UNIT 13 GOOD LABORATORY PRACTICES, GOOD MANUFACTURING PRACTICES AND GOOD CLINICAL PRACTICES

Structure

13.1 INTRODUCTION

In the previous unit on evaluation and quality control of pharmaceuticals, we have seen the importance of pharmacopoeias and formularies in specifying the active ingredients of medicines, their strength, various dosage forms and their quality control aspects. In this unit we will study the principles and requirements of Good Laboratory Practices (GLP), Good Manufacturing Practices GMP) and Good Clinical Practices (GCP). As the quality assurance is as an integral and vital aspect in the manufacture of pharmaceutical products, there is lot of relevance for the requirements of GLP, GMP and GCP in pharmaceutical industry.

Objectives

After studying this unit, you should be able to:

- explain principles of GLP, GMP and GCP;
- understand the responsibilities of quality assurance programme;
- explain the functions of GLP authority and GLP inspectors;
- describe the features of aseptic area in GMP;
- discuss the role of personnel in GMP;
- explain the importance of GCP;
- understand different phases of clinical trials;
- describe the importance of declaration of Helsinki and Schedule Y; and
- understand institutional review board/independent ethics committee.

13.2 GOOD LABORATORY PRACTICES (GLP)

A number of countries require manufacturers of pharmaceuticals, veterinary drugs, pesticides, cosmetics, processed food products, feed additives, industrial chemicals etc. to establish that use of these products do not pose any hazards to human health and the environment. Non Hazardous nature needs to be established through studies and data, which will be examined by the regulatory authorities of the concerned countries. Good Laboratory Practices (GLP) is a system which has been evolved by Organizations for Economic Co-operation and Development (OECD), used for achieving the above goals. To avoid different schemes of implementation that could impede international trade in chemicals, OECD member countries have pursued international harmonization of test methods and Good Laboratory Practices.

13.2.1 History of GLP

The Organizations for Economic Co-operation and Development (OECD) principles of GLP were first developed in 1978 by an international group of experts under the special programme on the control of chemicals. The GLP for the non clinical laboratory studies published by the US Food and Drug Administration (FDA) in 1976 provided the basis for the work of the expert group. It utilized common managerial and scientific practices and experience from various national and international sources. These principles of GLP were adopted by the OECD council in 1981. Later in 1995 and 1996 team of new group of experts revised and modified the principles of GLP and the current one is based on the consensus reached by that group.

In India, a national GLP compliance monitoring authority was established by the Department of Science and Technology (DST) in 2002. Presently India enjoys the status of provisional member of the OECD for GLP. India is an observer to the OECD's working group on GLP and also a member of the OECD test guidelines programme. The national GLP programme functions through an Apex body which consist of the following members.

i) **Chairman**

Secretary, Department of Science and Technology, Ministry of Science and Technology, Govt. of India.

Members

ii) Secretary, Department of Chemicals and Petrochemicals, Ministry of Chemicals and Fertilizers, Govt. of India.

iii) Secretary, Department of Agriculture and Cooperation, Ministry of Agriculture, Govt. of India.

iv) Secretary, Department of Health, Ministry of Health & Family Welfare, Govt. of India.

v) Drugs Controller General (India) Directorate General of Health Services, Govt. of India.

vi) Secretary, Department of Commerce, Ministry of Commerce & Industry, Govt. of India.

vii) Secretary, Ministry of Environment & Forests, Govt. of India.

viii) Secretary, Department of Fertilizers, Ministry of Chemicals & Fertilizers, Govt. of India.

ix) Secretary, Department of Consumer Affairs, Ministry of Consumer Affairs, Food & Public Distribution, Govt. of India.

x) Director General, CSIR and Secretary-DSIR Member-Secretary, Govt. of India.

xi) Head – National GLP Programme Department of Science & Technology, Govt. of India.

This body is responsible to ensure that the National GLP programme functions as per OECD norms and principles.

