NON-CLINICAL STUDIES FOR HERBAL PRODUCTS

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Outline

- Introduction
- Definition
- Relevance in Drug Development
- Objective of the Study
- Safety Study
- GLP and Guidelines
- Conclusion
- Acknowledgement

Introduction

- **The used of herbal products becoming popular in various society.**
- **The popularity of most products are of consumer preference**
- **Allopathic professional still careful in considering the product in treatment unless product's evidence-based information on the preclinical and clinical studies is available.**

Definition

Preclinical/ non-clinical studies: in vivo & in vitro experiment which the product (test article) are studied prospectively under laboratory in elucidating the safety & efficacy of the product.

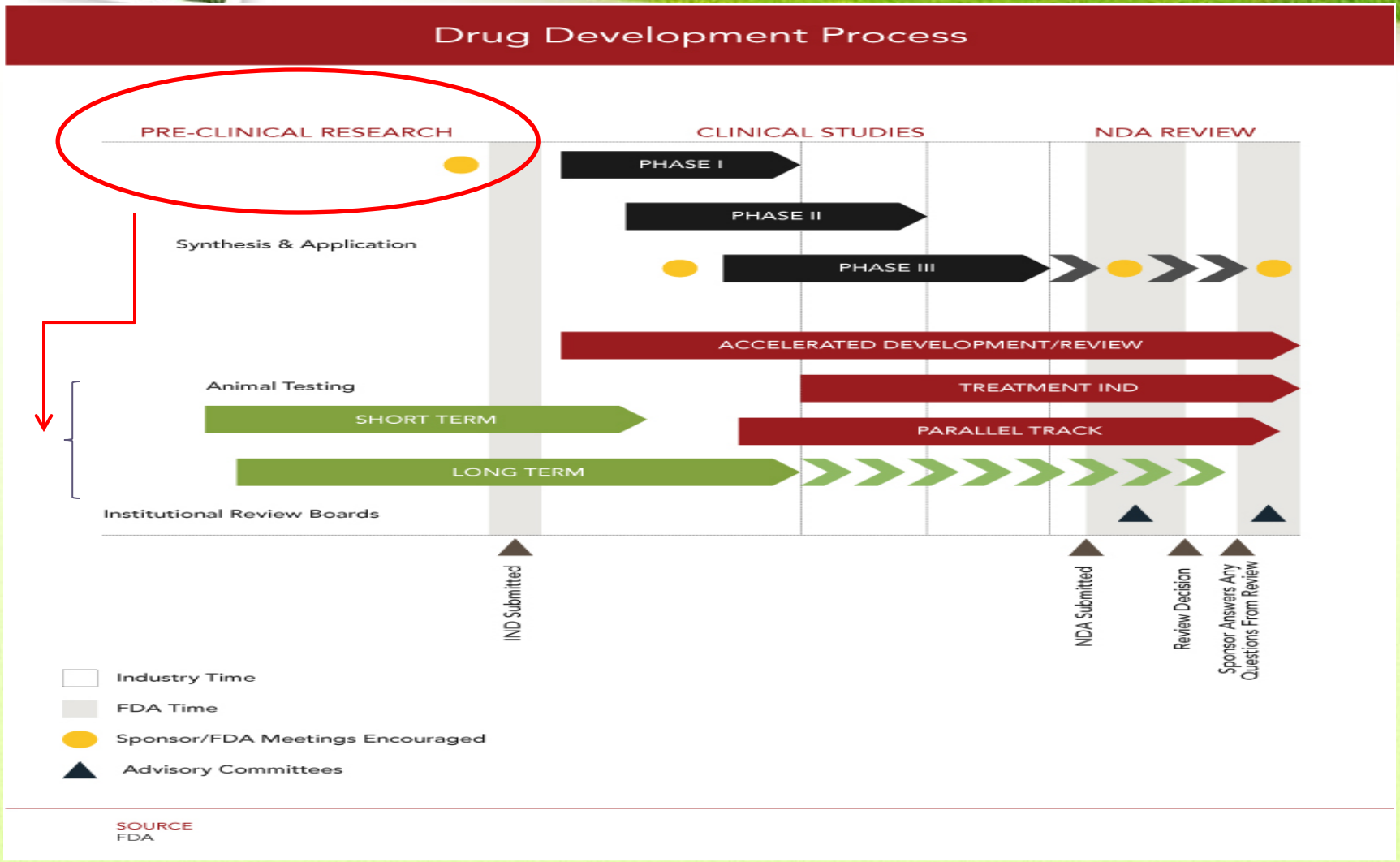
Non-clinical: Relevance in Drug Development

1. Identify the pharmacological properties (mode of action, metabolisme & comparative physiology)
2. Understand the toxicological profile (clinical trial, pre-clinical test)
3. Setting initial doses in humans
4. Identification of plausible adverse effects
5. Identification of reversible vs irreversible effects
6. Identification of useful biomarkers for monitoring toxicity during clinical trials
7. Drug labeling

