

Regulations, Good Clinical Practices, & Good Manufacturing Practices

HCCA Research Compliance Conference
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Goals & Objectives

◆ To understand:

- The affect of Good Clinical Practices on institutions conducting Clinical Research
- The affect of Good Manufacturing Practices on institutions conducting Clinical Research

◆ To discuss:

- The history of Good Clinical Practices and Good Manufacturing Practices
- To identify regulations that institutions are faced with
- Best practices and strategy for staying compliant with Good Clinical Practices and Good Manufacturing Practices

Clinical research, drug & device development have many integrated pieces that challenge each constituent differently

Government	Scientific Community	Business / Market
Regulations / Guidance	Promote Science / Education	Seeking Profit
Investigations / Misconduct	Provide Clinical / Patient Care	Provide Funds / Incentive
Funding / Support	Seeking Funds / Not for Profit	Brings Research to Market
Maintain Integrity	Reputation Risk	Influence / Direct Research
Penalties / Sanctions		

Introduction to Good Clinical Practices

The History of Good Clinical Practices (GCPs)

- ◆ **Prior to GCPs, various nations worked in isolation to assure safety, quality and efficacy of pharmaceutical products**
 - Regulations and guidelines varied from nation to nation with separate clinical trials and standards
 - Contributed to the high costs of research and development
 - Thus, to the high cost of consumer healthcare

- ◆ **The formation of the International Conference on Harmonization (ICH) led to the creation of the Consolidated Guidance on GCP**
 - The ICH consisted of the governments of the United States, EU and Japan coming together to develop common regulations for the pharmaceutical markets among member countries

GCPs Defined

◆ GCPs are generally accepted, international best practices for conducting clinical trials and device studies

- They are defined as an international ethical and scientific standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
- They are NOT statutes or regulations and do not have the force of law
- Compliance with GCPs provide public assurance that the rights and safety of participants in human subject research are protected and that the data that arises from the study is credible

The Core of the Consolidated GCP Guidance

The thirteen principles of GCP are the key to assuring the acceptance of clinical trial data among the nations involved

The Thirteen Principles of GCP Guidance	
1	Clinical 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 the applicable regulatory requirements
2	Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks
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
4	The available non clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial
5	Clinical trials should be scientifically sound, and described in a clear, detailed protocol
6	A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion
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

The Core of the Consolidated GCP Guidance Con't.

The thirteen principles of GCP are the key to assuring the acceptance of clinical trial data among the nations involved

The Thirteen Principles of GCP Guidance	
8	Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks
9	Freely given informed consent should be obtained from every subject prior to clinical trial participation
10	All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
11	The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements
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
13	Systems with procedures that assure the quality of every aspect of the trial should be implemented

Additional Guidance for Clinical Trials

- ◆ **Beyond these thirteen principles, GCPs address the additional key components of clinical trials, including:**
 - Institutional Review Boards (IRBs)
 - Investigators
 - Sponsors
 - Protocols and Protocol Amendments
 - Investigator's Brochure
 - Essential Documents

- ◆ **Each of these key components carries unique requirements, challenges, and risks. See following slides for more detail on these issues**

Additional Guidance for Clinical Trials: IRBs

- ◆ **Have the role to “safeguard the rights, safety, and well-being of all trial subjects”**
 - Review study documents that provide insight into the risks, benefits, commitments, and compensation of involved subjects that at a minimum include:
 - Investigator’s curriculum vitae and medical license
 - Study protocol, amendments and administrative changes
 - Investigator’s brochure and any safety reports or updates
 - Draft informed consent form and any proposed changes to the document
 - Language describing any payments or compensation to involved subjects
 - Advertisements and/or recruitment forms
 - Written documents provided to the patients that are related to the study
 - Review a proposed clinical trial within a reasonable period of time
 - Document its findings in writing, clearly identifying the trial, the documents reviewed and the dates for the following:
 - Modifications required prior to its approval/favorable opinion
 - Disapproval/negative opinion; and
 - Termination/suspension of any prior approval/favorable opinion GCP Guidelines

