Regulatory Aspects of Clinical Trials in Malaysia

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OUTLINE

- Introduction
- Guidelines and Legal Requirements
- Application Process
- Audit and Inspection
Objectives of Clinical Trial Assessment

- Adequate disclosure of potential risks
- CMC is acceptable
- Data integrity
- Societal benefits from trial
- Ethics review
- Regional & international guidelines
- Trial has Scientific merit
- Protection of Clinical Trial Subjects
Note These statistics are based on the number of applications received by National Pharmaceutical Control Bureau for the clinical trial import license for unregistered products. Drug-related clinical trials for registered products which do not require clinical trial import license is not controlled by the Drug Control Authority.
PHASES OF CLINICAL TRIALS CONDUCTED IN MALAYSIA
(excluding bioequivalence studies)

Note  These statistics are based on the number of applications received by National Pharmaceutical Control Bureau for the clinical trial import license for unregistered products. Drug-related clinical trials for registered products which do not require clinical trial import license is not controlled by the Drug Control Authority.
No. of CTs Conducted by Therapeutic Class
(2003-2008)

Note: OTHERS: Hormone therapy, perfusion solution and endotoxin neutralizing agent.

These statistics are based on the number of applications received by National Pharmaceutical Control Bureau for the clinical trial import license for unregistered products.

Drug-related clinical trials for registered products which do not require clinical trial import license is not controlled by the Drug Control Authority.
PHASES OF CLINICAL TRIALS CONDUCTED IN MALAYSIA IN 2008 (excluding Bioequivalence Studies)

- Phase I: 29% (20 trials)
- Phase II: 4% (3 trials)
- Phase III: 4% (3 trials)
- Phase IV: 63% (43 trials)

Note: These statistics are based on the number of applications received by National Pharmaceutical Control Bureau for the clinical trial import license for unregistered products. Drug-related clinical trials for registered products which do not require clinical trial import license is not controlled by the Drug Control Authority.
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Guidelines and Legal Requirements

- Malaysian Guidelines for GCP (Updated 2004, NPCB website)
- Guidelines for Application of CTIL and CTX in Malaysia (updated, NPCB website).
The Guidelines should be read together in accordance to the legal requirements of.....

- Control of Drugs and Cosmetics Regulations 1984
- The Poison Regulations (Psychotropic Substances) 1989
- Sale of Drugs Act 1952

where controlled substances are involved
In the Malaysian Guidelines for GCP

1.55 Regulatory Authorities :-
are bodies having the power to regulate,
includes the authorities
■ that review submitted clinical data
■ that conduct inspection
( Competent Authorities )

1.26 Drug Control Authority (DCA)
■ An authority established for the purpose of
regulating the Control of Drugs and Cosmetics
Regulations, 1984
The members are:

- the director-general of health (chairman)
- the director of pharmaceutical services (alternate chairman)
- the director of the National Pharmaceutical Control Bureau
- 7 other members appointed by the Minister of Health
1984

THE DRUG CONTROL AUTHORITY (DCA)

………The 7 other members appointed by the Minister of Health are:

- a consultant physician in the public service;
- a pharmacist in the public service;
- 3 persons from any local universities with expertise in the pharmaceutical sciences; and 2 fully registered medical practitioners.
DCA’s Mission

- DCA has a broad public protection mission
  - Ensure the safe use of regulated products that are themselves safe and efficacious
  - Underlying this mission is DCA decision-making on product applications and labeling
  - Based on complete and accurate information from well-designed, ethically-conducted, and well-monitored clinical research
DCA’s Mission in Clinical Trials/Research is Also Broad

- Ensure Implementation of Good Clinical Practice (GCP) Standards
  - GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects
  - GCP embraces trial objectives, trial design, study oversight, data collection and quality assurance, study analysis, as well as human subject protection in studies that support product applications
Control of Drugs and Cosmetics Regulations 1984 (Revised 2006).
Regulation 2

- **Definition of Product**
  (a) a drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose;"
(b) a drug to be used as an ingredient for a preparation for a medicinal purpose; or

(c) a cosmetic
Control of Drugs and Cosmetics Regulations 1984 (Revised 2006)

Part III Registration and Licensing

Regulation 7. Prohibition against manufacture, sale, supply, importation, possession and administration

(1) No person shall manufacture, sell, supply, import or possess or administer any product unless

(a) the product is a registered product; and
(b) the person holds the appropriate licence required and issued under these Regulations
Regulation (15) Exemptions

Regulation 15(5) : Clinical Trial Exemption (CTX)

“Any person who wishes to manufacture any products solely for the purpose of producing samples for registration/clinical trials under these Regulations may on application be exempted by the Authority from the provisions of regulation 7(1).”
Control of Drugs and Cosmetics Regulations 1984

Regulation 12(1)(c): Clinical Trial Import Licence (CTIL)

A Clinical trial import licence in Form 4 in the Schedule,

- authorising the licensee to import any product for purposes of clinical trials,
- notwithstanding that the product is not a registered product
Control of Drugs and Cosmetics Regulations 1984

