufficient scientific justification (Please refer to Section P.5.6 - *Justification of Specification*).

For phase III Clinical Trial Applications

Specifications are expected to be re-assessed prior to the Phase III submission and reflect those intended for the marketing application, based on additional manufacturing experience and stability information.

3.2.P.5.2 Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications]

For Phase II and III Clinical Trial Applications

A brief description of the analytical methods used for the FPP should be provided for all tests included in the FPP specifications (e.g. reverse-phase HPLC, GC, etc.). Detailed descriptions of the step-by-step analytical procedures should not be submitted for Clinical Trial Applications, although this information should be available upon request.

Unless modified, it is not necessary to provide a copy of Schedule B compendial procedures.

3.2.P.5.3 Validation of Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications]

For Phase II and III Clinical Trial Applications

Suitability of the analytical methods and a tabulated summary of the validation information should be provided (i.e. results or values for specificity, linearity, range, accuracy, precision, robustness, limit of detection and limit of quantitation, where applicable). Complete validation reports should not be submitted for Clinical Trial Applications, although this information should be available upon request.

For substances which comply with a Schedule B monograph, reference to the monograph will be considered sufficient for all Clinical Trial Applications.

3.2.P.5.4 Batch Analyses

A description of batches and results of batch analyses should be provided.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as “within limits” or “conforms”. When reporting the analytical results it is important that the method used be identified (including Type and Source).

Batch analysis results for the FPP may be provided in either the Quality Overall Summary or by providing a copy of the Certificate of Analysis. In all cases, the batch numbers, batch sizes, dates and sites of production, and input Active Pharmaceutical Ingredient batches should be provided.

For Phase I Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided.

For Phase II Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of FPP may be provided as supporting data with a commitment that the batch analysis for the specific lot(s) to be used in that protocol will be submitted prior to dosing.

For Phase III Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial, or batch(es) considered representative thereof, should be provided.

3.2.P.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously summarized in Section S.3.2 - *Impurities*.

This information includes degradation products (e.g., from interaction of the Active Pharmaceutical Ingredient with excipients or the container closure system), solvents in the manufacturing process for the FPP, etc.. The tables in the Quality Overall Summary template in section S.3.2 can be used to summarize this information.

This section may also be used to report any new impurities found in the FPP during stress testing (e.g. photostability testing).

3.2.P.6 Justification of Specification(s)

[Information in this section is not required for Phase I Clinical Trial Applications.]

The sponsor should ensure the specification(s) includes all the tests and acceptance criteria appropriate for the FPP, and that reasonable limits for degradation products have been established. Acceptance criteria should be based on manufacturing experience, stability data, and safety considerations. For impurities/degradation products which are unique to the FPP, acceptance criteria should be supported by appropriate toxicology and safety studies.

3.2.P.7 Container Closure System

A description of the container closure system(s) to be used in the clinical trial should be provided, including the materials of construction for each packaging component. This includes packaging components that:

- a) are product contact surfaces
- b) are used as a protective barrier to help ensure stability or sterility
- c) are used for drug delivery
- d) are necessary to ensure FPP quality during transportation

For sterile products, details of the washing, sterilization and depyrogenation should be submitted in this section.

For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenteral, ophthalmic products, oral solutions), additional detail may be required.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized.

The tables in the Quality Overall Summary template can be used to summarize the information on the batches used in the stability studies. Full long term stability data is not required at the time of filing, provided some preliminary stability data is available on representative batches together with a commitment that the stability of the clinical trial samples (or representative batches) will be monitored according to the stability protocol until the shelf-life of the FPP has been established with confidence.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as “within limits” or “conforms”.

For sterile products, sterility should be reported at the beginning and end of shelf life. During development it is expected that sterility will be monitored on a routine basis (e.g. annual basis) until the shelf life has been determined with confidence. For parenteral products, sub-visible particulate matter should be reported at every test interval until a shelf life has been established. Bacterial endotoxins need only be reported at the initial test interval.

For FPPs which are reconstituted or diluted prior to administration, stability and compatibility studies covering the entire in-use period should be provided. Furthermore, for products which are diluted or reconstituted into a secondary container closure system (i.e., infusion kit), compatibility data should be submitted to support in-use conditions in that specific container closure.

Available long-term and accelerated stability data should be provided for the FPP at each stage of development to support its storage conditions and shelf-life.

Stress testing:

For certain FPPs, stress testing of dosage forms may be appropriate to assess the potential for changes in physical and/or chemical properties of the FPP. The nature of the stress testing will depend on the type of FPP being developed.

Proposed storage conditions and shelf life:

The proposed storage conditions with suitable tolerances (e.g., a temperature range with upper and lower criteria) and shelf life for the FPP should be provided. Alternative storage conditions may be acceptable with supporting scientific data.

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., “Do not refrigerate”, “Protect from light”, “Protect from moisture”).

3.2.P.8.2 Stability Protocol and Stability Commitment

If full long term stability data supporting the proposed shelf life is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or samples considered representative of the clinical batches, will be monitored throughout the duration of the clinical trial. A summary of the stability protocol (e.g. tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

3.2.P.8.3 Stability Data

Results of the stability studies (e.g. long-term and accelerated studies) should be presented in an appropriate format.

The actual stability results (i.e., raw data) used to support the clinical trial should be provided as an Attachment. For quantitative tests (e.g., as in individual and total degradation product tests and potency tests), it should be ensured that *actual numerical results* are provided rather than vague statements such as “within limits” or “conforms”.

For Phase II and III Clinical Trial Applications

In cases where analytical procedures are only used in stability studies (i.e. stability-indicating assay method) and were not previously summarized, details of the analytical procedure as well as a tabulated summary of validation information should be provided per the instructions in Section P.5.2 and P.5.3.

A Attachments

A list of Attachments should be provided (e.g., actual stability results (raw data), specifications for excipients, letters of access to Drug Master Files, letters of attestation of BSE/TSE-free material, etc.).

MODULE 4: NON CLINICAL STUDY REPORTS

The goals of the pre-clinical /nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. The information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.

The data should be organised as follows;

- Table of Contents of Module 4
- Study Reports
- Pharmacology
 - Primary Pharmacodynamics
 - Secondary Pharmacodynamics
 - Safety Pharmacology
 - Pharmacodynamic Drug Interactions
- Pharmacokinetics
 - Analytical Methods and Validation Reports (if separate reports are available)
 - Absorption
 - Distribution
 - Metabolism
 - Excretion
 - Pharmacokinetic Drug Interactions (nonclinical)
 - Other Pharmacokinetic Studies
- Toxicology
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Local tolerance
- Other Toxicity Studies
- Literature References

4.1 Applicants are required to conduct pre-clinical studies according to the ICH guidance document M3 (R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and guidelines of the Organisation for Economic Cooperation and Development (OECD). For biotechnology-derived products the applicants should follow ICH S6. The Nonclinical Study Reports should be presented in the order described in the guidance M4S.

4.2 The data that is submitted to TFDA on non-clinical safety studies should have originated in studies that have been conducted in compliance with the Principles of GLP. Laboratories that perform safety pharmacology and toxicology studies are required to have worked under the conditions of GLP.

- 4.3 The applicant shall be required to submit evidence of GLP via a declaration letter signed by the director of the research facility testifying to have conducted the studies as per GLP compliance for each study, and the quality assurance (QA) statement must list all QA activities and confirm that the study report reflects the raw data.
- 4.4 The test facility itself should be part of a national compliance monitoring programme at the country of origin and be listed as a compliant facility. If this latter prerequisite cannot be complied with because of lack of a national compliance monitoring programme then TFDA at its own discretion might arrange for the inspections to confirm GLP compliance.
- 4.5 This module is applicable to new Investigational products only. For product that have already been established an updated investigator's brochure is sufficient.

4.6 Investigator's brochure

- 4.7 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-benefit assessment of the appropriateness of the proposed trial.
- 4.8 The contents of the IB should be approved by the disciplines that generated the described data and medically qualified person should generally participate in the editing of an IB.
- 4.9 If the investigational product is locally marketed and its pharmacology is well established and widely understood by medical practitioners, an extensive IB may not be necessary a current Summary of Product Characteristics may be submitted as an alternative.
- 4.10 If a marketed product is being studied for a new use (i.e., a new indication) an IB specific to that new use should be prepared.
- 4.11 The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information.

MODULE 5: CLINICAL STUDY REPORTS

This document provides guidance on the organization of these study reports, other clinical data, and references within a Common Technical Document (CTD) for registration of a pharmaceutical product for human use. These elements should facilitate the preparation and review of a marketing application.

The clinical study reports will be required for clinical studies that are not first in humans (FIH). The reports provide details on clinical experience in humans regarding the investigational product.

This module is applicable to new Investigational products only. For product that have already been established an updated investigator's brochure is sufficient.

The data shall be organized as shown below.

5.1 Table of Contents of Module 5

The table of content should list all documents included in Module 5.

5.2 Tabular Listing of All Clinical Studies

If applicable, if data is available or have been requested it should be presented in a tabular format to facilitate the understanding and evaluation of the results.

5.3 Clinical Study Reports

Efficacy of the product as well as information on the safety of use should be addressed in this section. Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the content of this section

Refer ICH guidelines for the structure and content of clinical study report (E3).

- a) Reports of Biopharmaceutical Studies
- b) Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials where applicable,
 - (i) Plasma Protein Binding Study Reports
 - (ii) Reports of Hepatic Metabolism and Drug Interaction Studies
 - (iii) Reports of Studies Using Other Human Biomaterials
- c) Reports of Human Pharmacokinetic (PK) Studies where applicable,
 - (i) Healthy Subject PK and Initial Tolerability Study Reports
 - (ii) Patient PK and Initial Tolerability Study Reports

- (iii) Intrinsic Factor PK Study Reports
 - (iv) Extrinsic Factor PK Study Reports
 - (v) Population PK Study Reports
- d) Reports of Human Pharmacodynamic (PD) Studies
 - (i) Healthy Subject PD and PK/PD Study Reports
 - (ii) Patient PD and PK/PD Study Reports
- e) Reports of Efficacy and Safety Studies
 - (i) Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
 - (ii) Study Reports of Uncontrolled Clinical Studies
 - (iii) Reports of Analyses of Data from More Than One Study
 - (iv) Other Clinical Study Reports
- f) Reports of Post-Marketing Experience if available
- g) Case Report Forms and Individual Patient Listings. Refer ICH Guidelines on clinical trial studies

5.4 Literature References

A list of cited references should be provided. References that have not been provided should be available upon request.

MODULE 6: VETERINARY CLINICAL TRIALS

This module intends to provide guidance on authorization of clinical trials involving veterinary Investigational products. It provides guidance on the design and conduct of all clinical studies of veterinary products in the target species.