13.2.2 Definition and Scope

Good Laboratory Practices (GLP) is a system of controls and management for laboratories and research organizations to ensure the consistency and reliability of results as outlined in the OECD principles of GLP and national regulations. Good laboratory Practice embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, cosmetics, food and feed additives and contaminants, novel foods and biocides. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/ safety assessments.

GLP applies to non clinical studies conducted for the assessment of the safety of chemicals (test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives and industrial chemicals) to man, animals and the environment. These test items can be of synthetic, natural or biological origin and may also be sometimes living organisms. The purpose of these principles of GLP is to promote the development of quality test data and also traceability and integrity of data. Comparable quality of test data forms the basis for the mutual acceptance of data among countries. If individual countries can confidently rely on test data developed in other countries, duplicative testing can be avoided, thereby saving time and resources. The application of these principles should help to avoid the creation of technical barrier to trade, and further improve the protection of human health and the environment. Non-clinical health and environmental safety studies covered by the Principles of Good Laboratory Practice include work conducted in the laboratory, in greenhouses, and in the field. Unless specifically exempted by national legislation, these Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies required by regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary drug products and similar products, and for the regulation of industrial chemicals.

13.2.3 Powers and Functions of GLP Authority

The main functions of GLP Authority are:

i) Monitor the progress of the programme implementation;

ii) Establish National GLP Compliance/Monitoring system for test facilities on the basis of OECD Principles of Good Laboratory Practice;

iii) Grant GLP certification to the test facilities based on their compliance to the OECD Principles of Good Laboratory Practice and OECD Test Guidelines;

iv) Suspend/withdraw and/or terminate GLP Certification from its certified test facilities/laboratories, and/or may even inform relevant GLP Compliance Monitoring Authorities (belonging to OECD member country) should there be a need;

v) Constitute such other Technical Committees/or the Working Groups which it deems fit, to complete a particular cause or need or activity;

vi) Approve the rules and procedure that may be formulated for the smooth functioning of the programme, Technical Committee and Working Groups;

vii) Ensure that National GLP Compliance Monitoring/Authority operates its system in accordance with current OECD Council norms, maintain its international compatibility and mutual recognition; and

viii) Organize and conduct scheduled/unscheduled inspections for its GLP-certified laboratories.

13.2.4 Nature of the National GLP Programme

GLP certification is voluntary which undertakes such studies, either for its own purpose or for others, will be eligible to seek GLP certification. It will establish and continually update a network of GLP-certified laboratories. GLP certification is valid for a period of three years. GLP-certified laboratories shall be regularly monitored to ensure for their compliance to OECD Principles of Good Laboratory Practice and Test Guidelines by organizing the surveillance visits, that could be by informing the test facility or otherwise also, if required.

In those cases, where serious deviations which may have affected specific studies are found, the GLP Authority shall consider the need to inform the relevant National GLP Authority in other OECD member countries.

In needy situations, the National GLP Programme would cooperate with a national regulatory authority of a member country in the following ways:

- In organizing a particular study audit and by providing the results to the requesting regulatory authority.
- By facilitating to conduct and witness a study audit/inspection at the request from the Authority(ies) of a member country either for their inspectors or for their representative(s)' Inspectors from the member country.

National GLP programme has in-built feature of taking action against those test facilities which have been granted GLP certificate are not found to have complied with OECD Principles of Good Laboratory Practice and Test Guidelines which might affect the validity of studies conducted in the test

facility. Test facilities interested in GLP certification would be required to give an undertaking to National GLP Programme for agreeing to abide by its Terms and Conditions. GLP Authority (Apex Body) has its membership from the concerned Government Departments/Regulatory Authorities to ensure their inputs and to safeguard their interests.

