Clinical research regulation in USA-food and drug administration:

The US food and drug administration is a scientific, regulatory and public health agency. It is responsible for most food products, human and animal drugs, therapeutic agents and biological origin, medical devices, radiation emitting products for consume, medical and occupational use, cosmetics and animal feed.

The current staffs approximately 9100 employees are composed of chemist, pharmacist, physician, microbiologists, veterinarians, pharmacologist and laboratories. Agency scientists evaluate applications for new human drugs and biologics, complex medical devices, food and colour additives, infant's formula and animal drugs.

. The FDA monitors the manufacture, import, transport, storage and sale of about $1 trillion worth of products annually.

The FDA visits more than 16000 facilities a year

including manufacturing plants and clinical study sites.

There are several sets of regulations and laws that govern clinical trials:

- The first GXP REGULATIONS (GXP is a general team for good practice quality guidelines and regulations.

GXP encompasses good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP).

We will focus on GCP, since that is the most applicable clinical trials

- In the past, the GCP regulations varied significantly from country to country, but after international conference on harmonization issued guidelines, the differences have largely been resolved.
- Although united States, European union, Japan are the members of ICH, the most countries

have now adapted the output from conference.

•Specify:

GCP specifies how a clinical trial is performed.

The purpose of GCP is to:

•Protect patient safety and rights

•Ensure data integrity

•Specifically, GCP is meant to prevent careless errors, violations, fraud, and ethical issues.

GCP are required and important Because of the following:

→Clinical trials usually involve exposing patients to risk, by administering drugs of unknown efficacy and safety.

→The risk can be very severe and include death

→Decision (such as approval decisions) will be made on the basis of data from clinical trials there will affect health and safety of future patients who will receive the drug.

□Where to find GCP Regulations:

GCP can be found in several places:
The main sources are ICH guidelines that have been published.
The ICH guidelines are adapted in to law or regulations by individual countries by their law making bodies.

•In the United states they are found in:
21 CFR (Code of federal regulations) part 11: electronic records/electronic signatures
21 CRF part 50: protection of human subjects ---
21 CRF part 54: financial disclosures by investigators
21 CRF part 56: institutional review boards
21 CRF part 312: investigational new drug applications
21 CRF part 314: Application for FDA approval to market a new drug.

Other Regulation:
Health insurance portability and Accountability Act
Guidelines:
In addition to GCP, there are many regulations for

example; there are strict privacy laws in many countries. In the United State they are HIPAA regulations.
-These were paised in 1996 and have very stringent requirements and penalties including criminal penalties
HIPAA apply to covered entities which are health care providers health plan, health care clearinghouses.
-A pharmaceutical company typically is not covered entirely. However, it can become a hybrid or a covered entity by doing certain things, such as, for example, collecting information from patients in an outreach or patient support programs.

Protected Health Information (PHI):

- Created or received by Health care provider, health plan, health care clearinghouse; or employer
- Relates to physical or mental health or conditions provision of health care or payment of provision of health care.
- Identifies could be reasonably used to identify individuals.

- Includes demographics: data collected from an individual.

HIPAA applies to person for 2 years after death as well.

The penalties for negligent disclosures are $100 $25000/person/year. For wrongful disclosures, the fine can be up to $250,000 and 1-10 years in Rison.

- For clinical research, HIPAA disclosures are required from the covered entity (e.g the investigator) to -- Sponsor.

European Union Clinical Trial Directive

- The EU directive was first published by the EMEA (European Medicine Agency) in 2001.
- The purpose was to harmonize the initiation and conduct of clinical trials in European Union. Among other thing it was also designed to:
  - Protect patients, especially incapacitated and minors patients;
  - Standardize applications for starting trials;
  - Standardize EC process
  - Standardize pharmacoviligance data handling
  - Allow information exchange between European Union countries;
  - Mandate GCP inspection

The European medicine agency (EMEA) is a European agency for the evaluation of medicinal product. Until 2004, the European Medicines Agency was known as the European agency for the evaluation of medicinal products.

Roughly parallel to the U.S. FDA, but without

FDA-Style centralization: the EMEA was set up in 1995 with funding from the European Union and the pharmaceutical industries, as well as indirect subside from member. State, in an attempt to harmonize the work of existing national medicine regulatory bodies.

The scientific opinions of the agency are prepared by three committees responsible for medicines for human use:

- Committee for Medicinal Product for Human use (CMPH)
- Committee for Medicinal Product for Veterinary use (CMPV)
- Committee for Orphan Medicinal products (COMP)
- Committee on Herbal Medicinal product (HMPC)

Committee for Medicinal product for Human Use (CMPH):

- A chairman
- One member nominated by each of the 25 EU

member state.
- One member nominated by each of the EEA-EFTA State Iceland and Norway.
- Up to five co-opted members, chosen among experts nominated by member states or the EMEA the recruited, when necessary, to gain additional expertise in particular scientific area.
- CHMP members and alternates are nominated by member state in consultation with the EMEA Management Board.

Responsibilities:

The CHMP plays a vital role in the marketing procedures for medicines in European Union.
Conducting the initial assessment of medicinal product for which a community-wide marketing authorization is sought.
- The CHMP is also responsible for several post authorization and maintenance activities.
- Assessment of any medication or extension to

existing marketing authorization.
- In the mutual-recognition and decentralized procedures, the CHMP arbitrates in cases where there is a disagreement b/w member states concerning the marketing authorization of a particular medicinal product.
- The CHMP also acts in referral cases, initiated when there are concerns relating to the protection of public health.