Additional Guidance for Clinical Trials: IRBs

- ◆ **Each IRB should have written policies and procedures that describe**
 - membership
 - qualifications
 - requirements for a quorum
 - meeting schedule
 - initial, continuing, and expedited review processes
 - protocol deviations and violations
 - safety reporting
 - documentation of IRB decisions/opinions
 - reasons and process of appeal
- ◆ **A properly constructed IRB has at least five members with at least one non-scientific and one non-affiliated member**
- ◆ **The IRB must review its research studies at least once a year with the following being reported**
 - Deviations from the protocol to eliminate hazards to the trial subjects
 - Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial
 - Adverse drug reactions that are both serious and unexpected
 - New information that may affect adversely the safety of the subjects or the conduct of the trial
- ◆ **The IRB must keep records of IRB proceedings and review of protocols for a minimum of 3 years after completion of the trial**

Additional Guidance for Clinical Trials: Investigators

- ◆ **Accountable for every aspect of the clinical trial including the safety of the research participants, compliance with the contract and the protocol, and the integrity of the data**

- ◆ **Investigator Responsibilities Include**
 - Must be certain that (s)he has adequate resources to conduct the trial, meaning, sufficient time, staff, and patients accessible for recruitment
 - Must be responsible for the medical care of participating subjects and related medical decisions.
 - Have a critical role to play in providing informed consent to participants
 - Must ensure the accuracy, completeness, legibility, and timeliness of data reported to the sponsor in the Case Report Forms (CRF) and in all required reports
 - Must play an active role in safety reporting
 - **Serious Adverse Events (SAE)**: Any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization, results in persistent or significant disability or is a congenital anomaly or birth defect
 - **Adverse Events (AE)**: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment

Additional Guidance for Clinical Trials: Sponsors

- ◆ **Role is to design, finance, implement, manage, monitor, audit, and maintain a high quality and compliant study**

- ◆ **Sponsor Responsibilities Include**
 - Must have implemented a quality assurance program and written standard operating procedures to ensure trials are conducted in compliance with the protocol, GCP and applicable laws and regulations
 - Must designate qualified medical personnel who will be readily available to advise on trial related medical questions or problems and hire qualified individuals to ensure the integrity of the data generated
 - Required to monitor the investigator's compliance with IRB policies and procedures and to ensure that a valid IRB has approved the protocol
 - Are subject to very specific regulations on drug manufacture, label, distribution and destruction
 - Must determine operating conditions for the investigational product and should inform all parties of these determinations
 - Handle all the non-manufacturing responsibilities of the research

Additional Guidance for Clinical Trials – Misc.

- ◆ **Protocol and Protocol Amendments: A detailed roadmap to assist investigators and site staff in the day-to-day management of the clinical trial**
 - It should contain sufficient information on the background, purpose, procedures, timelines, safety, data collection, data analysis, and publication policy for the trial
 - The protocol should also clearly outline the inclusion and exclusion criteria for the study

- ◆ **Investigator’s Brochure: A detailed review of the physical, biochemical, and pharmaceutical properties of the investigational product**
 - It should contain enough information on the human metabolism and safety to inform the investigator of the known risks related to the product
 - The brochure should contain a section called “Summary of Data and Guidance for the Investigator” that provides the investigator with a clear understanding of possible risks to participants

- ◆ **Essential Documents: Institutions must maintain regulatory files of the study’s essential documents such as: the study protocol, informed consent forms, conflict of interest forms, budget documents, adverse event forms, etc.**

GCP Risk Areas

- ◆ **The role of the investigator carries significant responsibility and must be monitored**
 - Institutions must assure the investigator is following GCPs in all aspects of the trial
- ◆ **Sponsoring agencies expect high quality research and tend to choose institutions that have the best researchers, are nimble in the approval and contracting process, and are have favorable reviews from their monitoring teams**

Best Practice

Compliance officers and research professionals should be familiar with the monitoring reports produced by sponsoring organizations that typically describe the patient visits that are cleared for payment, any areas of safety concern, and/or research areas that need improvement

GCP Risk Areas Con't.