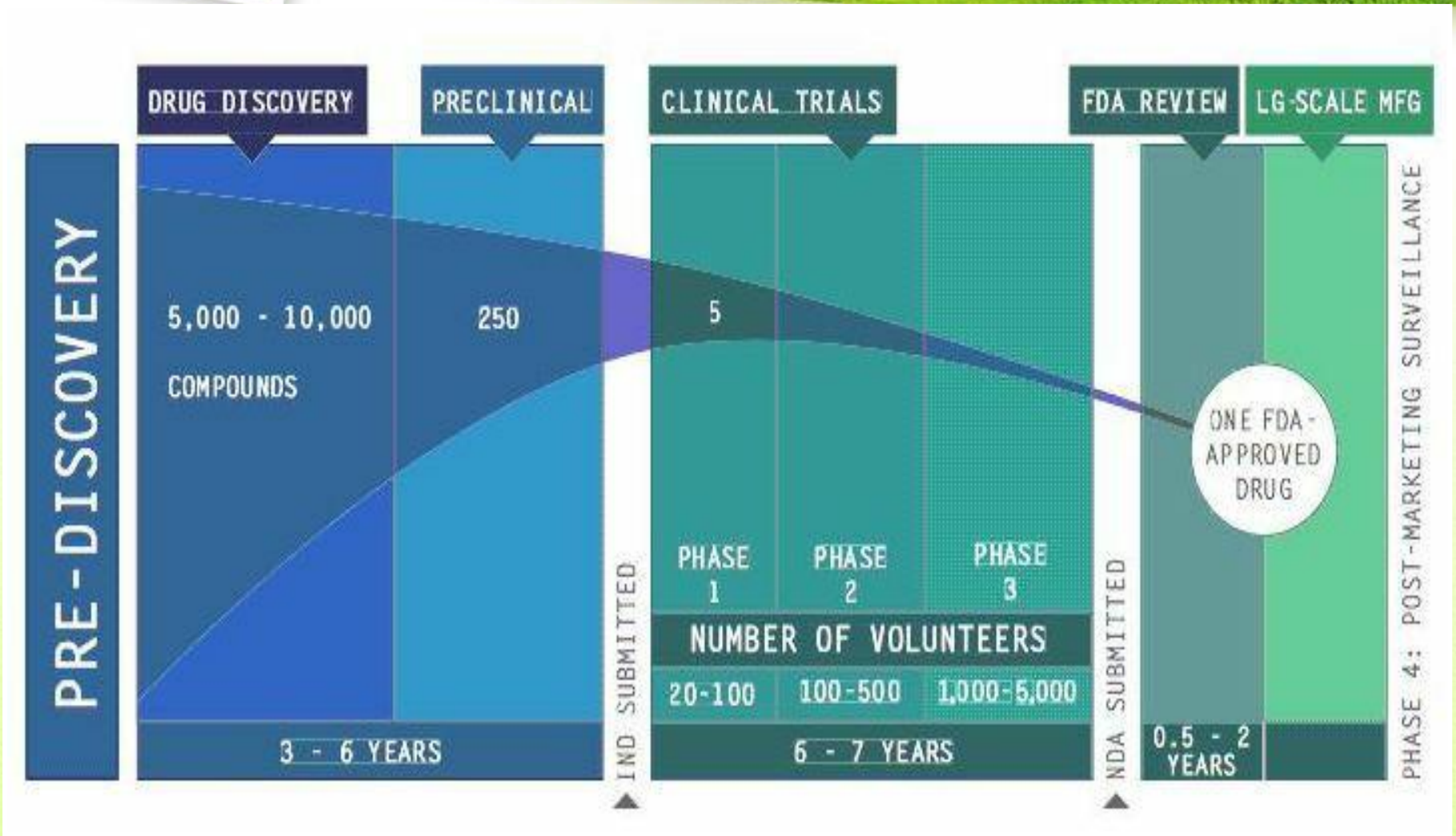
Objective

- **To prove the safety and efficacy of the products**
- **Allowing product go for higher claim**

