Introduction to Good Clinical Practice (GCP)

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Introduction to GCP

- Drug development
- What is GCP?
- A bit of history.
- Principles of GCP
- Conducting GCP compliant trial
- Malaysian GCP

Drug Development

The process of
- Discovering therapeutically useful compound
- Synthesizing and producing the compound
- Formulating it into usable form
- And finally, obtaining reliable and credible information on its administration (dosing), safety and efficacy.

Drug development is complex & costly

<table>
<thead>
<tr>
<th>Time, years</th>
<th>1960s</th>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost, USD million</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>500</td>
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Drug development is a step-wise process

- Pre-development
  Discover and synthesize new compound (NCE), understand its action, and assess its potential as a drug
- Development
  Provide information to support registration
  Pre-Clinical phase
  Clinical phase: Phase 1, Phase 2, Phase 3

Development: Pre-Clinical Phase

<table>
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<tr>
<th>Type of study</th>
<th>Objectives</th>
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| Pre-clinical studies in animals | • Toxicity studies: characterization of toxic effects
• Safety pharmacology studies: dose dependence, reversibility
• Pharmacokinetics studies: ADME |
| Quality | Characterization of formulations to be used |
### Development: Clinical Phase

| Phase 1 Human pharmacology | • Assess tolerance  
• PK and PD  
• Drug metabolism  
• Estimate activity |
|---------------------------|--------------------------------------------------|
| Phase 2 Therapeutic exploratory | • Explore use for targeted indication  
• Estimate dosage for subsequent studies  
• Basis for confirmatory study design |
| Phase 3 Therapeutic confirmatory | • Demonstrate efficacy  
• Establish safety profile  
• Basis for benefit/risk assessment & registration  
• Dose-response relationship |
| Phase 4 Therapeutic use | • Refine risk-benefit ratio  
• Special populations  
• Uncommon ADR  
• Refine dose  
• (New indication) |

### What is GCP?

**Good Clinical Practice (GCP)**

An international ethical and scientific quality standard for the design, conduct, performance, monitoring auditing, recording, analysis and reporting of clinical trials involving the participation of human subjects.

Compliance with this standard provides public assurance:

1. That the rights, safety, integrity, confidentiality and well being of trial subjects are protected consistent with the principles that have their origin in Declaration of Helsinki.
2. That the data and reported results are credible and accurate.

### GCP guidance documents

- FDA guidelines for sponsors and investigators in 1970s
- European Union GCP guidelines 1980s
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) started 1991

### History and Development

GCP and other rules on human research in drug development have now been formalized in many international and national guidelines and regulations.

- FDA guidelines for sponsors and investigators in 1970s
- European Union GCP guidelines 1980s
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### Aims of ICH

1. Unify registration requirements for new products
2. Reduce medicinal product development costs: more economical use of animal, human and material resources.
3. Accelerate medicinal product licensing times: avoid repeat testing in different regions.
4. Increases patent protection times through reducing delay in licensing times.
ICH Sponsors and Regions

EMEA: The European Commission
EFPIA: European Federation of Pharmaceutical Industries Association
FDA: CDER & CBER
PhRMA: Pharmaceutical Research and Manufacturers of America
JMHW: Japanese Ministry of Health and Welfare
JPMA: Japanese Pharmaceutical Manufacturers Association

GCP adoption in the Asia Pacific Region

- Original ICH GCP 1996
- Since then:
  - Singapore GCP 1998
  - Chinese GCP 1999
  - Thailand 2000
  - Indonesia 2001

Further ICH Structures

ICH Secretariat
- Provided by IFPMA

ICH Steering Committee
- Representatives from each ICH sponsor
- Observers from
  - WHO
  - CHPB
  - EFTA

ICH Process

Selection of topic (Concept Paper)

STEPS
1. Expert Working Group draft
2. Regulatory Consultation
3. Regulatory Final Draft
4. Steering Committee: recommendation for adoption
5. Incorporation of Guideline

2. THE PRINCIPLES OF ICH GCP

2.1 Trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and regulatory requirement(s).

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

2. THE PRINCIPLES OF ICH GCP - cont

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

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

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
2. THE PRINCIPLES OF ICH GCP - cont

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

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

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

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

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

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

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

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

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GCP rules of conduct

Subsequent chapters elaborate on these principles to provide a set of rules of conduct for trial:

3. IRB/IEC
4. Investigator's responsibilities
5. Sponsor's responsibilities
6. Trial protocol
7. Investigator's brochure
8. Essential documents

Conducting GCP compliant clinical trial

GCP compliant trial is a difficult and complex undertaking, but is necessary to protect subject and assure data quality.