- ◆ **Federal guidelines published by the Office of Research Integrity (ORI) require institutions that receive funding to develop procedures for “receiving and investigating reports of misconduct”**
- ◆ **Scientific Misconduct has become a real concern for institutions as it can be difficult to manage and it presents many unique challenges**

Best Practice

Best practice suggests institutions take this a step further and add additional elements to site policies by adding some or all of the following:

- **Violation of federal rules and regulations**
- **Abuse of confidentiality**
- **Authorship and publication violations**
- **Failure to report misconduct**
- **Obstruction of investigations and retaliation**

GCP Risk Areas Con't.

◆ Investigator Impropriety

- Protocol deviations, misuse of products and lack of communication on safety issues are examples of poor decisions on the part of the investigator that can lead to compliance risk

Best
Practice

The best way to manage these situations while preventing smaller issues from escalating is to review the official monitoring follow-up letters

◆ Human Subjects Protection and IRBs

- As the volume of research and clinical trials increases it is difficult for the IRBs to keep up with the number of studies that must be reviewed at each meeting

Best
Practice

A strategy for gaining insight into the problem is to track key metrics during IRB meetings to look for trends and conduct periodic audits of protocols reviewed to assure compliance with GCP and institutional policies

◆ Off-label Use of Humanitarian Device Exemptions (HDE) Devices

- Documentation of the rationale for the humanitarian use of the device is essential to this process
- HDE have created confusion in the research community because these devices are used to treat rare diseases
 - This creates risks for the institution since safety data is lacking for these devices

GCP Risk Areas Con't.

- ◆ **Privacy Boards and Health Insurance Portability and Accountability Act (HIPAA)**
 - Essential for achieving compliance with the regulations and helping protect institutions involved in research
 - Key priority is to monitor research participants' rights to privacy

- ◆ **Safety Reporting and Data Safety Monitoring Boards (DSMBs):**
 - Their role is to monitor patient safety data and make recommendations on continuation

Practice

Best

This information should be shared with all relevant IRBs and investigators to assure GCP principles are applied in the conduct of the trial

- ◆ **Monitoring Visits by Sponsors**
 - The purpose of these visits is to maintain compliance with the protocol, the clinical trial agreement, federal rules and regulations, human subjects protection, and GCP
 - Monitors must file a report after the completion of the visit, and send a follow-up letter to the site that describes the status of the study, the number of screened and enrolled subjects, essential documents that were not on file, discrepancies in drug accountability, and any protocol deviations or violations

Introduction to Good Manufacturing Practices

History of Good Manufacturing Practices (GMP)s

- ◆ **Similarly to GCPs, GMPs were developed out of a need for consistent methods to develop and manufacture drugs, devices, and food in the United States**

- ◆ **GMP regulations are promulgated and enforced by the FDA and primarily housed within the Federal Food, Drug, and Cosmetic Act**

- ◆ **GMPs are based on industry best practices that continually evolve as science, technology, and manufacturing techniques change**
 - Commonly referred as Current Good Manufacturing Practices (cGMP)s

cGMPs Defined

- ◆ cGMPs are methods, facilities, or controls used in the production of drugs, devices, foods, and biologicals. These manufacturing practices are designed to ensure the safety, identity, strength, quality, and purity of such products.

Good Manufacturing Practice Federal Regulations

CFR 21 Part 210, 211	cGMP in manufacturing, processing, packing, holding, finished pharmaceuticals
CFR 21 Part 820	Quality system regulations
CFR 21 Part 803	Medical device reporting
CFR 21 Part 821	Medical device tracking requirements
CFR 21 Part 806	Medical device reports on corrections and removals
CFR 21 Part 807	Medical device registration and listing
CFR 21 Part 312	Investigational new drug application
CFR 21 Part 610	General biological products standards

GMPs address several issues relating to production such as those listed below

GMPs Regulations Address:

Documentation/Records

Process and production controls

Physical plant, laboratory, and facility design

Personnel / Quality control oversight

Proper validation of processes

Maintain and calibrate equipment

Clinical trial requirements

GMPs Regulations also Address:

Materials Management

Packaging & Labeling

Storage & Distribution

Laboratory Controls

Rejection and Reuse Materials

Complaints & Recalls

Agents, Brokers, Distributors, Repackers, and Relabellers

Characteristics of GMP regulations and interpretations

GMP regulations are largely general and open for interpretation

Benefit:

- ◆ **Manufacturers and researchers are able to interpret and apply the regulations in ways that may work best for their unique situations**

Risk:

- ◆ **The flexibility may lead to confusion during the interpretation of the regulation and misapplied control mechanisms**

GMP – Documentation & Records

Sample GMP standards are listed below:

Maintain laboratory and production records - notebooks, electronic files, etc.