Relationship in Drug Development Pathway



Relationship in Drug Development Pathway



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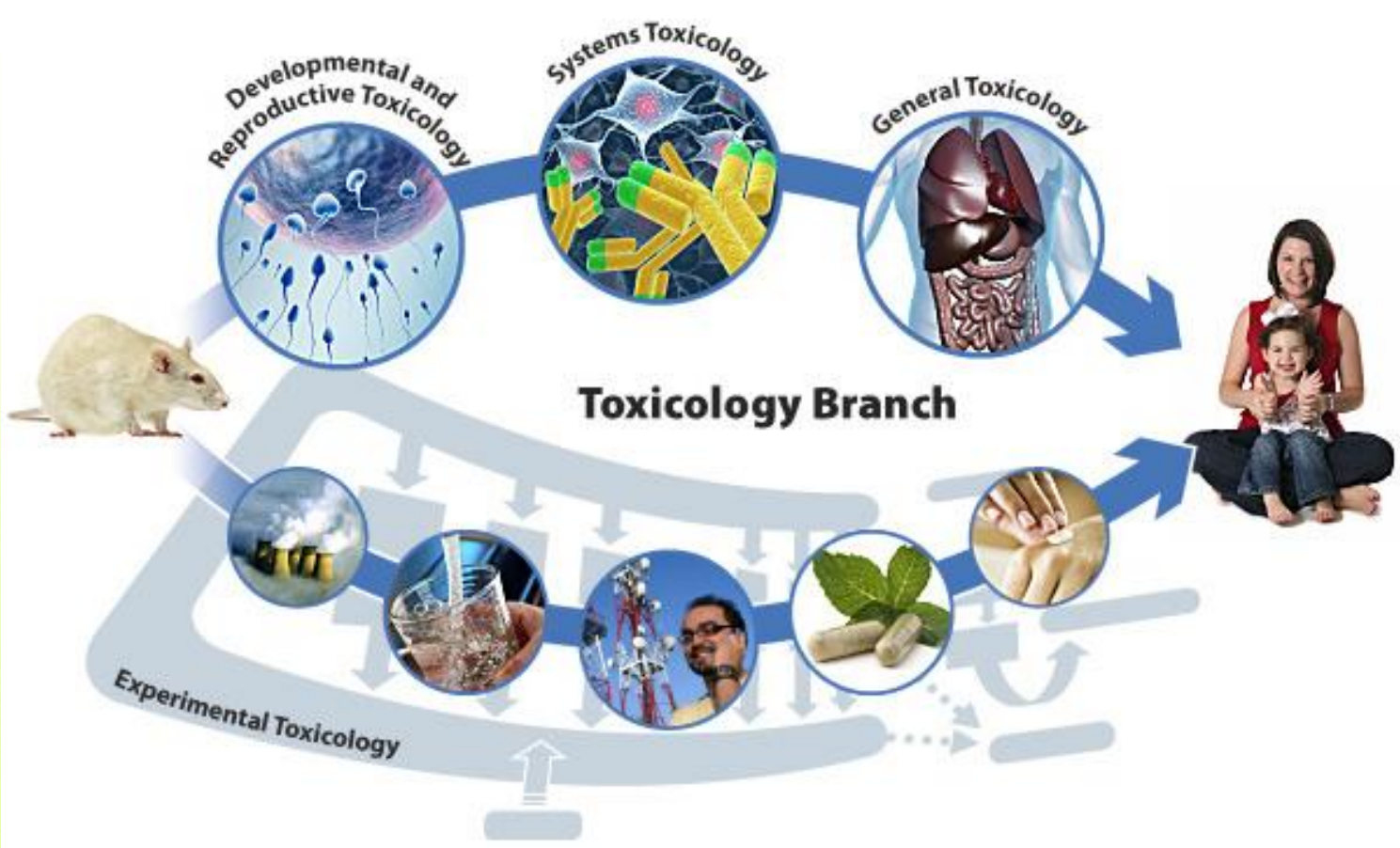
Non-clinical: Safety Study



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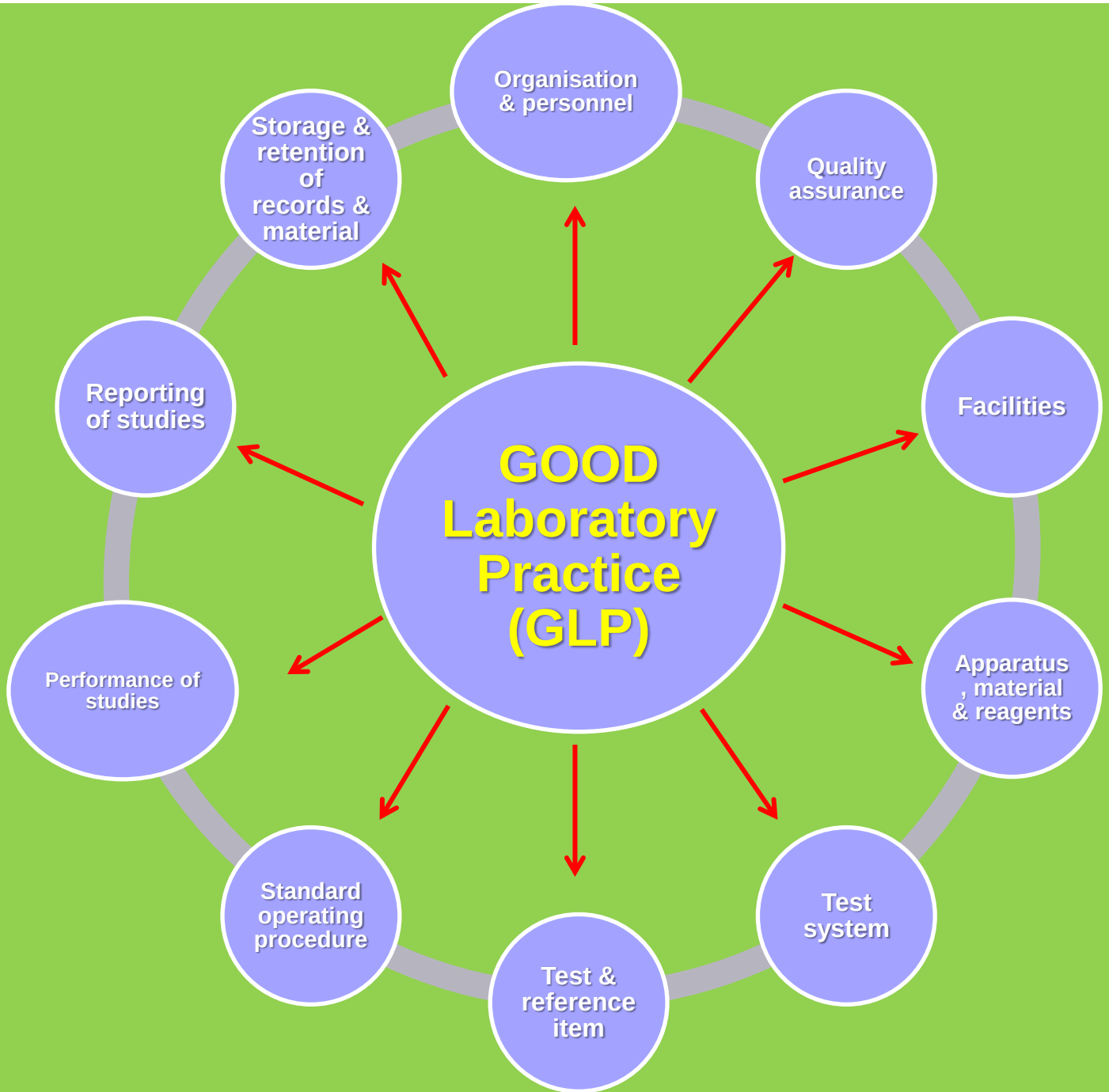
Non-clinical: Safety Study