This workshop is to help you conduct GCP compliant trial.

Malaysian Good Clinical Practice (MGCP)
• Launching of Malaysian GCP Guidelines - Oct 1999
• Objective is to ensure drug related trials in Malaysia are conducted in accordance with international ethics and scientific standards
• Based on ICH-GCP Guideline with modifications to suit local requirements

Some of the differences from the ICH GCP and amendments made are as follows:

1.6 Approved Training in Good Clinical Practice
Training which is approved by the National Committee for Clinical Research (NCCR). The content of the training must incorporate the co-curriculum as stipulated by the committee

• 1.13 Clinical Trial Exemption (CTX)
An approval by the DCA authorizing the applicant to manufacture any local product for the purpose of clinical trial.

• 1.14 Clinical Trial Import Licence (CTIL)
A license in Form 4 in the schedule of The Control of Drugs and Cosmetics Regulations of 1984, authorizing the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product.
1.26 **Drug Control Authority**

A regulatory authority established for the purpose of regulatory control of drugs and cosmetics regulations, 1984

1.29 **Herbal /Animal Medicinal Products**

Plant/animal-derived materials or products with therapeutic or other human health benefits which contain either raw or processes ingredients from one or more plants/animals.

1.38 **Investigational Product**

A pharmaceutical form of an active ingredient including plant/animal derived medicinal products 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 (off-label use), or when used to gain further information about an approved use.

1.46 **National Committee for Clinical Research (NCCR)**

A committee established for the purpose of coordinating and promoting clinical research in Malaysia, chaired by the Deputy Director of Health (Research & Technical Support), MOH

**CRC**

**Investigator**

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

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 (a)-(u):

4.8.10 (u) The source of the investigational
product that may be culturally
unacceptable.

Investigator

4.8.9 If a subject is unable to read or if a legally
acceptable representative is unable to read, an
impartial witness should be present........ ............
the subject or the subject's legally acceptable
representative orally consented to the subject's
participation in the trial and, if capable of doing
so, has signed and/or thumbprinted and
personally dated the informed consent form, the
witness should sign and personally date the
consent form.

Investigator

4.11.1 All serious adverse events (SAEs) detected or
being notified should be reported within 2 working days
to the sponsor except for those SAEs that the protocol
or other document (e.g., Investigator’s Brochure)
identifies as not needing immediate reporting. The
immediate report should be followed within 7 days
by detailed, written report. The investigator must comply
with the applicable regulatory requirement(s) related to
the reporting of unexpected serious adverse drug
reactions to the regulatory authority(ies) and IRB/IEC

Investigator

5.6.1 The sponsor is responsible for selecting the
investigator(s)/institution(s). Each
investigator should be qualified by training
(including approved GCP training) and should
have adequate resources to properly conduct
the trial for which the investigator is selected.

Investigator

5.8.1 If required by the applicable regulatory
requirement(s), the sponsor must provide
insurance or must indemnify (legal and
financial coverage) the investigator/
institution against claims arising from the
trial, except for claims that arise from
malpractice and/or negligence.

Investigator

5.14.2 The sponsor should not supply an
investigator/institution with the investigational
product(s) until the sponsor obtains all required
documentation (e.g. approval/favourable opinion
from IRB/IEC and regulatory authority(ies). All
importation of clinical trial drugs should go
through customs even though a clinical trial
import licence has been obtained.

Investigator

5.8.1 If required by the applicable regulatory
requirement(s), the sponsor must provide
insurance or must indemnify (legal and
financial coverage) the investigator/
institution against claims arising from the
trial, except for claims that arise from
malpractice and/or negligence.
5.20.3 The DCA will enforce the rules and punitive action will be decided by the DCA.