- 6.1 All trials involving unregistered veterinary medicines for the purpose of generating data to support a marketing authorization or for other purposes shall not be conducted without prior authorization from TFDA.
- 6.2 Unless otherwise justified clinical trials shall be carried out with control animals (controlled clinical trials). The effect obtained should be compared with a placebo or with absence of treatment and/or with the effect of an authorized medicinal product known to be of therapeutic value.
- 6.3 The clinical trials application procedures, application form, protocol, pre-clinical and clinical summaries should be as presented in the Module 1-5 of these guidelines.
- 6.4 The design, conduct, monitoring, recording, auditing, analysis and reporting of clinical studies in target species should be conducted and documented in accordance with the principles of Good Clinical Practice (GCP) for veterinary clinical studies as prescribed in Annex 18. The studies should be conducted in consideration of the welfare of the study animals, the effects on the environment and the study personnel, and to residues in the edible products derived from food-producing study animals.
- 6.5 Applicants are therefore required to follow requirements as outlined in these guidelines as well as those of current VICH guideline for Good Clinical Practice (VICH GL9).
- 6.6 TFDA shall grant approval after Ethical clearance has been issued by the Ministry responsible for livestock development.

MODULE 7: MEDICAL DEVICES AND DIAGNOSTICS TRIALS

The guidance is intended to assist researchers, medical device manufacturers, members of research ethics committees. Investigators and sponsors in understanding arrangements for regulation and ethical review of trials of medical devices in Tanzania.

- 7.1 Clinical trials involving investigational medical devices including diagnostics must have an approval from TFDA before being conducted. Clinical investigations are subject to different levels of regulation, depending on the level of risk. An investigational device should be classified as a serious risk device if its studies pose life-threatening harm, could cause permanent physical damage or impairment, or would require medical intervention to prevent such damage.
- 7.2 Sponsors or Manufacturers should submit an application to conduct clinical investigation of unregistered Class B, C, and D devices in clinical trials and in vitro diagnostic devices.
- 7.3 Ethical clearance from NEC should always be sought for a clinical investigation of a non-CE marked medical device, a performance evaluation of an in vitro diagnostic device, or other research involving a medical device.
- 7.4 Approvals are not required for post market surveillance of “non-interventional” post-market surveillance studies of a CE Marked product, which are considered to be service evaluations. These non-interventional studies of CE marked product are classified as follows;
 - The product is used within its intended purpose.
 - The assignment of any patient involved in the study to a particular therapeutic strategy or diagnostic procedure is not decided in advance by a protocol but falls within current clinical practice.
 - The decision to use the product is clearly separated from the decision to include the patient in the study.
 - No diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of current clinical practice.
 - Epidemiological methods are to be used for the analysis of the data arising from the study.

However, a post-market surveillance study should be submitted for regulatory review if it does not meet the criteria for non-interventional studies of CE marked products. In particular the following should always be treated as interventional studies and should be reviewed by TFDA:

- Randomised controlled trials;
- Case series studies involving additional research procedures, e.g. additional blood samples or radiography, or investigations outside those that would normally be employed in the routine management of the patient.

It should be noted that all post-market surveillance studies require a protocol and an informed consent form to obtain consent for access to medical notes and processing of identifiable patient data.

7.5 Application procedure

An application to authorize a clinical trial involving a medical devices or diagnostics shall be made in accordance with provisions provided in module 1 of these guidelines. In addition the following documentation will be required;

- 7.5.1 Device Description, design and materials including User manual, catalogue of IFU of the device.
- 7.5.2 Marketing history
- 7.5.3 Risk assessment and standard list
- 7.5.4 Toxicology and biological safety
- 7.5.5 Sterilization validation
- 7.5.6 Electrical safety
- 7.5.7 Safety and usefulness of medicinal substance
- 7.5.8 Safety and appropriateness of use of tissues of animal origin
- 7.5.9 Signed and approved protocol with data compiled as prescribed in Annex 3 and current ISO standards.
- 7.5.10 Certificate of ISO/ Quality audit (ISO 13485) for manufacture of the device if applicable.
- 7.5.11 The Investigational product dossier with data compiled in a common submission template (CSDT) as prescribed in TFDA Guidelines for Submission of Documentation for Registration of Medical Devices, Second Edition, 2016 and Guidelines for Submission of Documentation for Registration of In-Vitro Diagnostics, 2016.

7.6 Conduct of clinical trials involving medical devices and diagnostics

The design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices should be as prescribed in the ISO 14155-2011 (en) Clinical investigation of medical devices for human subjects – Good Clinical Practice and ISO14971: 2007 Medical devices – application of risk management to medical devices guidelines.

7.7 Importation of investigational device and diagnostics

Devices must be labelled “for investigational use only”. TFDA guidelines for importation and exportation of medical devices including in-vitro diagnostics should be followed prior to importation.

Annex 1: CLINICAL TRIAL APPLICATION FORM (CTA)

To be completed by Applicants for all Clinical Trials

Study Title:	
Protocol No:	
Version No:	Date of protocol:
Investigational product's name, number or identifying mark:	
Comparator product (if applicable):	
Concomitant medications (if applicable):	
Date(s) of TFDA approval of previous protocol(s):	
Sponsor:	
Applicant:	
Contact Person:	
Address:	
Telephone Number:	Fax Number:
Cell phone Number:	
E-mail address:	

FOR OFFICIAL USE ONLY	
Date original application received:	Proposed Clinical Trial Committee meeting date:
Application/Reference No.:	
Application Fee paid:	
Signature:	Date:
<i>(All future communications to TFDA regarding the application should quote the above application/reference number)</i>	

Acknowledgement of Receipt of Application (To be completed by TFDA receiving officer). Cover sheet to be sent to the applicant once details above are completed.	
Receipt of the application is hereby acknowledged.	
Name:.....	
Signature:.....	
Date:.....	Stamp:

SECTION 1: CHECKLIST AND TABLE OF CONTENTS

(Please check the boxes and indicate pages where each document below is located in the submission file)

1. Covering letter
2. Application Form
3. General investigational plan
4. Capacity building plans
5. Overall Summary of the clinical trial Protocol (Hard copy and in MS Word)
6. Signed and approved protocol
7. Participant Information Leaflet (PIL), Informed Consent Forms (English and Swahili versions) and any other information to be given to participants.
8. Declarations by Principal investigator, Co/Sub investigators and Monitor(s)
9. Joint declaration by Sponsor (or representative) and National Principal Investigator
10. Certified copy of insurance policy cover of study participants
11. Ethical clearance certificate/copy of acknowledgement from NIMR (Parallel submission)
12. Curriculum vitae (CVs) of investigator(s)
13. Blank Case Report Forms (CRFs)
14. Serious Adverse Events reporting form to be used in the study
15. Nonclinical Overall Summary (Hard copy and in MS Word)
16. Clinical Study Reports
17. Investigator's Brochure (IB)
18. Prescribing information sheets
19. Quality Overall Summary – Chemical Entities (Hard copy and in MS Word)
20. Certificate of GMP for manufacture of the Investigational products
21. Certificate of GMP manufacture of the Placebo/Comparator (if applicable)
22. Trial product Mock up labels and package Insert/s for other trial medicines
23. Evidence of accreditation/certifications of the designated Laboratories/other evidence of GLP
24. Letters of Access authorizing TFDA to Drug master Files, Site Reference Files
25. Full, legible copies of key, peer-reviewed published articles supporting the application
26. Investigational Medicinal product dossier
27. Chemistry, manufacturing and quality control data of active ingredient and finished product/dosage form
28. Pharmacology and toxicology data
29. Previous human experience data
30. Prototype product label

For clinical trials involving medical devices and in-vitro diagnostics, item 1-17 and the following additional documents should be submitted;

1. Device Description, design and materials including User manual, catalogue of IFU of the device.
2. Marketing history
3. Risk assessment and standard list
4. Toxicology and biological safety
5. Sterilization validation
6. Electrical safety
7. Safety and usefulness of medicinal substance
8. Safety and appropriateness of use of tissues of animal origin
9. Signed and approved protocol with data compiled as prescribed in Annex 3 and current ISO standards.
10. Certificate of ISO/ Quality audit (ISO 13485) for manufacture of the device if applicable.
11. The Investigational product dossier with data compiled in a common submission template (CSDT) as prescribed in TFDA Guidelines for Submission of Documentation for Registration of Medical Devices, Second Edition, 2016 and Guidelines for Submission of Documentation for Registration of In-Vitro Diagnostics, 2016.

NB: incomplete applications will not be processed

SECTION 2: ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Title of the Study:

Protocol Number/Identification:

Version number

Date of final protocol:

Part 1: CONTACT DETAILS (Name/Address/Tel/Mobile/Fax/E-Mail)

1.1 Applicant:

1.2 Sponsor:

1.3 Local contact person:

1.4 National principal investigator:

1.5 International principal investigator: (if applicable)

1.6 Monitor:

1.7 Study coordinator:

Part 2: DETAILS OF INVESTIGATIONAL PRODUCT(S)

2.1 Name(s) and brief description of Investigational product to be used in trial:

[A summary of the chemistry and manufacturing data, formulation, composition, excipients and strength should be provided. Complete chemistry and manufacturing data should be included in the investigator's brochure. Product(s) registration number(s) and date(s) of registration, if applicable, should be included]

For medical devices and in-vitro diagnostics

(Brand name of the device, common name or preferred name, description of the device as per Global Medical Device Nomenclature (GMDN) or as applicable, GMDN code, category of the device, Model/series/system (if applicable) risk class, declaration of conformity (DoC) if applicable, intended use of the device, names and complete address of the manufacturing site(s), market approval status in GHTF member countries and /or other countries)

2.2 Name(s) and brief description (as above) of comparator product(s) and product registration number(s) and date(s) of registration if applicable: [As in 2.1, where applicable. Prescribing information sheet for registered comparator products should be included]

2.3 Name(s) and brief description (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and product registration number(s) if applicable [As in 2.1, where applicable. Prescribing information sheet for registered products should be included]

- 2.4 If any of the above products are marketed locally, explain whether locally-sourced products will be used in the trial:
- 2.5 Details of packaging, storage conditions and shelf-life of IMP:
- 2.6 Registration status of IMP, for the indication to be tested in this trial, in other countries [i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority] [Attach as an Annex if necessary]

Part 3: DETAILS OF INVESTIGATORS AND TRIAL SITE(S)

- 3.1 Details of investigator(s):
[Designation and title of principal investigators/investigators] Include Name/Address/Tel/Mobile/Fax/E-Mail
- 3.2 Current work-load of investigator(s):
[Number of studies currently undertaken by investigators as principal and/or co- or sub-investigator, and the total number of patients represented by these studies. Time-commitments of researcher(s) in relation to clinical trial work and non-trial work]
- 3.3 Details of Trial Site(s):
[Name of site, physical address, contact details, contact person, etc]
- 3.4 Capacity of Trial Site(s):
[Number of staff, names, qualifications, experience -- including study coordinators, site facilities, emergency facilities, other relevant infrastructure]

Part 4: TRIAL STUDY PARTICIPANTS

- 4.1 Number of local participants:
- 4.2 Total number of participants worldwide (where applicable):
- 4.3 Total enrolment in each local site/centre: [If competitive enrolment, state minimum and maximum number per site.]
- 4.4 Volunteer base from which local participants will be drawn
- 4.5 Retrospective data indicating potential of each site to recruit required number of participants within envisaged duration of trial: [Attach as an Annex if necessary]