- Safety study/pre-clinical toxicity studies is highly regulated and required to compliance with **Good Laboratory Practice (GLP).**

Non-clinical:GLP

Definition of GLP:

Quality system concerned with the organisational process and the conditions under which **non-clinical health and Environmental safety** studies are planned, performed, monitored, recorded, archived and reported.


GOOD Laboratory Practice (GLP)
Organisation & personnel
Quality assurance
Facilities
Apparatus , material & reagents
Test system
Test & reference item
Standard operating procedure
Performance of studies
Reporting of studies
Storage & retention of records & material

Organisation & personnel

Sponsor

Archivist

TFM

QA

Analyst

Study director

Veterinarian & assistant

Test item personnel

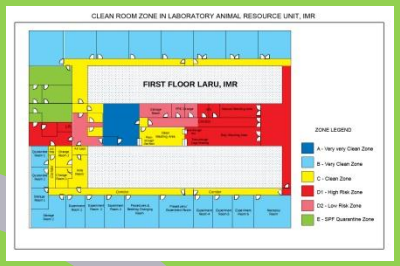
Facility personnel

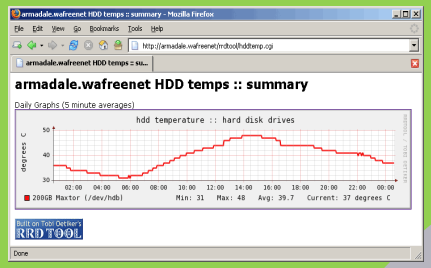
Quality Assurance

- Not involve with the study
- Perform 3 different Audit : Study, facility and processes
- State QA statement in study plan and final report