Track records through research and production

Batch Package Records (BPR)

Equipment usage, calibrating, cleaning, maintenance

Laboratory control records

Distribution records

Records maintained

Electronic signatures on documents are acceptable, provided they are authenticated and secure

GMP – Process and production control

Example GMP standards are listed below:

Standards for weighing, measuring, storing, controlled

Time limits (if applicable and necessary)

In-process assurance, sampling and controls

Blending, mixing, diluting substances

Contamination controls

All SOPs must be consistently documents, updated, and followed. During an inspection or audit, regulators typically take a product and follow it through from start to finish using the documented SOP looking for deficiencies

GMP – Physical plant, laboratory facilities design

Example GMP standards are listed below:

Design and Construction

- Single use versus multiuse facility, proper separation

Utilities

- Air quality - Filtered, recirculation, one-pass
- Natural Gas
- Dust, humidity, temperature

Water

- Municipal versus well versus sterilized

Containment

Lighting (placed to facilitate cleaning in all areas)

Sewage and Refuse

Sanitation and Maintenance

- Cleanability, products used, etc.

GMP – Personnel / Quality control oversight

Sample GMP standards are listed below:

Quality should be the responsibility of all persons involved in manufacturing

Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel

All quality related activities should be recorded at the time they are performed

There should be a quality unit(s) which is independent of production, and which fulfills both quality assurance (QA) and quality control (QC) responsibilities

In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule

- Audit findings and corrective actions should be documented

There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the processes

- Responsibilities of all personnel engaged in the manufacture should be documented in writing

GMP - Validation

Example GMP standards are listed below:

Policies, intentions, approaches, systems, cleaning procedures, and all other protocols should be validated/documentated

- Critical parameters, limitations, ranges and standards should be established

A written validation protocol should be established that specifies how validation of a particular process will be conducted

Appropriate qualification of equipment and ancillary systems should be completed

- Design qualification, Installation qualification, Operational qualification, Performance qualification

Validate processes to ensure protocols are being followed

- Number of process validations depends on complexity of the tasks

Cleaning and maintenance validation should be obtained

GMP – Equipment maintenance & calibration

Example GMP standards are listed below:

Equipment used should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance

- Production equipment should only be used within its qualified operating range
- Closed or contained equipment should be used whenever appropriate
- Any substances necessary for the operation of equipment, such as lubricants, heating fluids or coolants, should not contact tested items so as to alter their quality

Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment

Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture

Control, weighing, measuring, monitoring and test equipment that is critical for assuring quality should be calibrated according to written procedures and an established schedule

GMP – Clinical trials

Example GMP standards are listed below:

Not all the controls are appropriate for investigational use during drug or device development

The controls used in the manufacture of Active Pharmaceutical Ingredients (API) for use in clinical trials should be consistent with the stage of development of the drug

- Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages

Appropriate GMP concepts should be used in the development of APIs in clinical trials

During all phases of clinical development, including the use of small scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use

GMP – Clinical trials Con't.

Example GMP standards are listed below:

Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing

- When a material is considered hazardous, a supplier's analysis is sufficient
- Production of APIs should be documented in laboratory notebooks, batch records, or other appropriate means

Although changes are expected, as knowledge is gained and the production is scaled up, every change in the production, specifications, or test procedures should be adequately recorded

- A system for retaining reserve samples of all batches should be in place

A system should be in place to ensure that information gained during the development and the manufacture of APIs is documented and available

- A system for retaining production and control records should be used
- This system should ensure that records are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

