GCP/GMP/GLP

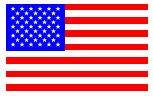
Module 7 Topic 3

Various regions of the world ...

Europe

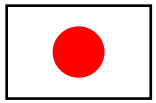
US

Japan



USA

European Union



Japan

Pharmaceutical Research & Manufacturers of America

European Federation of Pharmaceutical Industry Associates

Japanese Pharmaceutical Manufacturers Association

THIS LED TO…..

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH - GCP

- Established - 17th January 1997
- NOW APPLIED GLOBALLY

ICH GCP

Definition

“An international 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, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.”

The Principles of GCP as per the ICH

- Clinical trials should be conducted in accordance with the ETHICAL PRINCIPLES that have their origin in the **Declaration of Helsinki**
- A trial should be initiated only if the anticipated benefits justify the risks
- The rights, safety and well-being of the trial subjects **are the most important considerations**
- Trials should be scientifically sound and described in a clear and detailed protocol
- The protocol must have received **prior** approval from the Ethics Committee or IRB

The Principles of GCP as per the ICH

Contd…

- The medical care of patients must always be the responsibility of a **qualified physician**
- Each individual involved in the trial must be qualified by education, training or experience to perform his/her task
- **Freely given** informed consent must be obtained from every subject **prior** to the trial
- All clinical trial information should be recorded in a way that allows its accurate reporting, interpretation and **verification**

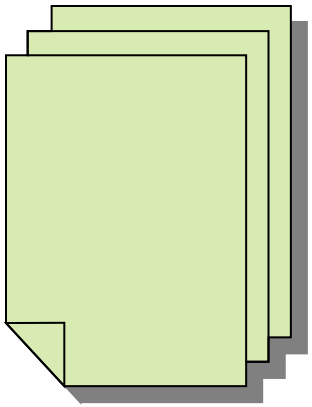
The Principles of GCP as per the ICH

Contd…

- The **confidentiality of the subjects** (patients) should be protected at all times
- All investigational products should be manufactured, handled and stored in accordance with **good manufacturing practices** (GMP)
- All products should be used only in accordance with the **approved protocol**
- Systems that **assure quality** should be implemented at all levels

Documentation

- Key to all successful studies.
- Allows verification of quality and integrity.
- Is a must for GCP compliance:
  - Paper (audit) trail
  - Filing
  - Archiving



As per ICH - GCP:

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

Commandments of Documentation

- If it happens write it down
- Use version numbers and dates
- Establish a good filing system (SOP)
- File so as to retrieve, not retain
- Use Fade free paper
- Retain and archive all data
- Hard copy of computer information
- Ensure controlled access

Standard Operating Procedures

- standardization & uniformity
- instructions & procedures
- clear, concise, practical SOPs
- for documentation, filing and archiving

Remember…

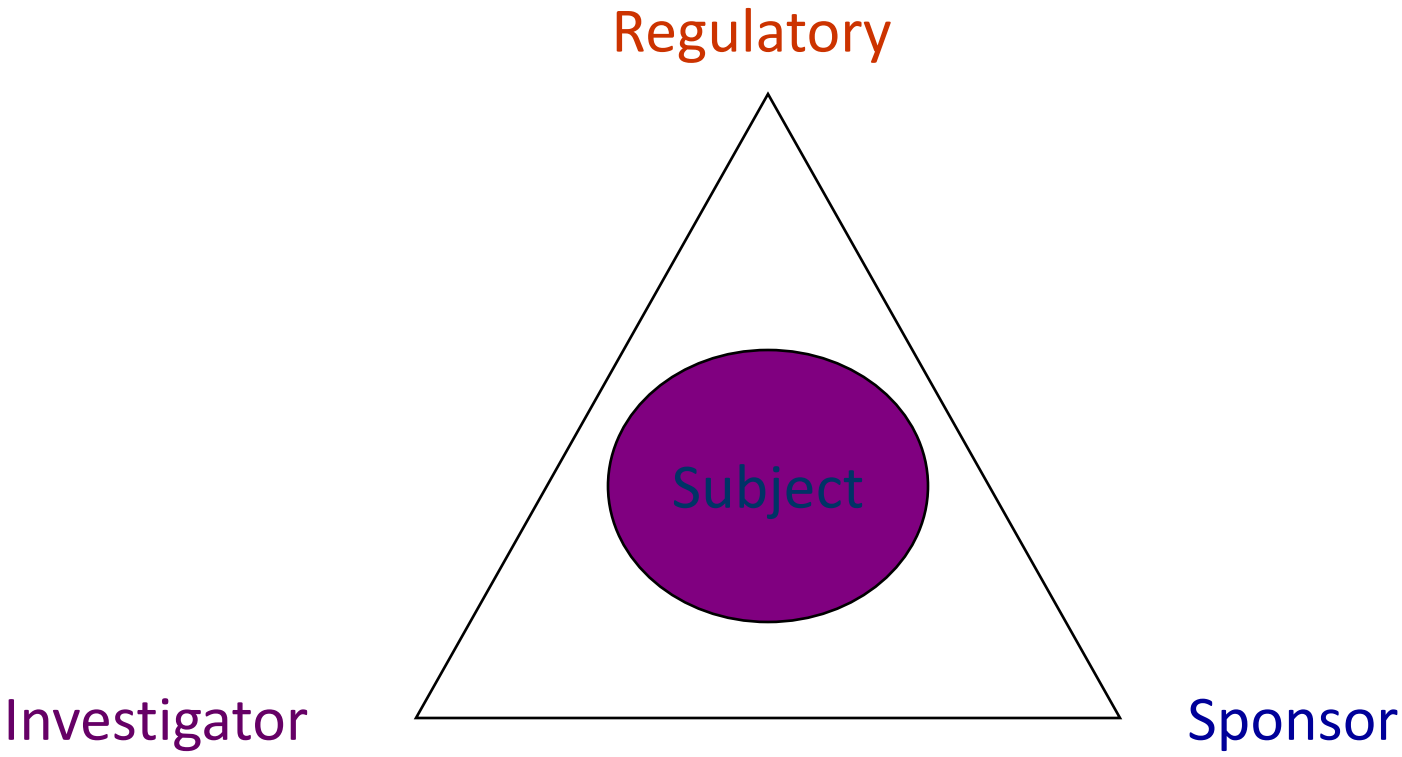
If it is not documented
- it never happened!!!