Facilities

Good separation





Monitored & controlled

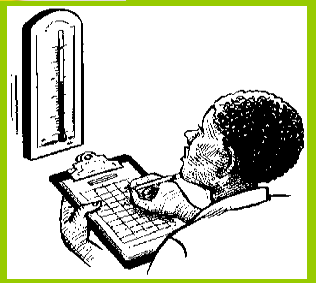
Suitable size, construction & location

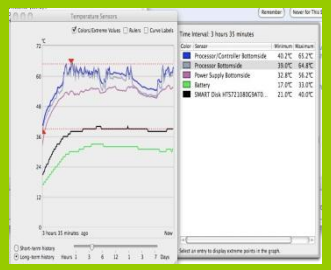
Comply to requirement

For every activity

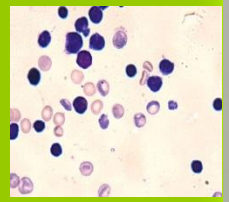
Apparatus , material and reagents

1. Suitable
2. Inspected
3. Clean
4. Maintain
5. Calibrated
6. Logbook





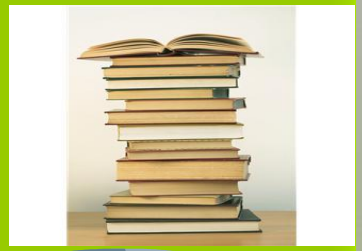
Test System

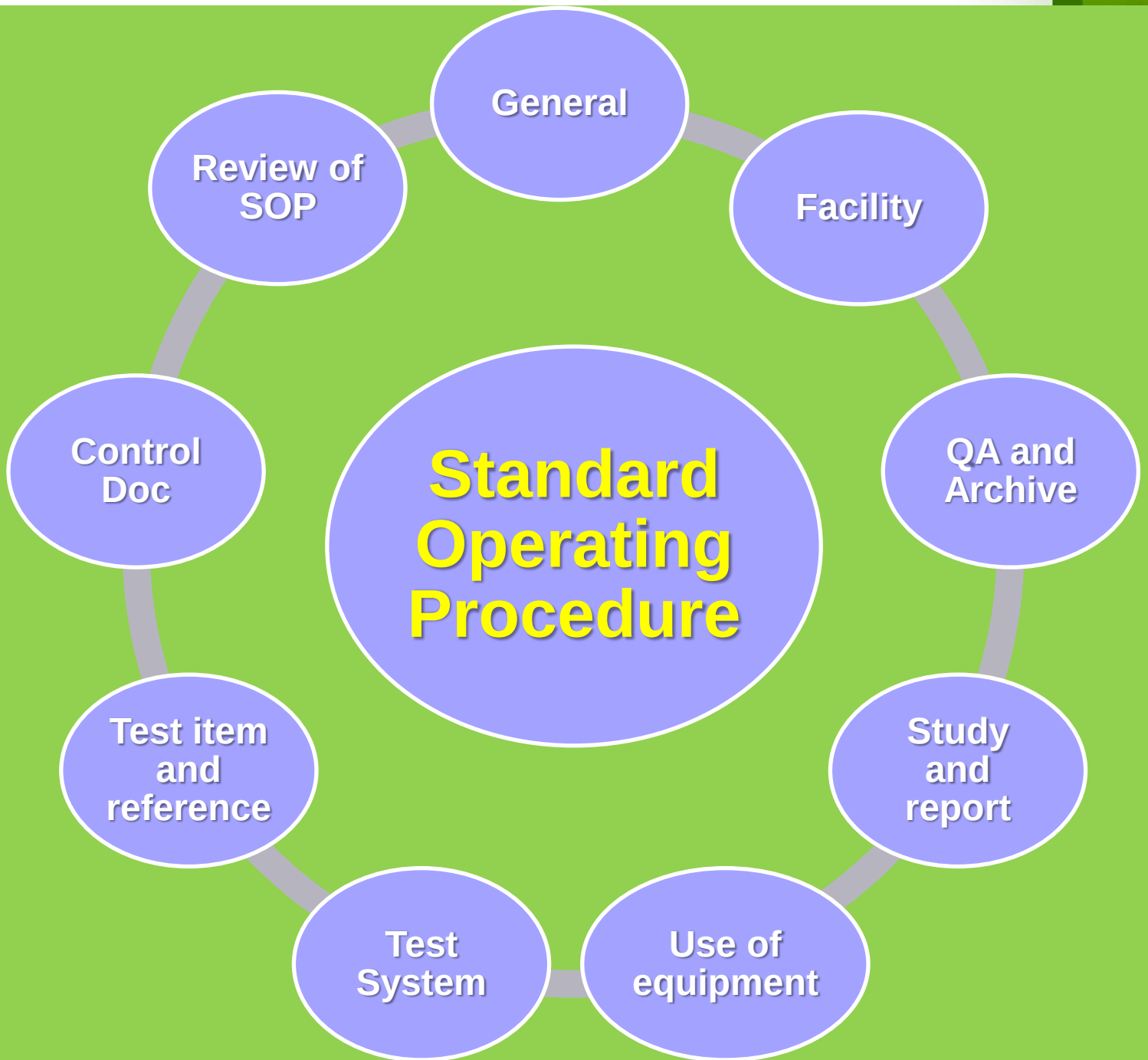


1. Animal - in vivo
2. Cell culture/ bacteria – in vitro
3. Record on source & condition
4. Proper identification and handling
5. Acclimatize and record
6. Proper housing and food & water
7. Record of observation Reporting of studies

Standard Operating Procedure

- **SOPs for all activities involve :**
  - **e.g. General, facility, QA, Archive, Study and Report, Use of Equipment**
- **Written, endorsed and used**
- **Controlled**
- **Reviewed periodically**



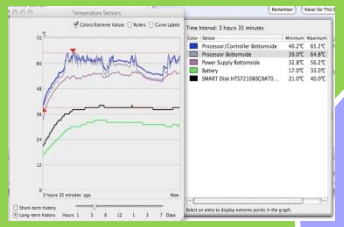

Standard Operating Procedure
General
Facility
QA and Archive
Study and report
Use of equipment
Test System
Test item and reference
Control Doc
Review of SOP

Characterisation ; composition, concentration

Achieve sample

Test & reference item

The amount /dossage



Storage condition

Route of administration

Stability

Performance of the Study

Study Director prepare the study plan & perform the study

- Appoint the study team
- QA statements on Study Plan
- Type of Study : Guideline No
- The important Dates
- Test item : COA and preparation
- Justification of the test system chosen
- Facility & Equipment requirement
- Observation and other data collection
- Item/records for Achieve