13.2.5 GLP Inspectors

National GLP Programme has opted in its system, to empanel as its Inspectors, the experts who are currently employed with Government test facilities/ organizations, and whose qualification(s), experience, etc. are meeting those prescribed by the Technical Committee. Function and the power of the inspector are:

i) Inspectors evaluate the technical competence of the applicant test facility in all respects for its compliance to OECD Principles of Good Laboratory Practice and OECD Test Guidelines. They are trained by National GLP Compliance Monitoring Authority and /or OECD on GLP Principles.

ii) GLP inspectors are responsible for conducting inspection of a test facility based on the study and analysis of application received from the test facility, carrying out opening and closing briefings in the test facility. They are also responsible for preparing inspection reports with his/her recommendations, whether or not the test facility under consideration qualify for grant of GLP compliance status, to be placed before the technical committee.

iii) Inspectors are monitored by the national GLP office for their performance.

iv) Inspectors have access to confidential and commercially valuable information of the test facility, required for its assessment while conducting inspections and study audits. Inspectors shall not disclose such confidential and commercially valuable information obtained during the course of inspection and study audit of a test facility to any one except the National GLP Office.

v) Inspectors will not normally enter a test facility against the will of its management. However, if there is sufficient evidence to prove that the test facility is not adhering to GLP principles and access to data from the test facility is *essential* to protect the interest of human health and environment. National GLP office may organize unscheduled/ spontaneous inspection/study audit any time. Access to the inspection team shall have to be granted by the test facility at all reasonable times and facilities, data and records for proper inspection shall be made freely available to inspectors. Refusal to comply shall result in suspension of GLP-certificate.

vi) Inspectors are provided with a copy of the application submitted by the test facility and the same is returned to the National GLP office.

vii) Inspectors submit all reports of test facility inspection/study audit only to the National GLP Office. No copies of such reports or related information is to be provided to test facilities other than that covered during opening and closing briefings during the inspection.

13.2.6 GLP – Principles and Requirements

i) **Test Facility Organization and Personnel**

Each test facility management should ensure that the Principles of GLP are complied with, in its test facility and ensure that a sufficient number of qualified personnel, appropriate facilities, equipment and materials are available for the timely and proper conduct of the study. A record of the qualifications, training, experience and job description for each professional and technical individual has to be maintained. The personnel have to understand the functions they are performing.

ii) **Quality Assurance Programme (QAP)**

The test facility should have a documented quality assurance programme to assure that studies performed are in compliance with the principles of GLP. Quality Assurance Programme (QAP) should be carried out by an individual(s), designated by and directly responsible to management and who are familiar with the test procedures.

iii) **Facilities**

The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimize disturbances that would interfere with the validity of the study. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study. The test facility should have a sufficient number of rooms or arrears to assure the isolation of test systems and the isolation of individual projects.

iv) **Apparatus, Material and Reagents**

Apparatus, including validated computerized systems, used for the generation, storage and retrieval of data should be adequate capacity. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to SOPs. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurements.

v) **Test Systems**

Apparatus used for the generation of physical/chemical data should be suitable located and of appropriate design and adequate capacity. The integrity of the physical/ chemical test systems should be ensured. In case of biological test items, proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data. Newly received animal

and plant test systems should be isolated until their health status has been evaluated. In any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, should be humanely destroyed.

vi) **Test and Reference Items**

Records including test item and reference item characterization, date of receipt, expiry date, quantities received and used in studies should be maintained. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded. Storage containers should carry identification numbers, expiry date and specific storage instructions.

vii) **Standard Operating Procedures (SOPs)**

A test facility should have written Standard Operating Procedures (SOPs) approved by test facility management that are intended to ensure the quality and integrity of the data generated by that test facility. Revisions to SOPs should be approved by test facility management. Each separate test facility unit or area should have immediately available current SOPs relevant to the activities being performed therein. Published text books, analytical methods, articles and manuals may be used as supplements to these SOPs.

viii) **Performance of the Study**

For each study, a written plan should exist prior to the initiation of the study. The study plan should be approved by dated signature of the Study Director and verified for GLP compliance by Quality Assurance Personnel as specified. The study plan should also be approved by the test facility management and the sponsor, if required by national regulation or legislation in the country. Amendments to the study plan should be justified and approved by dated signature of the Study Director and maintained with the study plan. Deviations from the study plan should be described, explained, acknowledged and dated in a timely fashion by the Study Director and/ or Principal investigator.

ix) **Reporting of Study Results**

A final report should be prepared for each study. In the case of short term studies, a standardized final report accompanied by a study specific extension may be prepared.