Other important activities of the CHMP and its working parties include:
- The provision of assistance to companies researching and developing new medicines
- The preparation of scientific and regulatory guidelines for pharmaceutical industries
- Co-operation with international partners or harmonization of regulatory requirements for medicines.

The directive applies to all medicinal trials that are interventional it applies to both commercial and non-commercial trials.

The directive does not automatically become effective across European Union. Each country must implement it by passing laws enacting them.

They can add more detail during the implementation.

•Now, there are five detailed guidance documents associated with directives:

1. European clinical trial database (EudraCT) --
2. The request for authorization of clinical trial on medicinal products for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.
3. The application, format and documentation to be submitted in an application for an EC opinion.
4. The European database of SUSARS (Eudravigilance)
5. The collection, verification, and presentation of adverse reaction reports.

EudraCT

European regulatory authorities need a database in order to provide each of them with an overview of clinical trials being conducted in the community. This database is needed to facilitate communication on these clinical trials b/w the authorities, to enable each to undertake better the oversight of clinical trial and investigational medicinal product development, and to provide the enhanced protection of clinical trial subjects and patients-- receiving investigational medicinal products.

EudraCT Number

The unique EudraCT number for clinical trial has the format

YYYY-NNNNNN-CC

YYYY-is the year in which the number is issued
NNNNNN-is a six sequential number
CC-is check digit

The directive requires that for a clinical trial application, the following must be submitted to a competent authority:

- Application form with the Eudract number
- Protocol
- Investigator's brochure(IB)
- Investigational Medicinal product number
- Country Specific Information.

Regulatory Authorities In India

- Clinical trials in India are regulated by schedule Y of the drug and cosmetics rules.
- The rules are enforced by the office of the DCGI (Drug control general of India) who is also responsible for monitoring all clinical trials submitted to that office for approval.
- Today India is considered as the most favored destination for conduct of the clinical trials, sponsored by both international and Indian companies. Apart from the unique criteria possessed by India to attract global players, the main criteria which given the advantage to India, is the momentum at which ICMR and DCGI has adopted themselves to the Global Regulatory Guidelines. All this scope and improvement has been well recognized and appreciated considering the fact that India's involvement in Global GCP is only a decade old.

List of regulatory bodies in India

DCGI	Drugs Control General of India
ICMR	Indian Council of Medical Research
GEAC	Genetic Engineering Approval Committee
DBT	Department of Biotechnology
AERB	Atomic Energy Review Board
DTAB	Drug Technical Advisory Board
DGFT	Director General of Foreign Trade

Drug Control General of India (DCGI)

DCGI is a regulatory apex body under government of India, which oversees all clinical trial undergoing in India. This agency reviews the clinical study protocol and associated relevant documents. It is mandatory to obtain its approval before starting trials on human in India.

It is governed by rules in amended schedule Y in addition to the experts at DCGI's office. They also avail the external experts and other government agencies like ICMR, GEAC, DBT, AERB, DTAB and DGFT.

DCGI heads the Central Drug Standard Control Organization (CDSCO) and discharge the functions attached to the central government.

The DCGI also has the responsibility of laying down regulatory measures and amendment of Act and rules, laying standards for drugs, cosmetics, diagnostics, devices and updating the Indian pharmacopeia.

Indian Council of Medicinal Research (ICMR)

The Indian council of medical research, New Delhi, the apex body in India for the formulation, co-ordination and promotion of biomedical research, is one of the oldest medical research bodies in the world.

The council promotes biomedical research in the country through intramural as well as extramural research.

Intramural research is carried out currently through the council's 21 permanent research institutes/centers which are mission-oriented national institutes located in different parts of India.

Genetic engineering approval committee (GEAC)

The GEAD consists of experts in the field of genetic engineering and molecular biology, experts drawn from Indian council of agricultural research, (ICAR, ICMR, Drug controller of India, Department of Atomic energy Ministry of science and technology. Ministry of central pollution control Board.)

Clinical trials involving use of genetic engineered

products would be referred by DCGI to GEAC for recommendations. Based on recommendations received DCGI provides approval for conduct of clinical trials involving genetically engineered products.

Department of Biotechnology (DBT)

- Department of Biotechnology set up under the ministry of science and technology in 1986, gave a impetus to the development of field of modern biology and biotechnology in India.

DTB plays important role in the conduct of clinical trials by supporting the DCGI in reviewing the studies which are related to the field modern biology and biotechnology in India, Stem cells Research and trials are governed by DBT. All clinical trials in the area of stem cells have to be cleared by the DBT.

Atomic Energy Review Board (AERB)

The regulatory authority of AERB derived from

the rules and notification promulgated under the Atomic Energy Act and Environmental Act, 1986. The mission of the board is to ensure that use of ionizing radiation and nuclear energy in India does not cause undue risk to health and environment. Currently, the Board consists of full time Chairman, an ex-office member and secretary.

□ Drug Technical Advisory Board (DTAB)

The Drug Technical Advisory Board, is a highest technical body under the drug and cosmetic Act, has endorsed the adoption of GCP guidelines for clinical trial in India.

□ Director General of Foreign Trade (DGFT)

DGFT overseas import and export of all biological samples from/to overseas countries. This apex body is responsible for issuance of import and export license.

- Parallel submission can be made to DCGI and

DGFT on obtaining approval from DCGI to conduct the trial, DGFT gives permission to import drugs there by reducing the timelines for study start up.