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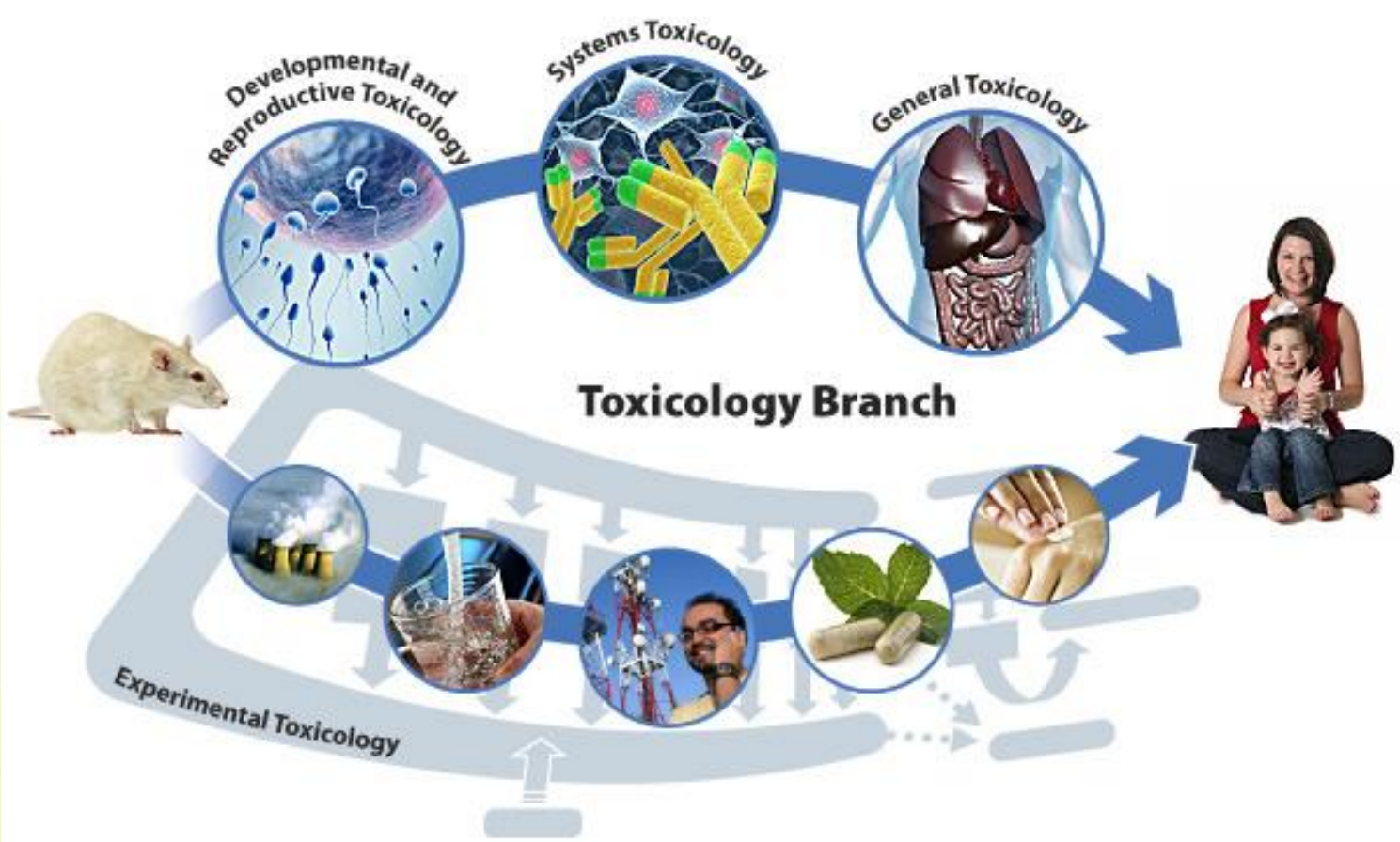
Reporting of studies
Study Director and team
ID of the Study
Statement from QA on GLP Compliance
Record of Amendment & Deviation
Test item : COA and preparation
Test system
Type of Study : Guideline No
The important Dates
Analysis of Data and discussion
Conclusion

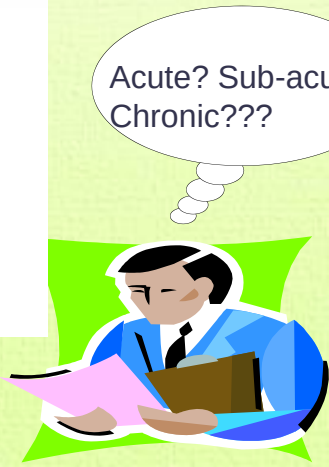
Archive

Storage & retention of records & material

- Designated place & Facility
- Proper condition & safe
- Disaster Recovery plan
- Security : physical, access
- Records of documents Retained
- Record of Material Retained
- Duration of keeping
- Database of the item kept
- Transfer & Retrieval
- Disposal

Non-clinical: Safety Studies





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Type of the Study : Determine by the regulator

- The type of product : nutraceutical/cosmetics/food supplement
- Proposed application : oral/topical
- The intended claim : low or Medium or high
- Regulatory requirement may vary from country to country
- With the membership of state/country to OECD or MAD community, data can be mutually accepted for the registration and marketing of the products to other countries

Guideline and regulation

A **guidance** and a **guideline** are the same.