Part 5: OTHER DETAILS

- 5.1 Provide an explanation if the trial is to be conducted locally only and not in the host country of the applicant / sponsor:
- 5.2 Estimated duration of trial:

- 5.3 Details of other Regulatory Authorities to which applications to conduct this trial have been submitted, but approval has not yet been granted. Include date(s) of application:
- 5.4 Details of other Regulatory Authorities which have approved this trial. Include date(s) of approval and number of sites per country:
- 5.5 Details of other Regulatory Authorities or Research Ethics Committees which have rejected this trial, if applicable, and provide reasons for the rejection:
- 5.6 Details of and reasons for this trial having been suspended at any stage by other Regulatory Authorities, if applicable:
- 5.7 Previous studies using this agent which have been approved by the Authority:
Approval number:
Title of the study:
Protocol number:
Date of approval:
Principal Investigator:
Date(s) of progress report(s):
Date of final report:
- 5.8 If any sub-studies are proposed as part of this protocol, indicate whether these will also be conducted locally. If not, please explain:

Part 6: ETHICS

- 6.1 Ethics Committee responsible for each site, date of approval or date of application:
- 6.2 Attach copy of response(s) positive or negative made by, and/or conditions required by Ethics Committee(s) if available]
- 6.3 Details of capacity building component of the trial, if any:
- 6.4 Details of ICH-GCP training of investigators, monitors, study co-coordinators in terms of conducting this trial:
- 6.5 Detailed monitoring plan for each site: [Attach as an Annex if necessary]
- 6.6 Details of trial insurance: [e.g. insurer, policy holder, policy number, insurance cover, period of validity]
- 6.7 Details of possible conflict of interest of any person(s)/organization(s) who/which will be involved in the trial:
- 6.8 Remuneration/compensation to be received by investigators, trial participants or others: [Indicate breakdown of costs to be covered, if applicable. Indicate compensation to be received by participants for travel and incidental expenses.]

SECTION 3: DECLARATION BY APPLICANT

Title of the Study:	
Protocol No:	
Version No:	Date of Protocol:

Study investigational medicinal product:

I/We, the undersigned has/have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

I/We, hereby declare that all information contained in, or referenced by, this application is complete and accurate and is not false or misleading.

I/We, agree to ensure that if the above said clinical trial is approved, it will be conducted according to the submitted protocol and all applicable legal, ethical and regulatory requirements.

Applicant

Date

National Principal Investigator

Date

**National Co-coordinator/Other
(State designation)**

Date

ANNEX 2: OVERALL SUMMARY/SYNOPSIS – CLINICAL TRIAL PROTOCOL TEMPLATE

*(This template should be filled in and submitted in **Microsoft word format** with bookman old style font size 11 black ink)*

1. GENERAL INFORMATION

Title of Study	
Protocol Identification Number/code	
Protocol Version Number (where applicable)	
Date of Protocol	
TFDA Application Number	
Ethical Clearance Number/ Date of Approval	
Name of Investigational Product or Intervention	
Therapeutic Classification	
Dosage Form(s) and Strength(s)	
Route(s) of Administration	
Name of Comparator Product (where applicable)	
Name and address(es) of the Applicant	
Name and address(es) of the Sponsor	
Name and address(es) of the Principal Investigator (PI)	
Name and address(es) of the Study Monitor	
Name and address(es) of Study Site(s)	
Name and address of the manufacturer of investigational product	
Name and address of the manufacturer of comparator product (if applicable)	
Phase of Trial	
Duration of study	

FOR OFFICIAL USE ONLY:

<p>Assessors Recommendation:</p> <p><input type="checkbox"/> Recommended (no outstanding issues)</p> <p><input type="checkbox"/> Query raised</p> <p><input type="checkbox"/> Rejected</p>	Comments (if any)
Name of 1st Assessor	
Signature of 1st Assessor	Date assessment
Name of 2nd Assessor	
Signature of 2nd Assessor	Date of assessment

ASSESSOR’S INTRODUCTION / DISCUSSION:

--

PROPOSED COMMENTS/QUERIES TO BE FORWARDED TO THE APPLICANT:

(Instructions; Please insert the protocol summary in respective sections below the subtitles and delete the guidance notes in blue.)

2. Background and Rationale

(Insert a brief, concise introduction into the clinical problem and previous treatments and developments, i.e., pertinent data from previous preclinical/clinical pharmacology studies and therapeutic exploratory studies taking into account relevant scientific literature (citations by consecutive numbering, with list at end of this section; important or not readily available references may be included with the paper submission, if appropriate). This section should also contain information on the new drug). Provide rationale for conducting the study in Tanzania

Assessor's comments:

3. Objective of the trial

(Insert the objectives that are the same as the objectives contained in the protocol. Include the primary objective and secondary objectives)

Primary Objective(s):

Secondary Objective(s):

Assessor's comments:

4. Endpoints

(Insert the endpoints that are the same as the endpoints contained in the body of the protocol. Include the primary endpoint and important secondary endpoints)

Primary Endpoint(s):

Secondary Endpoint(s):

Assessor's comments:

5. Design

5.1 Insert summary description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design). Provide a simple summarized snapshot of your study design not to exceed a single page. This section should include a diagram that provides a quick to 1 page. Please present an overview of your study design in a schematic diagram and tables. The data presentation can be adapted depending on the nature of your study and can be customized according to your protocol.

Example: complete the tables with study-specific information and adapt the table(s) to illustrate your study design.

Arm 1	Sample size	Intervention A
Arm 2	Sample size	Intervention B

Include instructions for progressing to next phase (if applicable):

<i>Include a schematic diagram to show the design, procedures and stages including study arms, visits, time-points, interventions etc.</i>
<i>5.2 Summary of the randomization method and procedures to allocate participants to treatment groups;</i>
<i>5.3 Blinding (methods of blinding (masking) and other bias reducing techniques to be used);</i>
<i>5.4 Summary description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s), including packaging, and labeling of the investigational product(s);</i>
<i>5.5 Maintenance of trial treatment randomization codes and procedures for breaking codes;</i>
<i>5.6 Total study duration (anticipated starting/ finishing dates);</i>
<i>5.7 Expected duration for each subject including post treatment period etc;</i>
Assessor's comments:
6. Study participants
<i>6.1 Provide a brief description of specific characteristics of the trial participants (e.g. disease/ stage/ indication/ conditions/ treatment etc.) as applicable and of diagnostic criteria and assessment</i>
<i>6.2 State the Inclusion criteria:</i>
<i>6.3 State the Exclusion criteria</i>
Assessor's comments:
7. Premature Withdrawal / Discontinuation Criteria
7.1 Withdrawal criteria:
<i>7.1.1 Enumeration of all conditions / criteria and management for drug/ patient's withdrawal or (premature) discontinuation, including voluntary withdrawal by subject without prejudice to future treatment by the physician. The type and timing of the data to be collected for withdrawn participants.</i>
<i>7.1.2 State whether and how participants are to be replaced.</i>
<i>7.1.3 The follow-up for participants withdrawn from investigational product treatment/ trial Treatment</i>
<i>7.2 State the stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial;</i>
8. Drug Formulation
<i>8.1 (Brief description of the study drug(s) and formulation to be used in the clinical trial. The relationship to the formulations used in the preclinical and/or other clinical trials should be delineated, as applicable. This may also include disclosure of the formulation intended to be marketed and/or any bridging studies which may be necessary, planned, initiated and/or already performed if different formulations have been used during clinical development.)</i>

8.2 <i>Instructions for safe handling;</i>
8.3 <i>State the accountability procedures for the investigational product(s), placebos and comparator(s) and disposal;</i>
Assessor's comments:
9. Dosage Regimen
9.1 <i>Rationale for dose selection</i>
9.2 <i>Provide the following regarding the treatment(s) to be administered:</i> 9.2.1 <i>The name(s) of all the product(s):</i> 9.2.2 <i>Dose(s):</i> 9.2.3 <i>The dosing schedule(s):</i> 9.2.4 <i>The route/mode(s) of administration:</i> 9.2.5 <i>The treatment period(s):</i> 9.2.6 <i>Follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial:</i> 9.2.7 <i>Concomitant Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial:</i> 9.2.8 <i>Procedures for monitoring participant's compliance:</i> 9.2.9 <i>Wash-out period (Description for pre-, during- and post-trial, as applicable)</i>
Assessor's comments:
10. Pre-study Screening and Baseline Evaluation
<i>(Describe in summary the process of clinical validation for participation in the clinical trial, including methodology / schedule of events.)</i>
11. Treatment / Assessment Visits
<i>(Insert the schedule of all events / visits / procedures during the clinical trial)</i>
Assessor's comments:
12. Efficacy Variables and Analysis
12.1 <i>Description and validation of primary endpoint(s), i.e. responses/changes from baseline over time in relation to clinical trial events. Description and validation of related secondary changes (secondary endpoints) following from clinical trial events.</i>
12.2 <i>Provide specification of the efficacy parameters.</i>
12.3 <i>Describe the methods and timing for assessing, recording, and analyzing efficacy parameters</i>
Assessor's comments:

13. Assessment of Safety
13.1 <i>Specification of safety parameters:</i>
13.2 <i>The methods and timing for assessing, recording, and analyzing safety parameters:</i>
13.3 <i>Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.</i>
13.4 <i>The type and duration of the follow-up of subjects after adverse events</i>
13.5 <i>RISKS: (Identify potential risks and mitigation strategies (e.g. need for and risks associated with long)</i>
13.6 <i>term immunosuppression)</i>
13.7 <i>DATA and SAFETY MONITORING PLAN (DSMP): (Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)</i>
13.8 <i>Immune Monitoring and immunosuppression: (Describe and justify the plan for immunosuppression and immune monitoring (if applicable)</i>
Assessor's comments:
14. Assays/methodologies
14.1 <i>Briefly describe any specialized assays or methodologies that will be used in this clinical study or supporting study/studies (Provide a more detailed summary of assay methods and summarize assay qualification/validation. Indicate where specialized testing will be conducted)</i>
14.2 <i>The names and contact addresses of the laboratories to be used for the study;</i>
14.3 <i>State the location of the attached draft Material Transfer Agreements (MTAs) in the submission;</i>
14.4 <i>State the duration for long term storage of samples and the area to be stored</i>
Assessor's comments:
15. Statistical analysis plan
15.1 <i>Specify the planned sample size to be used in the study and its justification</i>
15.2 <i>Summary of description of the statistical methodologies to be used to evaluate the effectiveness of the investigational product, including the hypotheses to be tested, the parameters to be estimated, the assumptions to be made and the level of significance and the statistical model to be used.</i>
15.3 <i>Analysis of trial parameters (primary/ secondary endpoints), population, demographics, as applicable.</i>
15.4 <i>Efficacy analysis methods and results of efficacy end-point analysis.</i>
15.5 <i>Safety analysis methods and results of safety end-point analysis.</i>
15.6 <i>Exploratory end-point analysis: evaluation effect(s) (or lack of effects) of relevant biochemical/ pharmacological etc parameters, as applicable.</i>
15.7 <i>Pharmacokinetic endpoint analysis, as applicable.</i>
15.8 <i>Interim analysis and role of Data Safety Monitoring Board, as applicable</i>
Assessor's comments:
16. Outcome criteria
<i>(Describe criteria that would define whether you would or would not move forward with the</i>