Report of Principal Investigators or Scientists involved in the study should be signed and dated by them. The final report should be signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the data. Correction and additions to a final report should be in the form of amendments. Amendments should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director.

x) **Storage and Retention of Records and Materials**

All the required documents related to quality assurance programmes, personnel etc. should be retained in the archives for the period specified by the appropriate authorities. In the absence of a required retention period, the final disposition of any study materials should be documented. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented. Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation.

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What is GLP?

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13.3 GOOD MANUFACTURING PRACTICES (GMP)

Good Manufacturing Practice (GMP) is a term that is recognized worldwide for the control and management of manufacturing and quality control testing of food and pharmaceutical products. GMP takes the holistic approach of regulating the manufacturing process and laboratory testing during the process itself. GMP gives much significance for the documentation of every aspect of the process, activities, and operations involved with drug and medical device manufacture.

Apart from the general GMP requirements, specific regulations are prescribed for various dosage forms i.e. injections, tablets, capsules and oral liquid items.

If the documentation showing how the product was made and tested (which enables traceability and, in the event of future problems, recall from the market) is not correct and in order, then the product does not meet the required specification and is considered *contaminated*. Additionally, GMP requires that all manufacturing and testing equipment has been qualified as suitable for use. It also requires operational methodologies and procedures (such as

manufacturing, cleaning, and analytical testing) utilized in the drug manufacturing process have been validated (according to predetermined specifications), to demonstrate that they can perform their purported function(s).

13.3.1 Location and Surroundings

The pharmaceutical manufacturing unit shall be situated in a clean and tidy environment free from any type of contamination including external environmental including open sewage, drain, public lavatory etc.

The building for the manufacturing unit shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions and to avoid various hazards including entry of insects, pests or rodents and mix up between different categories of drugs and raw materials.

Interior surface (like walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units to maintain conditions including temperature and, wherever necessary, humidity, as defined for the relevant product. These conditions shall be appropriate to the category of drugs and nature of the operation. The factory premises and working area shall be suitable to the comforts conveniences of the personnel working and shall be regularly monitored for compliance with required specifications.

The manufacturing premises shall be clean and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material. A validated cleaning procedure shall be maintained. The manufacturing areas shall not be used for storage of materials, except for the material being processed.

13.3.2 Water System

There shall be validated system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce Purified Water conforming to Pharmacopoeial specification. Purified Water so produced shall only be used for all operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf.

The disposal of sewage and effluents (solid, liquid and gas) from the manufactory shall be in conformity with the requirements of Environment Pollution Control Board. All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 1996.

13.3.3 Warehousing Area

Warehousing areas shall be designed and adapted to ensure good storage conditions. They shall be clean, dry and maintained with acceptable temperature limits, where special storage conditions are required (e.g. temperature, humidity). Storage areas shall have appropriate house-keeping and rodent, pests and vermin control procedures and records maintained. Adequate areas shall be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items.

There shall be a separate sampling area in the warehousing area for active raw materials and excipients. If sampling is performed in any other area, it shall be conducted in such a way as to prevent contamination, cross-contamination and mix-up.

13.3.4 Production Area

The production area shall be designed to allow the production in a scientific and professional manner. There shall be provision for attracting the risk of cross-contamination. Self-contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live micro-organisms. Separate dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as Beta-Lactum, sex hormones and cytotoxic substances.

Working and in-process space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel to avoid cross-contamination and to minimize risk of omission or wrong application of any manufacturing and control measures. Pipe-work, electrical fittings, ventilation openings and similar services lines shall be designed, fixed and constructed to avoid creation of recesses.