Remember, **proper documentation** ensures standardization and is the key to all successful studies !

The Tenets of GCP

- Study plan should be well designed by Sponsor
- Every study must follow scientific principles
- IRB must approve study - to ensure protection of rights and safety of subjects
- Informed consent must be freely given
- Sponsor should monitor study for GCP compliance
- Investigator is accountable for all drugs or devices
- Data should complete and accurate
- Records must be kept properly for the time period required
- A Quality Assurance plan must be in place.

Players in clinical research



GCP makes various demands of each

For a GCP-compliant clinical trial...

.....and universally acceptable data...

Each player must be fully aware of his responsibilities as per

Investigator Responsibility

Adequate Resources

- The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and function, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and function and should implement procedure to ensure the integrity of the trial-related duties and functions performed and any data generated

Investigator Responsibility

Records and Report

Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary(e.g. via an audit trail)

Sponsor Responsibility

Quality Management

- Quality management includes the design of efficient clinical trial protocol and tools and procedure for data collection and Processing, as well as the collection of information that is essential to decision making the methods used to assure and control the quality of the trial should be Proportionate to the risk inherent in the trial and the importance of the information collected. Protocols, case report forms and other operational documents should be clear, concise and consistent

Sponsor Responsibility

The quality management system should use a risk-based approach as described below

Critical process and data identification

- The sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results

Risk identification

- Risk should be considered at both the system level (e.g. standard operating procedures, computerized systems, personnel) and clinical trial level(e.g. trial design, data collection, informed consent process)

Sponsor Responsibility

Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk control by considering:

- The likelihood of errors occurring
- The extent to which such errors would be detectable
- The impact of such errors on human subject protection and reliability of trial results

Sponsor Responsibility

Risk Control

- Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreement between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedure and training in processes and procedures
- Detection of deviation from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed

Sponsor Responsibility

Risk Communication

- The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution

Sponsor Responsibility

Risk Review

- Review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience

Risk Reporting

- The quality management approach implemented in the trial and summarize important deviation from the predefined quality tolerance limits and remedial action taken in the clinical study report
  (ICH E3. 9.6 Data Quality Assurance)

Trial Management, Data Handling, and Record Keeping

- The sponsor should base their approach to validation of such system on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results

Trial Management, Data Handling, and Record Keeping (Contd)

- The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionally testing, data collection and handling system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized system should be clear, and the users should be provided with training in their use

Monitoring (Contd)

- On-site monitoring is performed at the sites at which the clinical trial is being conducted Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons(e.g. data managers, biostatisticians)
- Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data

Monitoring

- The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approach that improve the effectiveness and efficiency of monitoring
- The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

- Identify missing data, inconsistent data, data outliers, unexpected lack of variability
- Examine data trends such as the range, consistency ,and variability of data within and across sites.
- Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
- Analyze site characteristics and performance metrics.
- Select sites and/or processes for targeted on-site monitoring.

GMP

Definition:

WHO defines Good Manufacturing Practices (GMP) as “that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.”

Why GMP is important

- A poor quality medicine may contain toxic substances that have been unintentionally added
- A medicine that contains little or none of the claimed ingredient will not have the intended therapeutic effect

Ten Principles of GMP

- Design and construct the facilities and equipments properly
- Follow written procedures and Instructions
- Document work
- Validate work
- Monitor facilities and equipment
- Write step by step operating procedures and work on instructions
- Design ,develop and demonstrate job competence
- Protect against contamination
- Control components and product related processes
- Conduct planned and periodic audits

List of important documents in GMP

- Policies
- SOP (Standard Operating Procedure)
- Specifications
- MFR (Master Formula Record)
- BMR (Batch Manufacturing Record)
- Manuals
- Master plans/ files
- Validation protocols
- Forms and Formats
- Records

What are cGMPs?