<i>subsequent development plan, based upon primary and designated secondary objectives)</i>
17. Data management
<i>(Describe procedures for recording, processing, handling, and retaining raw data and other study documentation)</i>
18. Monitoring plan
<i>(Summary of the monitoring plan) State the location of the detailed monitoring plan in the submission</i>
Assessor's comments:
19. Ethical considerations
19.1 <i>State the ethical clearance reference number and institutions that have approved the trial Institution review Board ethical clearance: Number and date NIMR ethical clearance number and Date:</i>
19.2 Insurance Details : 19.2.1 <i>Insert local Insurance Company name and address:</i> 19.2.2 <i>policy cover number:</i> 19.2.3 <i>Validity:</i> 19.2.4 <i>Expiry Date:</i> 19.2.5 <i>State the location of the Insurance cover in the submission:</i>
19.3 Participant Information sheets and Informed Consent forms: <i>(The contents should be as per ICH guidelines, these guidelines and declaration of Helsinki)</i> 19.3.1 <i>.State the version number and dates for both English and Swahili versions</i> 19.3.2 <i>State the location of the Participant Information sheets and Informed Consent forms in the submission</i>
19.4 <i>State the amount to be reimbursed to the participants</i>
19.5 <i>Treatment and/or management of participants and their disease condition(s) after completion of trial</i>
19.6 <i>Follow-up of trial study participants after the conclusion of the trial</i>
19.7 <i>In case of transfer of materials, provide Material Transfer Agreement (MTA) highlighting among other things, the following:</i>
19.8 <i>Identification of the provider and recipient</i>
19.9 <i>Identification of the material and the volume of material</i>
19.10 <i>Definition of the trial and how the material will and will not be used.</i>
19.11 <i>Maintenance of confidentiality of background or supporting data or information, if any</i>
19.12 <i>Indemnification and warranties (where applicable)</i>
19.13 <i>Details on post-trial access to the products</i>
Assessor's comments:

ANNEX 3: CONTENTS OF STUDY PROTOCOL

3.2.1 Study Protocol

The clinical trial study protocol must contain at least the following information in the ICH E6 (R2) format.

3.1 General Information

- 3.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- 3.1.2 Name and address of the sponsor and monitor (if other than the sponsor).
- 3.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- 3.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
- 3.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- 3.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- 3.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

3.2 Background Information

- 3.2.1 Name and description of the investigational product(s).
- 3.2.2 A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
- 3.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.
- 3.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- 3.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and TFDA requirement(s).
- 3.2.6 Description of the population to be studied.

3.2.7 References to literature and data that are relevant to the trial and that provide background for the trial.

3.3 Trial Objectives and Purpose

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

3.4 Trial Design

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

- 3.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- 3.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- 3.4.3 A description of the measures taken to minimize/avoid bias, including:
 - (a) Randomization.
 - (b) Blinding.
- 3.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
- 3.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- 3.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- 3.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- 3.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.
- 3.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

3.5 Selection and withdrawal of study participants

3.5.1 Participants inclusion criteria.

3.5.2 Participants exclusion criteria.

3.5.3 Participants withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

- (a) When and how to withdraw participants from the trial/ investigational product treatment.
- (b) The type and timing of the data to be collected for withdrawn participants.
- (c) Whether and how participants are to be replaced.
- (d) The follow-up for participants withdrawn from investigational product treatment/trial treatment.

3.6 Treatment of study participants

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

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

3.6.3 Procedures for monitoring participant's compliance.

3.7 Assessment of Efficacy

3.7.1 Specification of the efficacy parameters.

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

3.8 Assessment of Safety

3.8.1 Specification of safety parameters.

3.8.2 The methods and timing for assessing, recording, and analyzing safety parameters.

3.8.3 Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.

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

3.9 Statistics

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

- 3.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- 3.9.3 The level of significance to be used.
- 3.9.4 Criteria for the termination of the trial.
- 3.9.5 Procedure for accounting for missing, unused, and spurious data.
- 3.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- 3.9.7 The selection of study participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

3.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit TFDA inspection(s), providing direct access to source data/documents.

3.11 Quality Control and Quality Assurance

3.12 Ethics

Description of ethical considerations relating to the trial should include the following issues:

- 3.12.1 Choice of investigators
- 3.12.2 Monitors and monitoring plan
- 3.12.3 Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and TFDA requirements
- 3.12.4 Insurance and indemnity measures
- 3.12.5 Patient Information leaflets and Informed Consent forms for any proposed archiving of biological specimens for later research or for genetics research.
- 3.12.6 Treatment and/or management of participants and their disease condition(s) after completion of trial
- 3.12.7 Institutional ethics committee capacity to monitor site and conduct of trial

3.12.8 Provide an explanation if minimum recommended compensation for a participant is not being provided.

3.12.9 Follow-up of trial study participants after the conclusion of the trial

3.12.10 In case of transfer of materials, provide Material Transfer Agreement (MTA) highlighting among other things, the following:

- (a) Identification of the provider and recipient
- (b) Identification of the material and the volume of material
- (c) Definition of the trial and how the material will and will not be used.
- (d) Maintenance of confidentiality of background or supporting data or information, if any
- (e) Indemnification and warranties (where applicable)

3.13 Data Handling and Record Keeping

3.14 Publication Policy

Publication policy, if not addressed in a separate agreement.

ANNEX 4: REQUIREMENTS REGARDING INFORMED CONSENT OF TRIAL SUBJECTS

1. In obtaining and documenting informed consent, the investigator should comply with National Ethics Committee (NEC) requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki **Annex 17**. Prior to the beginning of the trial, the investigator should obtain Ethical Clearance from NEC and TFDA approval
2. Informed consent to study participants shall be administered in Kiswahili and all information to be given to study participants both oral and written must be in Kiswahili. The consent form together with the accompanying information shall be in Kiswahili.
3. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive NEC and TFDA approval in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
4. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
5. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
6. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the and the NEC and TFDA approval.
7. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
8. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
9. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

10. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
11. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
- (a) That the trial involves research.
 - (b) The purpose of the trial.
 - (c) The trial treatment(s) and the probability for random assignment to each treatment.
 - (d) The trial procedures to be followed, including all invasive procedures.
 - (e) The subject's responsibilities.
 - (f) Those aspects of the trial that are experimental.
 - (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
 - (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
 - (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
 - (j) The compensation and/or treatment available to the subject in the event of trial-related injury.
 - (k) The anticipated prorated payment, if any, to the subject for participating in the trial.
 - (l) The anticipated expenses, if any, to the subject for participating in the trial.
 - (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
 - (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

- (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
 - (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
 - (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
 - (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
 - (s) The expected duration of the subject's participation in the trial.
 - (t) The approximate number of subjects involved in the trial.
12. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
13. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
14. Except as described above, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.
15. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:
- (a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
 - (b) The foreseeable risks to the subjects are low.
 - (c) The negative impact on the subject's well-being is minimized and low.
 - (d) The trial is not prohibited by law.
 - (e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be

particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

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

ANNEX 5: DECLARATION BY PRINCIPAL INVESTIGATOR

Name:

Title of the study:

Protocol and site:

I, the undersigned, declare that:

1. I am familiar with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and understand the responsibilities and obligations of the Principle Investigator (PI) within the context of this study.
2. I have notified the Tanzania Food and Drugs Authority (TFDA) of any aspects of the study with which I do not/am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I have thoroughly read, understood, and critically analyzed the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).
4. I will conduct the trial as specified in the protocol and in accordance with TFDA requirements and ICH – GCP principles.
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time.
6. I will not commence the trial before written authorization from the National Ethics Committee and TFDA has been obtained.
7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.
8. I will ensure that every participant (or other involved persons), shall at all times be treated in a dignified manner and with respect.
9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. [*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal associations with other persons or organizations that may inappropriately influence (bias) his or her actions*].
10. I have*/have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with ICH-GCP (*Attach details).
11. I have*/have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details).
12. I will submit all required reports within the stipulated time-frames.

Signature:

Witness:

Date:

Date:

ANNEX 6: DECLARATION BY CO- AND SUB-INVESTIGATOR

Name:

Title of the study:

Protocol number:

Principal Investigator's Name:

Site:

Designation:

I, the undersigned, declare that:

1. I am familiar with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and understand the responsibilities and obligations of the Investigator within the context of this study.
2. I will carry out my role in the trial as specified in the protocol and in accordance with Good Clinical Practice (ICH - GCP).
3. I will not commence with my role in the trial before written authorizations from National Ethics Committee and TFDA have been obtained.
4. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or if they are not legally competent, from their legal representatives.
5. I will ensure that every participant (or other involved persons, such as relatives) shall at all times be treated in a dignified manner and with respect.
6. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. [*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]
7. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.
8. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

ANNEX 7: DECLARATION BY MONITOR

Name:

Title of the study:

Protocol number:

Site:

I, the undersigned, declare that:

1. I am familiar with the International Conference on Harmonization-Good Clinical Practice (ICH - GCP) and understand the responsibilities and obligations of the clinical trial monitor within the context of this study.
2. I have notified TFDA of any aspects of the above with which I do not/am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I will carry out my responsibilities as specified in the trial protocol and in accordance with TFDA requirements and ICH-GCP.
4. I declare that I have no financial or personal relationship(s) which may inappropriately influence me in monitoring this clinical trial.
5. I have*/have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with GCP. (*Attach details.).
6. I have*/have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details).
7. I will submit all required reports when needed.

Signature:

Date:

Witness:

Date:

ANNEX 8: JOINT DECLARATION BY SPONSOR (OR REPRESENTATIVE) AND NATIONAL PRINCIPAL INVESTIGATOR CONCERNING SUFFICIENT FUNDS TO COMPLETE STUDY

Title of the study:

Protocol:

I, <full name>, representing <sponsor or representative>

and

I, <full name>, Principal Investigator/National Principal Investigator

hereby declare that sufficient funds have been made available to complete the above-mentioned study.