The manufacture of medicines shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage and / or active pharmaceutical products.

13.3.5 Ancillary Areas

Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas. Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users. Toilets, separate for males and females, shall not be directly connected with production or storage areas. There shall be written instructions for cleaning and disinfection of such areas.

Maintenance workshops shall be separate and away from production areas. Whenever spares, changed parts and tools are stored in the production area,

these shall be kept in dedicated rooms or lockers. Tools and spare parts for use in sterile areas shall be disinfected before these are carried inside the production areas. The animal house shall be separate and isolated from other areas and shall comply with the respective regulations and approved guidelines.

13.3.6 Quality Control Area

The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall be provided for biological, microbiological and radioisotopes testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purpose. Quality control laboratories shall be independent of the production areas. separate areas shall be provided for physico-chemical, biological, microbiological or radio-isotope analysis. Instrument room with adequate area has to be provided for sensitive and sophisticated instruments. The head of the quality control laboratory shall be independent of the manufacturing unit. The testing shall be conducted under the direct supervision of competent technical staff who shall be whole time employees of the licensee.

13.3.7 Personnel

Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from Tuberculosis, skin and other communicable or contagious diseases. Thereafter, they should be medically examined periodically, at least once a year. Records shall be maintained thereof. The licensee shall provide the services of a qualified physician for assessing the health status of personnel involved in different activities. All persons prior to and during employment shall be trained in practices which ensure personnel hygiene. A high level of personal hygiene shall be observed by all those engaged in the manufacturing processes. Instructions to this effect shall be displayed in change rooms and other strategic locations.

All employees shall be instructed to report about their illness or abnormal health condition to their immediate supervisor so that appropriate action can be taken. All personnel shall wear clean body coverings appropriate to their duties. Before entry into the manufacturing area, there shall be change rooms separate for each sex with adequate facilities for personal cleanliness such as wash basin with running water, clean towels, hand dryers, soaps, disinfectants, etc. The change room shall be provided with cabinets for the storage of personal belongings of the personnel. Smoking, eating, drinking, chewing or keeping plants, food, drink and personal medicines shall not be permitted in production, laboratory, storage and other areas where they might adversely influence the product quality.

All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. Each critical step in the process relating to the selection, weighing and measuring of raw material

addition during various stages shall be performed by trained personnel under the direct personal supervision of approved technical staff. The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labelled with the name of the product, batch number, batch size and stage of manufacture. Each label should be initialled and dated by the authorized technical staff.

13.3.8 Raw Materials

The licensee shall keep an inventory of all raw materials to be used at any stage of manufacture of drugs and maintain records as per Schedule U. All incoming materials shall be quarantined immediately after receipt or processing. All materials shall be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation by a 'first in/first expiry, first out' principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed. All incoming materials shall be purchased from approved sources under valid purchase vouchers. Wherever possible, raw materials should be purchased directly from the producers and store with appropriate labels as per specification.

13.3.9 Equipment

Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general any adverse effect on the quality of products. Each equipment shall be provided with a logbook, wherever necessary. Balances and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in process control operations and these shall be calibrated and checked on a scheduled basis in accordance with Standard Operating Procedures and records maintained.

13.3.10 Documentation and Records

Documentation is an essential part of the quality assurance system and, as such, shall be related to all aspects Good Manufacturing Practices (GMP). Its aim is to define the specifications for all materials, method of manufacture and control, to ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a bath of drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch.

The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated Standard Operating Procedures (SOP) shall be retained for at least one year after the expiry date of the finished product. Data may be recorded by electronic data processing systems or other reliable means, but Master Formulae and detailed operating procedures relating

to the system in use shall also be available in a hard copy to facilitate checking of the accuracy of the records. Wherever documentation is handled by electronic data processing methods, authorized persons shall enter modify data in the computer. There shall be record of changed and deletions. Access shall be restricted by .passwords or other means and the result of entry of critical data shall be independently checked. Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available.