- Provide direction and a course(s) of action
- Not legally binding
- Public comments are considered, but responses are optional

Regulation

- A rule or a law by which conduct is governed
- Legally binding
- Published through notice and rulemaking, e.g., CRF, FR
- Substantive public comments MUST be responded to in the preamble of the final rule

Non-clinical Studies Guidelines

Importance of guidelines

- Harmonisation, Consistency, Transparency
- Guidance to industry & assessors
- Guidelines
  - ICH (International Conference Harmonisation)
  - US – EPA (Environmental Protection Agency)
  - EMEA (European Medicine Agency)
  - OECD (Organisation for Economic Co-operation Development) Guidelines
  - WHO Guidelines

e.g : OECD Guidliens for Section 4 : Health Effect

Summary of Considerations in the Report from the OECD Expert Groups on Short and Long Term Toxicology

No.	Title	Original Adoption	No. of Updates	Most Recently Updated
401	Acute Oral Toxicity	12 May 1981	1	Date of Deletion: 20 December 2002
402	Acute Dermal Toxicity	12 May 1981	1	24 February 1987
403	Acute Inhalation Toxicity	12 May 1981	0	---
404	Acute Dermal Irritation/Corrosion	12 May 1981	2	24 April 2002
405	Acute Eye Irritation/Corrosion	12 May 1981	2	24 April 2002
406	Skin Sensitisation	12 May 1981	1	17 July 1992
407	Repeated Dose 28-Day Oral Toxicity Study in Rodents	12 May 1981	1	27 July 1995

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Non-clinical study

Type of studies reviewed by Regulators

- Basic pharmacology
- Safety pharmacology
- Pharmacokinetics
- Toxicology
- Genotoxicology
- Carcinogenicity

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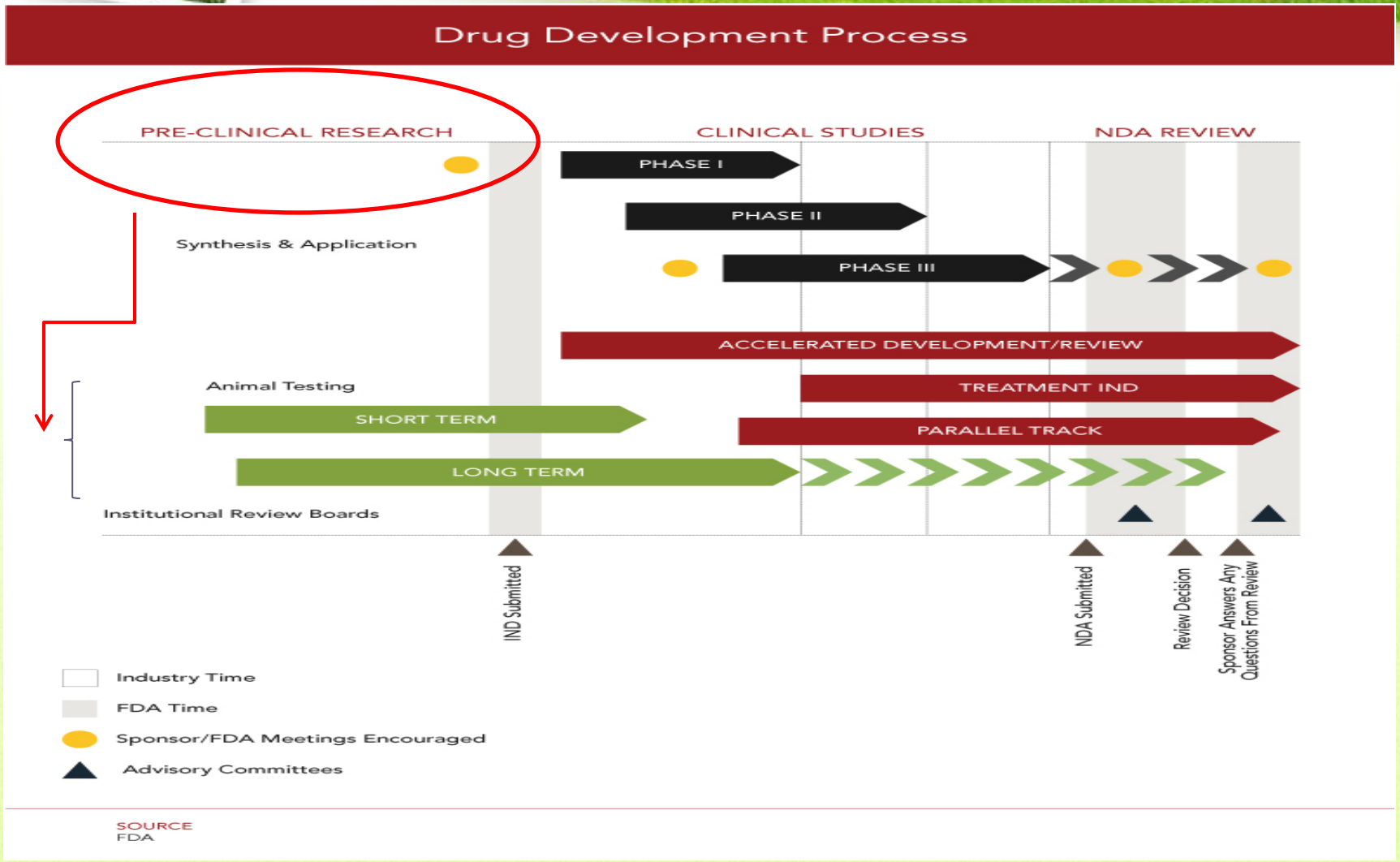
Relationship in Drug Development Pathway