Signed

Date

SPONSOR (or representative)

Name

Address

Contact details

Signed

Date

PRINCIPAL INVESTIGATOR (or National PI)

Name

Address

Contact details

ANNEX 9: RECOMMENDED FORMAT FOR CURRICULUM VITAE (CV) OF INDIVIDUALS CONDUCTING CLINICAL TRIAL(S)

Title of the study:

Protocol number:

Designation:

[E.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Study Coordinator, Monitor, Local Monitor, Clinical Research Associate]

Personal details

Name:

Work Address:

Telephone Number:

Fax Number:

Cell-phone Number:

E-mail address:

Academic and professional qualifications

Professional registration number (where applicable)

Current personal medical malpractice insurance details

Relevant related work experience (brief) and current position

Participation in clinical trials research in the last three years [Study title, protocol number, designation. If multiple trials, only list those with relevance to this application, or in the last year]

Peer-reviewed publications in the past 3 years

Date of last ICH-GCP training [As a participant or presenter]

Any additional relevant information supporting abilities to participate in conducting this trial [briefly]

Signature:

Date:

ANNEX 10: NONCLINICAL OVERALL SUMMARY TEMPLATE

*(This template should be filled in and submitted in **Microsoft word format** with bookman old style font size 11 black ink) it is recommended that the total length of the three nonclinical Written Summaries in general not exceed 100-150 pages. Details on this summary should as inserted as prescribed in the CTD module 2 and 4.*

GENERAL INFORMATION

Title of Study	
Protocol Identification Number/code	
Protocol Version Number (where applicable)	
Date of Protocol	
TFDA Application Number	
Ethical Clearance Number/ Date of Approval	
Name of Investigational Product	
Therapeutic Classification	
Dosage Form(s) and Strength(s)	
Route(s) of Administration	
Name and address(es) of the Applicant	
Name and address(es) of Study Site(s)	
Phase of Trial	

FOR OFFICIAL USE ONLY:

<p>Assessors Recommendation:</p> <p><input type="checkbox"/> Recommended (no outstanding issues)</p> <p><input type="checkbox"/> Query raised</p> <p><input type="checkbox"/> Rejected</p>	<p>Comments (if any)</p>
<p>Name of 1st Assessor</p>	
<p>Signature of 1st Assessor</p>	<p>Date assessment</p>
<p>Name of 2nd Assessor</p>	
<p>Signature of 2nd Assessor</p>	<p>Date of assessment</p>

ASSESSOR’S INTRODUCTION / DISCUSSION:

--

PROPOSED COMMENTS/QUERIES TO BE FORWARDED TO THE APPLICANT:

--

Table of Contents [\(Insert table of contents\)](#)

2.6.1 Introduction

2.6.2 Pharmacology Written Summary (CTD modules 2.6.2 and 4.2.1)

2.6.2.1 Brief Summary [<Insert summary>](#)

2.6.2.2 Primary Pharmacodynamics [<Insert summary>](#)

2.6.2.3 Secondary Pharmacodynamics <Insert summary>

2.6.2.4 Safety Pharmacology <Insert summary>

2.6.2.5 Pharmacodynamic Drug Interactions <Insert summary>

2.6.2.6 Discussion and Conclusions <Insert summary>

2.6.2.7 Tables and Figures <Insert summary>

2.6.3 Pharmacology Tabulated Summary <Insert tables>

Assessor's overall conclusions on pharmacology

--

2.6.4 Pharmacokinetics Written Summary (CTD modules 2.6.4 and 4.2.2)

2.6.4.1 Brief Summary <Insert summary>

2.6.4.2 Methods of Analysis <Insert summary>

2.6.4.3 Absorption <Insert summary>

2.6.4.4 Distribution <Insert summary>

2.6.4.5 Metabolism (interspecies comparison) <Insert summary>

2.6.4.6 Excretion <Insert summary>

2.6.4.7 Pharmacokinetic Drug Interactions <Insert summary>

2.6.4.8 Other Pharmacokinetic Studies <Insert summary>

2.6.4.9 Discussion and Conclusions <Insert summary>

2.6.4.10 Tables and Figures <Insert summary>

(Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary).

2.6.5 Pharmacokinetics Tabulated Summary

Assessor's overall conclusions on pharmacokinetics

--

2.6.6 Toxicology (CTD modules 2.6.6)

2.6.6.1 Brief Summary

2.6.6.2 Single-Dose Toxicity

2.6.6.3 Repeat-Dose Toxicity

2.6.6.4 Genotoxicity

2.6.6.5 Carcinogenicity

2.6.6.6 Reproductive and Developmental Toxicity

2.6.6.7 Local Tolerance

2.6.6.8 Other Toxicity Studies

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures (either here or included in text)

- 2.6.6.11 Antigenicity (where applicable)**
- 2.6.6.12 Immunotoxicity**
- 2.6.6.13 Dependence**
- 2.6.6.14 Metabolites**
- 2.6.6.15 Studies on impurities (Studies for qualification of impurities: single or repeat dose, genotoxicity, reproduction. See ICH guidelines)**
- 2.6.6.16 Other studies**

2.6.7 Toxicology Tabulated Summary

Assessor's overall conclusions on toxicology

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ANNEX 11: QUALITY OVERALL SUMMARY – CHEMICAL ENTITIES CLINICAL TRIAL APPLICATION

*(This template should be filled in and submitted in **Microsoft word format** with bookman old style font size 11 black ink). Details on this summary should as inserted as prescribed in the CTD module 3.*

Title of Study	
Protocol Identification Number/code	
Protocol Version Number (where applicable)	
Date of Protocol	
TFDA Application Number	
Name of Investigational Product or Intervention	
Therapeutic Classification	
Dosage Form(s) and Strength(s)	
Route(s) of Administration	
Clinical trial Design (<i>extract from the protocol</i>)	
Name of Comparator Product (where applicable)	
Name and address(es) of the Applicant	
Name and address(es) of the Sponsor	
Name and address(es) of the Principal Investigator (PI)	
Name and address(es) of the Study Monitor	
Name and address(es) of Study Site(s)	
Name and address of the manufacturer of investigational product	
Name and address of the manufacturer of comparator product (if applicable)	
Phase of Trial	

FOR OFFICIAL USE ONLY:

Assessors Recommendation: <input type="checkbox"/> Recommended (no outstanding issues) <input type="checkbox"/> Query raised <input type="checkbox"/> Rejected	Comments (if any)
Name of 1st Assessor	
Signature of 1st Assessor	Date assessment
Name of 2nd Assessor	
Signature of 2nd Assessor	Date of assessment

ASSESSOR'S INTRODUCTION / DISCUSSION:

--

PROPOSED COMMENTS/QUERIES TO BE FORWARDED TO THE APPLICANT:

--

INTRODUCTION

(a) Information on the comparator product:

Proprietary (Brand) Name of FPP	
Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)	
Company Name	
Dosage Form(s)	
Strength(s)	
Country from which the Clinical Supplies were Obtained for the Lot to be Used in this Clinical Trial (as well as the market status in that country)	

(b) If the information in any section (or subsection) has previously been submitted (in its entirety, without changes), and approved by TFDA, do not resubmit that section. Provide the following information on the cross-referenced submission(s):

Section (and subsections)	Cross-Referenced Submission Name	TFDA approval certificate number	Date Approved

2.3. S ACTIVE PHARMACEUTICAL INGREDIENT (NAME, MANUFACTURER)

2.3. S.1 General Information (name, manufacturer)

2.3. S.1.1 Nomenclature (name, manufacturer)

- (a) Recommended International Non-proprietary name (INN):
- (b) Compendial name, if relevant:
- (c) Chemical name(s):
- (d) Company or laboratory code:
- (e) Other non-proprietary name(s) (e.g., national name, USAN, BAN):
- (f) Chemical Abstracts Service (CAS) registry number:

Note: For Phase I Trials only (a) and (b) is required

2.3. S.1.2 Structure (name, manufacturer)

- (a) Structural formula, including relative and absolute stereochemistry:
- (b) Molecular formula:
- (c) Molecular mass:

2.3. S.1.3 General Properties (name, manufacturer)

- (a) Physical description (e.g., appearance, colour, physical state):
- (b) Physical form (e.g., preferred polymorphic form, solvate, hydrate):
- (c) Solubilities (e.g., aqueous/nonaqueous solubility profile, tabular format, reporting in mg/mL):
- (d) pH and pKa values:
- (e) Other relevant information:

2.3. S.2 Manufacture (name, manufacturer)

2.3. S.2.1 *Manufacturer(s) (name, manufacturer)*

- (a) Name, address, and responsibility of each manufacturer, including Contractors, and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:
- (b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

2.3. S.2.2 *Description of Manufacturing Process and Process Controls (name, Manufacturer)*

- (a) Flow diagram of the synthetic process(es):

Note: For Phase II & III include also the following should be submitted:-

- (b) Detailed narrative description of the manufacturing process(es):

2.3.S.2.3 *Control of Materials (name, manufacturer)*

- (a) For Active Pharmaceutical Ingredient manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), provide an attestation (with supporting documentation, if applicable) confirming that the material is free of BSE/TSE agents:

Note: For Phase II & III include also the following should be submitted:-

- (b) Information on starting materials:

2.3. S.2.4 *Controls of Critical Steps and Intermediates (name, manufacturer)*

- (a) Summary of the controls performed at critical steps of the manufacturing Process and on intermediates:

2.3. S.3 Characterisation (name, manufacturer)

2.3. S.3.1 *Elucidation of Structure and other Characteristics (name, manufacturer)*

- (a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and

Summary of the interpretation of evidence of structure:

- (b) Discussion on the potential for isomerism and identification of Stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations):
- (c) Summary of studies performed to identify potential polymorphic forms (including solvates):
- (d) Summary of studies performed to identify the particle size distribution of the Active Pharmaceutical Ingredient:
- (e) Other characteristics:

2.3. S.3.2 Impurities (name, manufacturer)

- (a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:
 - (i) List of drug-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products, metabolites), including chemical name, structure and origin:

Drug-related Impurity (chemical name or descriptor)	Structure	Origin

- (b) List of process-related impurities (e.g., residual solvents, reagents, catalysts), including compound name and step used in synthesis:
- (c) Actual levels of impurities (e.g., drug-related and process-related) found in Batches used in nonclinical and clinical studies:

Impurity (drug-related and process-related)	Acceptance Criteria	Results (include batch number and use) (e.g., clinical)		

2.3. S.4 Control of the Active Pharmaceutical Ingredient (name, manufacturer)

2.3. S.4.1 Specification (name, manufacturer)

- (a) Specification for the Active Pharmaceutical Ingredient:

Test	Acceptance Criteria	Analytical Procedure (Type and Source)

2.3. S.4.2 Analytical Procedures (name, manufacturer)

- (a) Summary of the analytical procedures (e.g., suitability, key method parameters, conditions):

2.3. S.4.3 Validation of Analytical Procedures (name, manufacturer)

- (a) Tabulated summary of the validation information (e.g., system suitability testing, validation parameters and results):

2.3. S.4.4 Batch Analyses (name, manufacturer)

- (a) Description of the batches to be used in this clinical trial (or representative batches):

Batch Number	Batch Size	Date of Manufacture and Site of Production	Use (e.g., clinical)

- (b) Summary of results for the batches to be used in this clinical trial or Representative batches (should include tests, types of analytical procedures (type and source), and actual results):

2.3. S.4.5 Justification of Specification (name, manufacturer)

- (a) Justification of the Active Pharmaceutical Ingredient specification (e.g., manufacturing experience, stability, historical batch analysis results, safety considerations):

For Phase one trial only Batch analysis report is required.