13.3.11 Labels and Other Printed Materials

Labels are absolutely necessary for identification of the drugs and their use. The Printing shall be done in bright colours and in a legible manner. The label shall carry all the prescribed details about the product. All containers and equipment shall bear appropriate labels. Different colour coded tablets shall be used to indicate the status of a product (for example under test, approved, passed, rejected). Printed packaging materials and product leaflets relating to different products shall be stored separately to avoid mix up chances. Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the quality control department of the licensee.

13.3.12 Quality Assurance

This is a wide-ranging concept concerning all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that products are of the quality required for their intended use.

The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that the pharmaceutical products are designed and developed in a way that takes account of the requirement of Good Manufacturing Practices (GMP) and other associated codes such as those of Good Laboratory Practices (GLP) and Good Clinical Practices (GCP).

13.3.13 Quality Control System

Quality control shall be concerned with sampling, specifications, testing, documentation, release procedures which ensure that the necessary and relevant tests are actually carried and that the materials are not released for use, nor products released for sale or supply until their quality has been judged to be satisfactory. It is not confined to laboratory operations but shall be involved n all decisions concerning the quality of the product. It shall be ensured that all quality control arrangements are effectively and reliably carried out the department as a whole shall have other duties such as to establish evaluate, validate and implement all quality control procedures and methods.

Every manufacturing establishment shall establish its own quality control laboratory manner by qualified and experience staff. The area of the quality control laboratory may be divided into chemical, instrumentation, microbiological and biological testing. Standard operating procedures shall be

available for sampling, inspecting and testing of raw materials, intermediate bulk finished products and packing materials and, wherever necessary, for monitoring environmental conditions.

The in-charge of quality assurance shall investigate all product complaints and records thereof shall be maintained. All instruments shall be calibrated and testing procedures validated before these are adopted for routine testing. Periodical calibration of instrument and validation of procedures shall be carried out. Each specification for raw materials, intermediates, final products, and packing materials shall be approved and maintained by the Quality Control Department. Periodic revisions of the specifications shall be carried out wherever changes are necessary.

13.3.14 Product 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. Whenever bottles are being used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, they should be rinsed with de-ionised water or distilled water, as the case may be.

Operations like removal of outer cardboard wrappings of primary packaging materials shall be done in the de-cartoning areas which are segregated from the washing areas. Wooden pallets, fibre board drugs, cardboard and other particle shedding materials shall not be taken inside the preparation areas.

13.3.15 Master Formula Records

There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by head of production and quality control. The master Formula shall include: -

a) the name of the product together with product reference code relating to its specifications;
b) the patent or proprietary name of the product along with the generic name, a description of the dosage form, strength, composition of the product and batch size;
c) name, quantity, and reference number of all the starting materials to be used. Mention shall be made of any substance that may .disappear. in the courts of processing;
d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
e) a statement of the processing location and the principal equipment to be used;

f) the methods, or reference to the methods, to be used for preparing the critical equipments including cleaning, assembling, calibrating, sterilizing;

g) detailed stepwise processing instructions and the time taken for each step;

h) the instructions for in-process control with their limits;

i) the requirements for storage conditions of the products, including the container, labelling and special storage conditions where applicable;

j) any special precautions to be observed; and

k) packing details and specimen labels.

13.3.16 Packing Records

There shall be authorized packaging instructions for each product, pack size and type. A batch packaging record shall be kept for each batch or part batch processed. It shall be based on the relevant parts of the packaging instructions, and the method of preparation of such records shall be designed to avoid transcription errors. Before any packaging operation begins, check shall be made and recorded that the equipment and the work stations are clear of the previous products, documents or materials not required for the planned packaging operations, and that the equipment is clean and suitable for use.