Regulation 30. General Penalty

(1) Any person who contravenes any of the provisions of these Regulations or any condition of any licence issued under these Regulations or any condition subject to which a product is registered under these Regulations commits an offence.
Contravention of Control of Drugs and Cosmetic Regulations 1984

- The penalty comes under parent acts Section 12, Sale of Drug Acts 1952 (Revised 1989)
Section 12(1) Sale of Drug Acts 1952 (Revised 1989)

“Any person who commits an offence against this Act or any regulation made under this Act for which no penalty is expressly provided shall be liable on conviction to a fine not exceeding RM 25000 or to imprisonment for a term not exceeding three years or to both, and for a second or subsequent offence he shall be liable on conviction to a fine not exceeding RM 50,000 or to imprisonment for a term not exceeding five years or to both.”
Section 12(2) Sale of Drug Acts 1952 (Revised 1989)

“Any body corporate who commits an offence against this Act or any regulation made under this Act for which no penalty is expressly provided shall be liable on conviction to a fine not exceeding RM 50,000, and for a second or subsequent offence it shall be liable on conviction to a fine not exceeding RM100,000.
Current Legal Provisions

- Weakness - No legal provisions addressing the Conduct of Clinical Trial

- Administrative provisions through Guidelines – not legal documents

  Malaysia GCP Guidelines for non-compliance
  5.20.3 The DCA will enforce the rules and punitive action will be decided by the DCA
Regulation 29. Directions

(1) The Director of Pharmaceutical Services may issue written directives or guidelines to any person or a group of persons as he thinks necessary for the better carrying out of the provisions of these Regulations and in particular relate to-

(l) clinical trials or

(2) Any person to contravenes any directives or guidelines issued by the Authority under subregulation (1) commits an offence.
CTIL and CTX Application

CTIL Application
- For unregistered products.
- Product when used or assembled (formulated or packaged) in away different from the approved form.
- Form BPFK 442.4
- Fees : RM 500 for each product
- Licence A for Poisons (where applicable)
- DCA approval based on:-
  - approval from IRB/IEC
  - complete information on investigational products

CTX Application
- For unregistered products-manufactured locally.
- Form BPFK 443.1
- Fees : Free of charge
- Licence A for Poisons (where applicable)
- DCA approval based on:-
  - approval from IRB/IEC
  - complete information on investigational products
CTIL and CTX Requirements

Who can apply?
- Principal Investigator (PI) or
- An authorized person from a locally registered pharmaceutical company (sponsor)

Details Required
- Annex A- Clinical Trial Protocol
- Annex B- Pharmaceutical Data
- Annex C- Investigator Brochure

* CTIL/CTX containing a ‘Scheduled Poison, should be made by a licence A holder
The holder of CTIL/CTX need not necessarily conduct the clinical trial himself/herself.

The PI / Sponsor is allowed to submit parallel application to the DCA and IEC.

A CTIL will not be issued prior to IEC approval.
Requirements

Annex A- Clinical Trial Protocol

- Name and dosage form of product
- Title and aim of the trial
- Description of the trial design
- Description of the subjects
- Treatment profile
- Operational aspects
- Adverse events
- Evaluation of results
- Approval by the principal investigator of the institution(s) where the clinical trial is to be done.
Requirements

- **Annex B - QUALITY** data of the investigational product
  - GMP statement from manufacturing / Certificate from Regulatory body
  - Certificate of analysis
  - Stability data (storage conditions)
  - Manufacturing data & formulation
  - Product labeling (coded & labeled: blinding)
Requirements

- **Annex C - SAFETY** data of investigational product
  - Non-clinical studies
  - Pharmacology; PK/PD studies
  - Toxicology studies

- Marketing Experience, PSUR, product status
- Risks and ADR anticipated

(Contents of the Investigator’s Brochure – Annex C)
Requirements

- **Annex C - EFFICACY** data of the investigational product
  - PK/PD Studies in human
    - in-house preliminary data
    - summaries of trials conducted (Phase I, II, III)

(Contents of the Investigator’s Brochure-Annex C)

- published clinical data
Review process for approval of CTIL/CTX

Application

ETHICAL

NPCB (CTR Unit)

(preliminary review)

Drug Evaluation Committee

DCA

 Applicant
Responsibility of the applicant

- Responsible for the product and all information supplied for the CTIL/CTX application and updating the information
- If a service of CRO is used, a letter /authorization should be submitted to DCA
- Any person who knowingly supplies any false or misleading information in connection with his application for CTIL/CTX commits an offence under Control of Drugs and Cosmetics Reg.1984
Clinical Trial Approval

- A requirement in many countries
- Procedure varies
- Legislation vs non legislation
Factors affecting approval

The speed of approval depends on:-

- How complete is the information submitted?
- How fast sponsor/ PI respond to queries ?
- Adherence to established procedures
- Ethical Approval
TIMELINE FOR APPROVAL in MALAYSIA