2.3. S.6 Container Closure System (name, manufacturer)

- (a) Description of the container closure system(s) for the storage and shipment of the Active Pharmaceutical Ingredient:

2.3. S.7 Stability (name, manufacturer)

2.3. S.7.1 Stability Summary and Conclusions (name, manufacturer)

- (a) Summary of stability studies to support this clinical trial (e.g., studies

conducted, protocols used, results obtained):

(b) Proposed storage conditions and re-test period (or shelf life, as appropriate):

2.3. S.7.2 Stability Protocol and Stability Commitment (name, manufacturer)

(a) If full long term stability data is not available at the time of filing, provide a summary of the stability protocol and a commitment for the continued monitoring of the Active Pharmaceutical Ingredient stability according to the protocol:

2.3. S.7.3 Stability Data (name, manufacturer)

(a) The actual stability results (i.e., raw data) may be found in:

(b) Summary of analytical procedures and validation information for those Procedures not previously summarized in 2.3.S.4 (e.g., analytical procedures used only for stability studies):

2.3. P FPP (NAME, DOSAGE FORM)

2.3. P.1 Description and Composition of the FPP (name, dosage form)

(a) Description of the dosage form:

(b) Composition of the dosage form:

(i) Composition, i.e., list of all components of the dosage form, and their amounts on a per unit basis (including overages, if any):

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)			
		Quantity per unit	%	Quantity per unit	%

(ii) Composition of all *components that are mixtures* (e.g., colourants, coatings, capsule shells, imprinting inks):-

(c) Description of reconstitution diluent(s), if applicable:

(d) Type of container closure system used for accompanying reconstitution diluent, if applicable:

(f) Qualitative list of the components of the placebo samples to be used in this Clinical trial, if different from the components listed in 2.3. P.1(b):

2.3. P.2 Pharmaceutical Development (name, dosage form)

- (a) Discussion on the development of the dosage form, the formulation, Manufacturing process, etc.:
- (b) For sterile, reconstituted products, summary of compatibility studies with Diluents/containers:

2.3. P.3 Manufacture (name, dosage form)

2.3. P.3.1 Manufacturer(s) (name, dosage form)

- (a) Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing of the batches to be used in this clinical trial:
- (b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):
- (c) Attestation that the dosage form was manufactured under Good Manufacturing Practices (GMP) conditions:

2.3. P.3.2 Batch Formula (name, dosage form)

- (a) List of all components of the dosage form to be used in the manufacturing process, and their amounts on a per batch basis (including overages, if any):

Strength (label claim)	
Batch Size(s) (number of dosage units)	
Component and Quality Standard (and Grade, if applicable)	Quantity per batch
Total	

2.3. P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

- (a) Flow diagram of the manufacturing process:
- (b) Detailed narrative description of the manufacturing process, including Equipment type and working capacity, process parameters (**for Phase II & III trials**)
- (b) For sterile products, details and conditions of sterilization and lyophilization:

2.3. P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

- (a) Summary of controls performed at the critical steps of the manufacturing

Process and on isolated intermediates (*for Phase II & III trials*)

2.3. P.4 Control of Excipients (name, dosage form)

2.3. P.4.1 Specifications (name, dosage form)

- (a) Specifications for non-compendial excipients and for compendial excipients Which include supplementary tests not listed in the monograph(s) may be found in:
- (b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):

2.3. P.4.5 Excipients of Human or Animal Origin (name, dosage form)

- (a) List of excipients that are of human or animal origin (including country of origin):
- (b) Summary of the information (e.g., sources, specifications, description of the Testing performed, viral safety data) regarding adventitious agents for excipients of human or animal origin:
- c) For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), provide an attestation (with supporting documentation, if applicable) confirming that the material is free of BSE/TSE agents:

2.3. P.4.6 Novel Excipients (name, dosage form)

- (a) Summary of the details on the manufacture, characterization, and controls, With cross references to supporting safety data (nonclinical and/or clinical) on novel excipients (i.e., those used for the first time in a FPP or by a new route of administration):

2.3. P.5 Control of FPP (name, dosage form)

2.3. P.5.1 Specification(s) (name, dosage form)

- (a) Specification(s) for the FPP:

Test	Acceptance Criteria	Analytical Procedure (Type and Source)

2.3. P.5.2 Analytical Procedures (name, dosage form)

- (a) Summary of the analytical procedures (e.g., key method parameters,

conditions, suitability):

2.3. P.5.3 Validation of Analytical Procedures (name, dosage form)

- (a) Tabulated summary of the validation information (e.g., system suitability testing, validation parameters and results):

2.3. P.5.4 Batch Analyses (name, dosage form)

- (a) Description of the batches to be used in this clinical trial (or representative batches):

Strength and Batch Number	Batch Size	Date of Manufacture and Site of Production	Input Drug Substance Batch	Use (e.g., clinical)

- (b) Summary of results for the batches to be used in this clinical trial or Representative batches (should include tests, types of analytical procedures (type and source), and actual results):

Note: For Phase one trial only Batch analysis report is required.

2.3. P.5.5 Characterisation of Impurities (name, dosage form)

- (a) Information on the characterization of impurities, not previously provided in

2.3. S.3.2 (e.g., summary of actual and potential degradation products):

2.3. P.5.6 Justification of Specification(s) (name, dosage form)

- (a) Justification of the Active Pharmaceutical Ingredient specification (e.g., manufacturing experience, stability, historical batch analysis results, safety considerations):

2.3.P.7 Container Closure System (name, dosage form)

- (a) Description of the container closure systems, including unit count or fill size, container size or volume:

- (b) Materials of construction of each primary packaging component:

- (c) For sterile products, details of washing, sterilization and depyrogenation Procedures for container closures:

2.3. P.8 Stability (name, dosage form)

2.3. P.8.1 Stability Summary and Conclusions (name, dosage form)

(a) Summary of stability studies to support this clinical trial (e.g., studies conducted, protocols used, results obtained):

(i) Description of stability study details:

Storage Conditions (°C, % RH, light)	Strength and Batch Number	Batch Size and Date of Manufacture	Container Closure System	Completed (and Proposed) Test Intervals

(ii) Summary and discussion of stability study results:

(b) Proposed storage conditions and shelf life (and in-use storage conditions and in-use period, if applicable):

2.3. P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

(a) If full long term stability data is not available at the time of filing, provide a summary of the stability protocol and a commitment that the stability of the clinical trial samples or representative batches will be monitored throughout the duration of the clinical trial or proposed shelf life:

2.3. P.8.3 Stability Data (name, dosage form)

(a) The actual stability results (i.e., raw data) may be found in:

(b) Summary of analytical procedures and validation information for those Procedures not previously summarized in 2.3.P.5 (e.g., analytical procedures used only for stability studies):

ATTACHMENTS

Attachment Number	Subject

ANNEX 12: APPLICATION FOR CLINICAL TRIAL PROTOCOL AMENDMENT

APPLICATION FOR APPROVAL OF:

- PROTOCOL AMENDMENT**
 INCREASE IN NUMBER OF STUDY PARTICIPANTS
 CHANGES IN DOSE/REGIMEN OF INVESTIGATIONAL MEDICINAL PRODUCT

Title of the study:

Protocol Number:

Date:

1. APPLICANT

- 1.1 Name
1.2 Address
1.3 Telephone
1.4 Fax number

2. TRIAL PARTICULARS (original application)

- 2.1 Trial Approval Number:
2.2 Date of Approval of original protocol:
2.3 Principal Investigator(s) approved for this trial:

Number of local sites approved for this trial:

Number of participants approved for this trial:

3. AMENDMENT PARTICULARS

(Please list requests for approval)

- 3.1 Does the applicant wish to increase the number of local study participants participating in this trial?

Yes
No

- 3.2 Does the applicant wish to change the dose/regimen of the investigational medicinal product?

Yes
No

- 3.3 Does this amendment request require a new consent form to be signed by the participant?

Yes

No

If “Yes” please submit new PIL together with this application.

Protocol Amendment Number:

Version Number and Date of Protocol Amendment (for each document submitted):

General motivation for the proposed amendment: [List all of the issues included in the amendment and provide the rationale for each amendment]

Details of the proposed protocol amendment: [For each amendment, provide reasons for amendment and clearly highlight changes to the original protocol; this can be done either as “old text” replaced with “new text” or with the old text deleted with a line through it and the new text in bold and underlined]

3.4 Will this amendment apply to all approved site(s)?

Yes

No

If No: Specify the investigator(s)/site(s) for which the amendment will apply:

4.1 **ETHICS COMMITTEE APPROVAL**

4.1 Have the Research Ethics Committee(s) responsible for each centre to which this amendment applies been notified?

4.2 Research Ethics Committee(s) responsible:

4.3 Date of application to Ethics Committee:

4.4 Date of approval by Ethics Committee:

I/We, the undersigned, agree to conduct/manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility should sign this form).

Applicant

Date

ANNEX 13: APPLICATION FOR ADDITIONAL INVESTIGATOR(S), CHANGE OF INVESTIGATOR(S) OR ADDITIONAL CLINICAL TRIAL SITE(S)

APPLICATION FOR APPROVAL OF:

- CHANGES IN INVESTIGATOR(S) AT APPROVED SITE (includes additional investigators)**
- ADDITIONAL SITE(S)**

Title of the study:

Protocol number:

Date:

1. APPLICANT

Name
Address
Telephone
Fax number

2. TRIAL PARTICULARS (original application)

Trial approval number:

Date of approval of original protocol:

Principal investigator(s) approved for this trial:

Number of local sites approved for this trial:

Number of participants approved for this trial:

3. INVESTIGATOR'S DETAILS

3.1 Name and address of additional Investigator(s)/Changes to Investigators: [Proof of ICH - GCP training must be provided for investigators who have not previously participated in clinical trials]

3.2 Summarise other ongoing/planned studies at the site involving the investigator: [Provide details of studies, including numbers of study participants, whether the investigator is involved in research in a full-time or part-time capacity, and any other details that may affect the capacity of the site at any one time]

3.3 Date of application to Ethics Committee:

3.4 Date of approval by Ethics Committee:

3.5 Is CV for additional investigator(s) attached?

Yes

No

3.6 Is the declaration of Intent attached?

Yes

No

(If yes, attach declaration)

4. CAPACITY OF THE SITE

Describe how the site is structured so as to be able to take on the work for which this application is being made: [Give details of support staff, facilities, back up and any other relevant infrastructure].

5. RATIONALE FOR APPLICATION

5.1 Briefly explain the reason for the new investigator/s or site(s):

I/We, the undersigned, agree to conduct/manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility should sign this form).

Applicant

Date

ANNEX 14: CONSIDERATIONS FOR INCLUSION OF WOMEN IN CLINICAL TRIALS AND ANALYSIS OF SEX DIFFERENCES

These guidelines provide guidance on the study and analysis of sex differences in clinical trials of therapeutic products in order to generate evidence to advice on the optimal use of therapeutic products in both women and men. Scientific evidence shows that there are often many clinically meaningful differences between male and female subjects. This guidance addresses considerations pertaining to the appropriate inclusion of women in all stages of clinical trials and research with the aim of identifying and analyzing sex-related differences that may affect the safety and efficacy of a therapeutic product.