- cGMP refers to the Current Good Manufacturing Practice regulations enforced by the US Food and Drug Administration (FDA)
- cGMP provide for systems that assure proper design, monitoring and control of manufacturing processes and facilities
- Adherence to the cGMP regulations assures the identity, strength, quality and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations

Packaging and holding of drugs

- Care shall be taken when using automatic tablet and capsule counting, strip and blister packaging equipment to ensure that all ‘rogue’ tablets, capsules or foils from packaging operation are removed before a new packaging operation is commenced
- There shall be an independent recorded check of the equipment before a new batch of tablets or capsules is handled

Packaging and holding of drugs

Finished pharmaceuticals

- Appropriate specifications for finished products shall include: -
  - The designated name of the product and the code reference
  - The formula or a reference to the formula and the pharmacopoeia reference
  - Directions for sampling and testing or a reference to procedures

Organization and Personnel

- Responsibilities of quality control unit
- Personnel qualifications
- Personnel responsibilities
- Consultants

Building and facilities

- Design and construction features
- Lighting
- Ventilation, air filtration, air heating and cooling
- Plumbing
- Sewage and refuse
- Washing and toilet facilities
- Sanitation
- Maintenance

Equipment

- Equipment design, size and location
- Equipment construction
- Equipment cleaning and maintenance
- Automatic, mechanical and electronic equipment
- Filters

Control of Components

- General requirements
- Receipt & storage of untested components, drug product containers and closures
- Testing and approval or rejection of components, drug product containers and closures
- Use of approved components, drug product containers and closures
- Retesting of approved components, drug product containers and closures

Containers and closures

All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validated test methods, sample sizes, specifications, cleaning procedure and sterilization procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used

Production and process control

- Written procedures; deviations
- Charge-in of components
- Calculation of yield
- Equipment identification
- Sampling and testing of in-process materials and drug products
- Time limitations on production
- Control of microbiological contamination
- Reprocessing

Packaging and labeling control

- Materials examination and usage criteria
- Labeling issuance
- Packaging and labeling operations
- Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
- Drug product inspection
- Expiration dating

Holding and distribution

- Warehousing procedures
- Distribution procedures

Records and reports

- General requirements
- Equipment cleaning and use log
- Component, drug product container, closure and labeling records
- Master production and control records
- Batch production and control records

GLP

Objectives of GLP

- GLP (Good Laboratory Practice) was first introduced in NewZealand.
- GLP makes sure that the data submitted are a true reflection of the results that are obtained during the study
- GLP also makes sure that not to indulge in any fraud activity by labs
- Promotes international acceptance of tests

Principles

- Test Facility Organization and Personnel
- Quality Assurance Programme
- Facilities
- Apparatus, Material, and Reagents
- Test Systems
- Test and Reference Items
- Performance of the Study
- Reporting of Study Results
- Storage and Retention of Records and Materials

Test Facility Organization and Personnel

- Test Facility Management's Responsibilities
- Study Director's Responsibilities
- Principal Investigator's Responsibilities
- Study Personnel's Responsibilities

Test Facility Management's Responsibilities

- Responsibilities of management as defined by these principles of good laboratory practice
- Sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the Study
- Ensure the maintenance of a record of the qualifications, training, experience
- Job description for each professional and technical individual
- Documented approval of the study plan by the Study Director

Study Director's Responsibilities

- Approve the study plan
- Any amendments to the study plan by dated Signature
- Availability of SOPS to the personnel. Raw data generated are fully documented and recorded
- Computerized systems used in the study have been validated
- Sign and date the final report to indicate acceptance of responsibility for the validity of the data
- Ensure that after completion (including termination) of the study, the study plan, the final report, raw data and supporting material are archived

Principal Investigator's Responsibilities

- The Principal Investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable Principles of Good Laboratory Practice
- Knowledgeable Instructions Recording Responsibilities Health precautions

Quality Assurance Programme

- Quality Assurance Personnel
- Study plan contains the information-verification
- Conduct inspections Study-based inspections Facility-based inspections Process-based inspections
- Records of such inspections should be retained

Facilities

- **Test System facilities**
  - Sufficient number of rooms or areas assure the isolation of test systems and the isolation of individual projects involving substances or organisms known to be or suspected of being bio-hazardous
  - There should be storage rooms or areas as needed for supplies and equipment
  - Areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems

Archive Facilities

- Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens
- Archive design and archive conditions should protect contents from untimely deterioration
- Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures

Apparatus, Material, and Reagents

- Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study
- Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures
- Apparatus and materials used in a study should not interfere adversely with the test systems

Storage and Retention of Records and Materials

- The study plan, raw data, samples of test and reference items, specimens and the final report of each study
- Records of all inspections performed by the Quality Assurance Programme, as well as master schedules
- Records of qualifications, training, experience and job descriptions of personnel
- Records and reports of the maintenance and calibration of apparatus
- Validation documentation for computerised systems