- EC, MOH                     6-8 wks
- Universities                4-8 wks
- National Heart Inst         3-6 wks
- DCA                         4-8 wks

*Note: Parallel submission to DCA & EC is allowed*
Conditions for CTIL/CTX in the Guidelines for Application of CTIL/CTX in Malaysia

- CTIL Valid for 3 years (Regulation 12(5) of the CDCR 1984)
- Endorsement of CTIL/CTX-evidence of importation & delivery of the product to the investigator(s)
- Reporting of SAE/SUSAR
- Changes of Information
Discontinuation of trial with reasons. CTIL/CTX should be returned

End of Study Summary, Interim & Final Study Report

Drug Accountability/Disposal
Records/document: shipment, receipt
- System for retrieving and documentation
- System for the disposition of unused investigational products

Archiving
- Responsibility of the investigator and the sponsor to archive safely all documents related to the trial
Audit & Inspection

5.19 of M’sian GCP Guidelines.

- By the local Regulatory Authority
- External Regulatory Authorities
  e.g.: FDA, USA
  EMEA, Europe
Audits and inspections

- Audit versus Inspection
  What is the difference?
1.7 What is an Audit?

- A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data recorded, analyzed, and accurately reported according to the protocol, sponsor’s SOPS, GCP, the applicable regulatory requirement(s).
1.34 What is an inspection?

The act by regulatory authority (ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or Contract Research Organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authority (ies).
Audits and Inspections

- Audits = Sponsor function
- Inspections = Regulatory function

Generally, sponsor audits are conducted along similar lines to a regulatory inspection
Aims of regulatory inspections:

- To ensure the rights and safety of study subjects have been protected.
- To determine the validity of the data submitted to the regulatory authority.
- To assess adherence to GCP guidelines and regulations.
- To assure the integrity of scientific testing and study conduct.
Definition of Fraud (1)

- Three general types of fraud:
  - **Altered Data**
    Generating biased data or changing data is legitimately obtained.
  - **Omitted Data**
    Not reporting data which has an impact on the study outcome
    - removing subjects from study population during analysis
    - not reporting or disguising adverse events
Definition of Fraud (2)

- Manufactured Data
  - Fabricating information or creating results without performing the work
    * Filing in data in CRFs when work not done
    * Photocopying data and using it for multi subjects
    * Creating fictitious subjects
Examples of known or suspected misconduct in the United Kingdom

- 1994 Paul Daengsvang Case
  - a general practitioner in Liverpool
Fact of the case

- In 1990 and early 1991, Cilag Ltd recruited several GPs including Dr. Paul Daengsvang to conduct multicentre phase II/III clinical trial study entitled, “Double-blind study of efficacy and safety of noberastine in the treatment of perennial allergic rhinoconjunctivitis”

- The trial was conducted to standards of GCP, and included an assessment of haematology and biochemistry. Patients were required to complete diary cards.
In the agreement, he would be paid £150 per patient who completed the study.

He recruited patients so quickly that he requested, and was granted, facilities to recruit an additional 10 patients.

The trial collected CRF and the returned record form raised suspicion because of the uncommon cleanliness of the patient diaries and “the perfection” of the study data.

A comparison was made with the progress and results in the other centres taking part in the study.
A site audit was carried out and found:

- Using real patients as phantom subjects in the trial, possibly requiring some of them to have unnecessary blood tests
- Using post-treatment blood samples taken from patients different from those at entry to the study
- Tempering with NHS records so as to provide spurious source document verification
- Completing some of the patient diaries himself
- Generating false data on certain case report
The Professional Conduct Committee of GMC found that there was a serious professional misconduct.

His name was erased from the medical register.
FDA Case Study #1: Impact of Inspection

Drug X in Long-Term Treatment of Condition Y

- Objective of the study to test the efficacy of drug X in outpatients when compared to placebo, as measured by the number of days until relapse
- Basis for site selection: site Eastern Europe showed a significant treatment response
FDA inspectional findings: there were in-patient hospitalizations for 24 subjects out of 35 subjects enrolled.

DSI recommended to review division to reject data from this site
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Disclaimer

FDA/Center for Drug Evaluation and Research
Office of Compliance
Division of Scientific Investigations
Update Frequency: Quarterly
Database Last Updated: October 2, 2009
Clinical Investigator Inspection List

Database Code Definitions

The following codes occur in the CLIL database: Classification, Deficiency, and Inspection Type. Some codes are no longer being used, but they still appear in the database.

Classification Codes

- MTF - Case closed with a Memo to File
- NAI - No Action Indicated. No objectionable conditions or practices were found during the inspection.
- VAI - Voluntary Action Indicated. Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.
  - VAI1 - Correction made on site
  - VAI2 - No response requested
  - VAI2C - Consent problems found
  - VAI3 - Response requested
  - VAI3C - Case closed
  - VAI3F - Follow-up for cause inspection issued
  - VAI3R - Response received and accepted
  - VAI3RC - 30-day response requested and case closed
  - VAI3RR - 30-day response requested, received and accepted
  - VAI4R - 30-day response requested
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THANK YOU