Extend of the Study

Phase 1 and 2 :

- Phase 1-2 Clinical Trials
  - repeat dose toxicity studies of appropriate length
- Phase 2 Clinical Trials
  - complete genotoxicity assessment (*in vivo* and *in vitro*)
  - repeat dose toxicity studies of appropriate length

Extend of the Study

Phase 3 Clinical Trials

- repeat dose toxicity studies of appropriate length
- male and female fertility
- post-natal development

Extend of the Study

Prior to "First Time in Humans"

- safety pharmacology
- pharmacokinetics/toxicokinetics (exposure data)
- single dose toxicity studies in 2 mammalian species
- expanded acute or repeat dose toxicity studies in a rodent and a nonrodent
- local tolerance
- *in vitro* evaluation of mutations and chromosomal damage
- hypersensitivity for inhaled and dermal drugs
- teratogenicity studies

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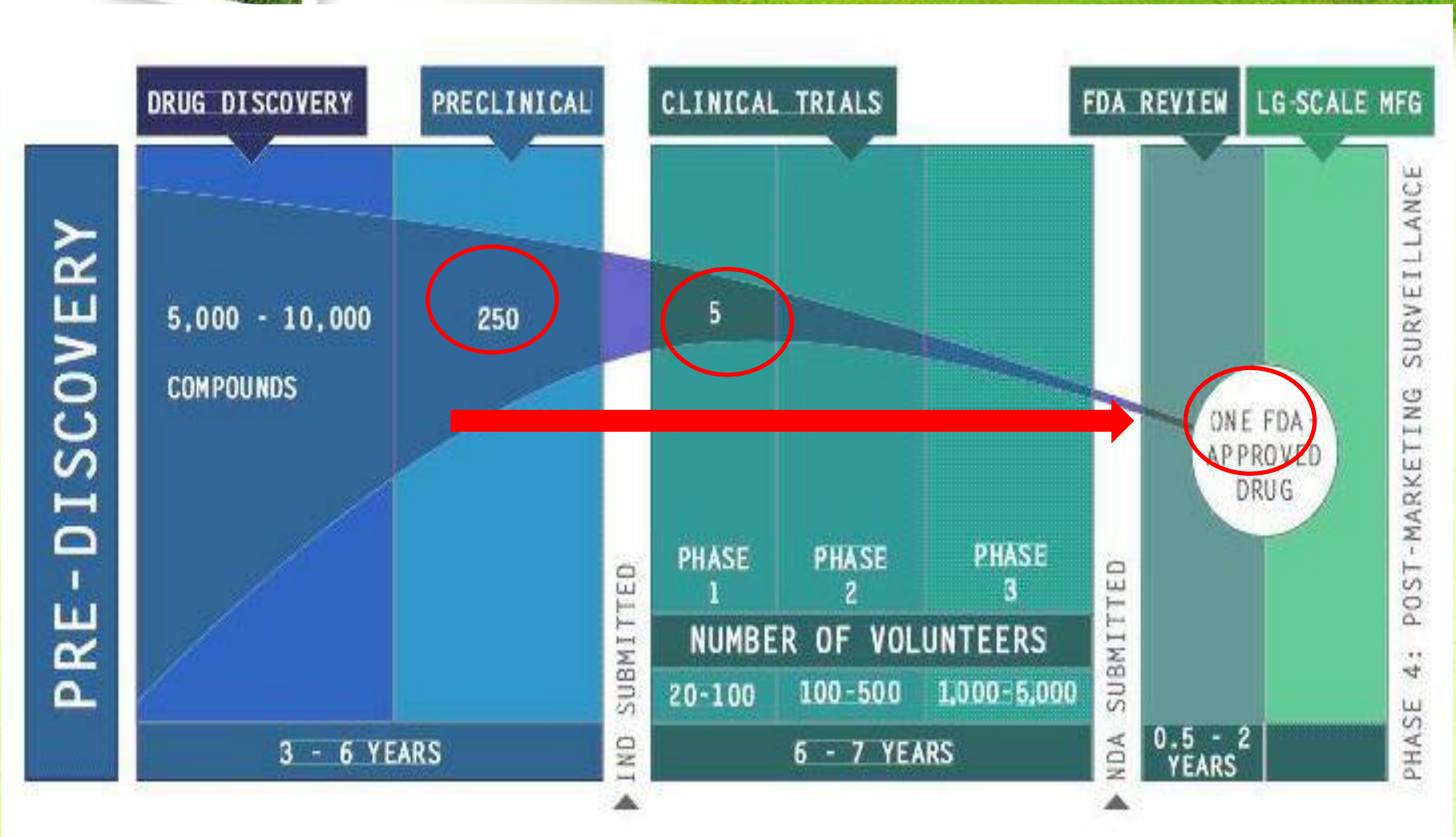
Relationship in Drug Development Pathway



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Conclusion

- Non-clinical studies for herbal medicine products is compulsory as it is one of the important phase in drug development
- Non-clinical and clinical studies determine the safety and efficacy of herbal medicine before being marketed as herbal medicine


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