- 1.1.1 Nonclinical studies submitted should be conducted in both male and female animals.
- 1.1.2 The timing of nonclinical studies, in relation to the inclusion of women of childbearing potential or pregnant women in clinical trials, should be carefully considered because of the potential for teratogenic effects of therapeutic products. Reference to ICH M3 R2: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals should be done.
- 1.1.3 Assessment of embryo-fetal development can be deferred until before Phase III for women of childbearing potential using precautions to prevent pregnancy in clinical trials.
- 1.1.4 Where abnormalities of reproductive organs or their function (spermatogenesis or oogenesis) have been observed in experimental animals following the administration of a substance, the decision to include subjects in a clinical trial should be based on a careful risk-benefit evaluation. This decision should take into account factors such as the abnormalities, the dosage needed to induce them, the consistency of the findings across species and their potential reversibility, the disease being treated, the availability of alternative therapies, and the proposed duration of the trial, and/or the treatment.

Design considerations in the conduct of clinical trials

- 1.1.5 The design of the clinical trial where therapeutic products are to be used by both women and men, the potential for sex-related differences in response to these products should be identified and assessed, since such differences may affect the safety and/or efficacy of the product.
- 1.1.6 Signals of potential clinically relevant differences by sex should be identified and analyzed throughout the entire clinical development program.
- 1.1.7 Early phase clinical studies/trials should guide the design and data analysis for subsequent clinical studies/trials to assess whether there are clinically relevant differences between women and men in response to therapeutic products. Such differences should ultimately be reflected in the product information.

- 1.1.8 Both women and men should be included in all phases of clinical trials, including early phases. Inclusion of both women and men in early phase trials would enable identification of potential sex-related differences in drug metabolism, which may have implications for differences in drug response. Early phase trials may suggest potential differences by sex, or uncertainty regarding whether or not differences exist, for follow-up in subsequent studies. This may not be possible or feasible for each product. In such instances, there should be a plan to develop the information needed.
- 1.1.9 While initial safety studies on a new drug are usually conducted in healthy volunteers, trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical. Inclusion of women of child bearing potential in these early phase trials involves a consideration of the risk/benefit ratio for a healthy female volunteer exposed to a potentially embryotoxic therapeutic product, relative to a female with a serious or life-threatening condition. The Informed Consent document should include sufficient information regarding the potential risks to inform women so that they may make informed decisions about the potential risks and benefits of the therapy and the trial.
- 1.1.10 The timing for inclusion of women in clinical trials, (including the timing for inclusion of women of childbearing potential) and the use of pregnancy prevention measures should be considered when designing clinical trials. Sponsors should refer to ICH M3R2: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, June 2009 for additional guidance on the timing of trials.
- 1.1.11 Physiologic differences between men and women may have implications for dose-finding studies, generally carried out in Phase I and early Phase II, and for analysis of adverse events. In this regard, dose-finding, pharmacokinetic and pharmacodynamic studies should include both men and women, in order to identify any potential sex-related differences in dose-response (i.e., women may require larger or smaller doses or different time courses than men to see a similar effect) and/or safety. If data from early studies suggest the presence of a potential clinically significant sex-related difference, sponsors are recommended to consider the result for hypothesis testing in subsequent trials. Subsequent studies need to be designed to determine if sex differences are meaningful and clinically relevant. For Phase III confirmatory studies in particular, subgroup analysis may be pre-specified and, ideally, be powered to accommodate these early findings.
- 1.1.12 If data from early phase trials do not indicate potential sex-related differences, it cannot be assumed that clinically relevant differences do not exist. It is therefore recommended that the statistical section of the study protocol for Phase III trials include pre-specified plans for assessing sex related differences on efficacy and safety. The pre-specified plans for assessing such differences should be carried out once the overall treatment effect has been shown to be significant. Post hoc analysis to assess sex related differences should only be carried out in trials that are already completed or ongoing, and the analysis should be labeled as post hoc. In addition, if there are scientific reasons to suggest the potential existence of sex related differences, stratification by sex

at the study design stage should also be considered. Where possible differences by sex are identified based on this analysis, this would be hypothesis generating and signal a need for further study prior to marketing. In cases where it is determined that additional data is required to assess sex related differences, and when such data is to be provided post-approval, TFDA encourages that post-market studies be implemented and conducted in a timely manner, and that the studies be designed appropriately, so as to provide as definitive an answer as possible, to the question of sex related differences.

- 1.1.13 In the context of a application, it is recommended that sponsors carry out and present an analysis to assess the influence of sex in the submission where data indicate that sex differences are a consideration, or where the product belongs to a class where sex differences are known. This analysis should be carried out for individual studies, as well as in the integrated analysis of efficacy and safety. A meta-analysis of the data from the various trials can be considered to assess the clinical significance of sex-related differences.
- 1.1.14 Where sex-related differences in therapeutic product response are identified, it is important to confirm the reasons for these differences (e.g. whether they are related to organ size/weight, physiological differences, including but not limited to pre- or post-menopausal state, or potential route of administration, dose, dosing regimen, dosage form or product formulation), in order to determine how to mitigate the effect of sex-related differences in the clinical setting, as appropriate.
- 1.1.15 Relevant findings as outlined above, with respect to sex differences in response to therapeutic products, should be reflected in the product monograph in each appropriate section and/or subsection.

Considerations regarding Informed Consent in clinical trials involving women

- 1.1.16 Fully informed consent is needed.
- 1.1.17 Sponsors have an obligation to fully inform clinical trial subjects, both female and male, in addition to all other risks, about (a) the potential risks of reproductive and foetal toxicity, including teratogenicity; and about (b) pregnancy prevention, so that prospective subjects understand how and when to take precautions to prevent pregnancy in the context of a trial.
- 1.1.18 The Informed Consent Form and the Investigator's Brochure should include all available information regarding the potential risk of foetal and reproductive toxicity. However, if the study excludes pregnant or breastfeeding women, and requires the use of birth control during the entire trial and a period after the trial is over, the emphasis on the potential foetal and reproductive toxicity may be reduced. While animal models cannot always predict all possible human toxicities, if animal reproductive toxicity studies are complete, the results should be presented with an appropriate explanation of their significance in humans.

- 1.1.19 If foetal and reproductive toxicity studies have not been completed other pertinent information should be provided, such as a general assessment of foetal toxicity in therapeutic products with related structures or pharmacologic effects. If relevant information is not available from reproductive toxicity studies, the Informed Consent Form as well as the Investigator's Brochure should explicitly note that the potential for reproduction and embryo-foetal risk cannot be excluded.
- 1.1.20 Adequate counseling will be provided to subjects concerning what is known or not known about foetal and reproductive toxicity, and about the importance of using a reliable method of contraception. Clinical trial subjects should also be apprised of procedures in place, should inadvertent pregnancy occur in the context of a trial.
- 1.1.21 If further information about reproductive and foetal toxicity about a product under investigation (including teratogenic effects) becomes available during the course of a clinical trial, this additional information should be provided to clinical trial subjects (via updated informed consent). Equally, the clinical trial investigator and TFDA should be notified.

Pregnancy prevention / contraception

In accordance with good clinical practice, clinical protocols should include measures to minimize the possibility of foetal exposure to the investigational product when the investigational product has been estimated to pose a risk to the health of the foetus and/or the pregnant woman. Precautions include:

- 1.1.22 **Use of reliable method(s) of contraception** and/or abstinence, for the duration of therapeutic product exposure. When the product under investigation (e.g. drug or natural health product) may lessen the effectiveness of a hormonal contraceptive agent, clinical trial subjects should be advised to use an additional non-hormonal method of contraception (e.g. double barrier methods) for the duration of the exposure. Information on the duration of contraception beyond the study period should be provided to subjects.
- 1.1.23 **Initial pregnancy testing** prior to participation in the clinical trial and, where necessary and appropriate, study entry only after a confirmed menstrual period. If pregnancy is confirmed prior to the start of the trial in general, the subject should not be enrolled in the trial. Exceptions may be considered on a case by case basis (e.g. cancer patients fully informed about the foetal risks).
- 1.1.24 **Additional pregnancy testing**, as necessary and appropriate, at predetermined intervals, based on risks and benefits. Considerations may include the length of the trial, the subject population and the specific product.

Where required, contraception should be extended beyond the last dose of the investigational product. The duration will differ by product (e.g. length of half-life) and will depend on what is known and not known about the product with respect to reproductive toxicity. The duration required will also depend on the pharmacokinetics/pharmacodynamics of the product and will usually be longer for biologics than for pharmaceuticals.

Inadvertent pregnancy in clinical trials

Despite precautionary measures to prevent pregnancy in clinical trials), pregnancies do occur, and can happen at any stage of a clinical trial. The following recommendations are offered for the management and follow-up of an inadvertent pregnancy, should it occur in the context of a clinical trial and when it is estimated that the investigational product poses a risk to the health of the foetus and/or the pregnant woman:

- 1.1.25 Subjects (female and male) should be advised to report, immediately, to the Investigator a suspected or confirmed pregnancy that occurs in the course of a clinical trial (including during any period of exposure that may exceed the length of the trial).
- 1.1.26 In addition to preventing and minimizing the risk of inadvertent pregnancy in a clinical trial, sponsors should have documented procedures for investigators to follow in case an inadvertent pregnancy occurs in the course of a clinical trial (including for any duration of exposure that may exceed the length of the trial).
- 1.1.27 If an inadvertent pregnancy occurs in the course of a clinical trial, treatment should generally be discontinued if this can be done safely and the pregnant subject withdrawn from the trial. However, exceptions may be considered on a case by case basis where the benefits to the subject of continuing in the trial clearly outweigh the risks to the foetus (e.g. cancer patients fully informed about the foetal risks).
- 1.1.28 Follow-up procedures regarding the course of the pregnancy should be discussed with the subject, as appropriate. Follow-up is recommended throughout the pregnancy and for an appropriate period thereafter, when the pregnancy results in a live birth, and is subject to the woman's consent.
- 1.1.29 The outcome of each pregnancy should be recorded and followed-up. For live births, longer term follow-up of a child is recommended, when possible and appropriate. It is recognized that the decision to follow up in the longer term, and the specific time frame for follow-up may vary with what is known, or not known about the reproductive and teratogenic risks of the product or class of products and other factors. In this regard, outcome data of foetal exposure comprise both structural malformations (typical birth defects) that are often, but not always, detected in the neonatal period, and non-structural or longer-term functional effects that are not easily detected in the immediate neonatal period. Some cardiac, renal and intestinal malformations are not always diagnosed immediately postpartum, and data regarding the incidence of these malformations is significantly influenced by duration of follow-up and availability of diagnostic tests.
- 1.1.30 Where congenital anomaly/birth defect occurs in the context of a clinical trial, sponsors are required to report this to the regulator within 15 days of becoming aware of the event. Spontaneous abortion within the context of a clinical trial should also be reported to the regulator within 15 days. This

information will also need to be captured in any safety update provided on the product, throughout its development.

Inclusion of pregnant and breastfeeding women in clinical trials

- 1.1.31 Pregnant and breastfeeding women are generally excluded from clinical trials because of real or perceived harm to the woman, the developing foetus and/or the infant. As a result, only limited information is available about effects of therapeutic products used by these populations to inform health care decisions.
- 1.1.32 Many women use therapeutic products during pregnancy and when breastfeeding for treatment of chronic conditions, or for conditions that arise during pregnancy, despite lack of evidence for safety or efficacy. In addition, some women may become pregnant while on medication.
- 1.1.33 The inclusion of pregnant and/or breastfeeding women in pre-market trials is encouraged when it is considered safe for the women, developing fetus and/or infant based on the guidance below. Post-market surveillance or clinical trials may be alternative or additional ways of gathering data.

Considerations for including pregnant women in clinical trials

A decision to enrol pregnant women in a specific trial should be individualized and based on a careful risk/benefit assessment taking into consideration: the nature and severity of the disease; the availability and results of previous nonclinical data on pregnant and non-pregnant animals, and results from clinical data; the availability of alternative therapy/therapies and knowledge about their associated risks; the stage of pregnancy in relation to overall development of the foetus, especially regarding foetal brain development; and the potential for harm to the woman, the foetus or child.

A key consideration in the study of therapeutic products used by pregnant women will be follow-up of the pregnancy, foetus and child. Longer term follow-up of a child is recommended when possible.

The inclusion of pregnant women in clinical trials should be considered when:

- 1.1.34 The specific use of the therapeutic product is for pregnant or breastfeeding women (e.g. for obstetrical or pregnancy related problems).
- 1.1.35 The studies are of agents that can be expected to address an unmet, or inadequately met, health need for pregnant women and/or foetuses (e.g. pregnant women with HIV; other life threatening conditions).
- 1.1.36 The studies are of agents which can be expected to improve pregnant women and/or foetal outcomes as compared to existing therapy.
- 1.1.37 Animal studies have been conducted, including studies on pregnant animals, and there is data on non-pregnant women on which to base an estimate of risk to the woman and/or foetus.

- 1.1.38 For a new drug or new indication there is anticipated or actual use of the drug in pregnant women and women of childbearing potential.
- 1.1.39 Research involving pregnant women should be research of potential health benefit to pregnant women or the foetus. Any potential benefit to foetuses should be weighed against possible risks to the pregnant women.
- 1.1.40 The risk to the foetus is not greater than that from established procedures routinely used in an uncomplicated pregnancy, or in a pregnancy with complications comparable to those being studied, and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.
- 1.1.41 The woman has to be fully informed of the risks to her, the foetus and the newborn. This condition will apply to any of the preceding circumstances.
- 1.1.42 Pharmacokinetic studies may be conducted in pregnant women, where, in addition to the above-noted considerations, the consequences of under or overdosing in pregnancy are great (e.g. narrow therapeutic range drugs, cancer chemotherapy) and/or pregnancy is likely to alter significantly the PK of a therapeutic product (e.g. drugs excreted by the kidneys). However, pharmacokinetic studies in pregnant women should not be conducted if the therapeutic product will not be used in clinical practice or it is known, or suspected, to have high risk to the foetus.

Considerations for including breastfeeding women in clinical trials

Studies in breastfeeding women include, but are not limited to, studies that measure the effects of a therapeutic product on milk production and composition, studies to determine whether the therapeutic product is present in human milk, or studies to determine whether dose adjustments are required during breastfeeding, as well as implications for the baby (e.g. impact on growth and/or development; severity/frequency of adverse events).

The inclusion of breastfeeding women in clinical trials should be considered when:

- 1.1.43 A new indication is being sought for an approved therapeutic product and there is evidence of use or anticipated use of the therapeutic product by breastfeeding women;
- 1.1.44 After market authorization, use of a therapeutic product in breastfeeding women becomes evident (e.g. via reports in the medical literature, general media, anecdotal information or adverse event reports);
- 1.1.45 There is concern that the consequences of uninformed dosages for use while breastfeeding are potentially serious and/or severe. This includes the following circumstances:
- 1.1.46 A therapeutic product is under review for market authorization and is expected to be used by women of reproductive age;

- 1.1.47 Marketed medications that are commonly used by women of reproductive age (e.g. antidepressants, anti-hypertensives, anti-infectives, anti-diabetics and analgesics);
- 1.1.48 The risk to the infant or mother is not greater than that from established procedures routinely used during breastfeeding, is comparable to those being studied, and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.

Post-market studies

- 1.1.49 As with pediatrics and other populations, it is anticipated that most studies regarding the safety and efficacy of therapeutic products in pregnant or breastfeeding women will be carried out following initial marketing for use in the general population. FDA strongly encourages the gathering of data on pregnant and breastfeeding women. This would include monitoring the outcome of a pregnancy with regard to the health of the woman and child, in the short and longer term. Methodologies for gathering information may include but are not limited to: observational studies; pregnancy registries and cohort studies; case control studies; case reports; database linkages; and interventional studies such as pharmacokinetic studies and foetal therapy studies.
- 1.1.50 Because of the size of the populations included in clinical trials in the pre-market stage, the information that results does not cover all aspects of the use of a FPP. Therefore, post-market studies are important to further inform health care decisions where pregnant and breast-feeding women are concerned. Post-market studies are also important to manage all aspects of the life-cycle of a drug and to be able to maintain current each therapeutic agent's benefits and risks.
- 1.1.51 There are circumstances in which consideration should be given to include pregnant or breastfeeding women in clinical studies, including clinical trials. In the vast majority of cases, studies will be conducted in pregnant or breastfeeding women already prescribed and taking the medication.
- 1.1.52 Gathering information from clinical studies where pregnant and/or breastfeeding women are included would confirm whether or not the therapeutic product crosses the placenta in humans and/or whether or not the product is excreted in milk.

ANNEX 15: SAE REPORTING FORM

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year	Years		Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										<input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)		19. THERAPY DURATION

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP

ANNEX 16: GOOD CLINICAL PRACTICE (GCP) PRINCIPLES

1. Applicants must be able to demonstrate that clinical trials are conducted according to generally accepted principles of good clinical practice.
2. Trials must be conducted in accordance with the applicable regulatory requirement(s)
3. Before a trial is initiated, foreseeable risks and inconveniences must be weighed against the anticipated benefit for the individual trial study participant and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
4. The rights, safety, and well being of the trial study participants are the most important considerations and must prevail over interests of science and society.
5. The available non-clinical and clinical information on an investigational medicinal product must be adequate to support the proposed clinical trial.
6. Clinical trials must be scientifically sound, and described in a clear, detailed protocol.
7. A trial must be conducted in compliance with a protocol that has received regulatory and ethics approval prior to initiation.
8. The medical care given to, and medical decisions made on behalf of, study participants must always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
9. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
10. Freely given informed consent must be obtained from every study participant prior to clinical trial participation.
11. All clinical trial information must be recorded, handled, and stored in a way that enables its accurate reporting, interpretation and verification.
12. The confidentiality of records that could identify study participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
13. Investigational medicinal product must be manufactured, handled, and stored in accordance with applicable good manufacturing practices (GMP) and must be used in accordance with the approved protocol.
14. Systems with procedures that assure the quality of every aspect of the trial must be implemented.

ANNEX 17: WORLD MEDICAL ASSOCIATION (WMA) DECLARATION OF HELSINKI (ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN STUDY PARTICIPANTS)

As adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of clarification on paragraph 29 added by the WMA General Assembly, Washington 2002

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principle to provide guidance to physicians and other participants in medical research involving human study participants. Medical research involving human study participants includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human study participants.
5. In medical research on human study participants, considerations related to the well-being of the human study participant should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human study participants is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research population is vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be study participant to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human study participants in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirements should be allowed to reduce or eliminate any of the protections for human study participants set forth in this Declaration.

B. Basic Principles for all Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human study participant.
11. Medical research involving human study participants must conform to general accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animal used for research must be respected.
13. The design and performance of each experimental procedure involving human study participants should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for study participants.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical human research involving study participants should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human study participant must always rest with a medically qualified person and never rest on the study participant of the research, even though the study participant has given consent.
16. Every medical research project involving human study participant should be preceded by careful assessment of predictable risk and burdens in comparison with foreseeable benefits to the study participant or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research project involving human study participants unless they are confident that the risk involved has been adequately assessed and can be satisfactorily managed. Physicians should cease any investigations if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human study participants should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the study participant. This is especially important when the human study participants are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the result of the research.
20. The study participants must be volunteers and informed participants in the research project.
21. The right of research study participants to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the study participant, the confidentiality of every patient's information and to minimize the impact of the study on the study participant's physical and mental integrity and on the personality of the study participant.
22. In research of human beings, each potential study participant must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The study participant should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the study participant has understood the information, the physician should then obtain the study participant's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the study participant is in a dependent relationship

with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research study participant who is legally incompetent, physically or mental incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a study participant deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reason for involving research study participants with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligation. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicity available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principle laid down in this Declaration should no be acceptable for publication.

C. Additional Principles for Medical Research Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to patients who are research study participants.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Footnote: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be study participant to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

ANNEX 18: THE PRINCIPLES OF VICH GCP

1. The purpose of the VICH GCP is to establish guidance for the conduct of clinical studies that ensures the accuracy, integrity and correctness of data. Due regard should be given to the welfare of the study animals, the effects on the environment and the study personnel, and to residues in the edible products derived from food-producing study animals.
2. Pre-established systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical studies are necessary to assure the validity of data and to ensure the ethical, scientific, and technical quality of studies. Data collected from studies designed, conducted, monitored, recorded, audited, analyzed and reported in accordance with this guidance can be expected to facilitate the review process, since the regulatory authorities can have confidence in the integrity of studies which follow such pre-established written procedures.
3. By following such pre-established written procedures, it is likely that sponsors can avoid unnecessary repetition of definitive studies. Any requirement for local effectiveness studies to confirm the findings of the definitive studies is not affected by this guidance document. In addition, other guidance may exist which define study design and effectiveness criteria for specific veterinary product categories. These studies also should be conducted according to GCP principles.
4. Each individual involved in conducting a clinical study should be qualified by education, training, and expertise to perform their respective task(s). These individuals should demonstrate, in a manner that is evident from the study documentation, the highest possible degree of professionalism in the recording and reporting of study observations.
5. The relevant regulatory authority should provide procedures that independently assure that the study animals and the human and animal food chains are protected. The relevant regulatory authority should also assure that informed consent has been obtained from the owner of the study animals.
6. Studies covered by Good Laboratory Practice (GLP), basic exploratory studies or other clinical studies not intended to be used for regulatory support are not included in the scope of this guidance. However, data derived from safety and pre-clinical studies may be required to be submitted to the relevant regulatory authority in order that subsequent clinical studies may be properly authorized prior to commencement.
7. Wherever possible, investigational veterinary products should be prepared, handled and stored in accordance with the concepts of good manufacturing practice (GMP) of the relevant regulatory authorities. Details of preparation, handling and storage of investigational veterinary products should be documented and the products should be used in accordance with the study protocol.
8. The assurance of quality of every aspect of the study is a fundamental

component of sound scientific practices. The principles of GCP support the use of quality assurance (QA) procedures for clinical studies. It is perceived that the sponsor would be the party responsible for the QA functions for these studies. All participants in clinical studies are encouraged to adopt and adhere to generally recognized sound QA practices.