13.3.17 Product Recalls

A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard. There shall be an established written procedure in the form of standard operating procedure for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated promptly so as to effectively reach at the level of each distribution channel. The distribution records shall be readily made available to the persons designated for recalls. The designated person shall record a final report issued, including reconciliation between the delivered and the recovered quantities of the products.

13.3.18 Complaints and Adverse Reactions

All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated/evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained. Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority.

13.3.19 Specific Requirements

Sterile products, being very critical and sensitive in nature, a very high degree of precautions, prevention and preparations and needed. Apart from the general requirements of good manufacturing practices for premises, materials etc. for

pharmaceutical products, some additional requirements shall be complied with for the manufacture of sterile products, parenteral preparations (small volume injectables and large volume parenterals) and sterile ophthalmic preparations.

Dampness, dirt and darkness are to be avoided to ensure aseptic conditions in all areas. There shall be strict compliance in the prescribed standards especially in the matter of supply of water, air, active materials and in the maintenance of hygienic environment. Location of services like water, steam, gases etc. shall be such that their servicing or repair shall not pose any threat to the integrity of the facility. Water lines shall not pose any threat of leakage to aseptic area. The manufacturing areas shall be clearly separated into support areas (e.g. washing and component preparation areas, storage areas etc.), preparation areas (e.g. bulk manufacturing area, non-aseptic blending areas etc.) change areas and aseptic areas.

13.3.20 Aseptic Areas

The sterile items have to be manufactured in aseptic conditions to make them free from micro-organisms. Extra care and precaution have to be taken in the design and construction of the aseptic areas. Walls, floors and ceiling should be impervious, non-shedding, non-flaking and non-cracking. Flooring should be unbroken and provided with a cove both at the junction between the wall and the floor as well as the wall and ceiling. Walls shall be flat, and ledges and recesses shall be avoided. Ceiling shall be solid and joints shall be sealed. Light-fittings and air-grills shall flush with the walls and not hanging from the ceiling, so as to prevent contamination. There shall be no sinks and drains in Grade A and Grade B areas. Doors shall be made of non-shedding material. These may be made preferably of Aluminium or Steel material. Wooden doors shall not be used. Doors shall open towards the higher-pressure area so that they close automatically due to air pressure.

Windows shall be made of similar material as the doors, preferably with double panel and shall be flush with the walls. If fire escapes are to be provided, these shall be suitably fastened to the walls without any gaps. The furniture used shall be smooth, washable and made of stainless steel or any other appropriate material other than wood. The manufacturing and support areas shall have the same quality of civil structure described above for aseptic areas, except the environmental standards which may vary in the critical areas. Change rooms with entrance in the form of air-locks shall be provided before entry into the sterile product manufacturing areas and then to the aseptic area. Separate exit space from the aseptic areas is advisable. Change rooms to the aseptic areas shall be clearly demarcated into – ‘black’ ‘gray’ and ‘white’ rooms – with different levels of activity and air cleanliness. The black change room shall be provided with a hand washing sink. The sink and its drain in the un-classified (first) change rooms may be kept clean all the time. The specially designed drain shall be periodically monitored to avoid presence of pathogenic micro-organisms. Change room doors shall not be opened simultaneously. An appropriate inter-locking system and a visual and/or audible warning system may be installed to prevent the opening of more than one door at a time.

13.3.21 Garments

The garments required for use by personnel working in aseptic area shall be of special type. Outdoor clothing shall not be brought into the sterile areas. The garments shall be made of non-shedding and tight weave material. Cotton garments shall not be used. The garments shall shed virtually no fibres or particulate matter. The clothing and its quality shall be adopted to the process and the work place and worn in such a way as to protect the product from contamination. Garments shall be single piece with fastenings at cuffs, neck and at legs to ensure close fit. Trouser legs shall be tucked inside the cover boots. Suitable design of garments shall either include a hood (head-cover) or a separate hood which can be tucked inside the over-all. Pockets, pleats and belts shall be avoided in garments. Zips (if any) shall be of plastic material. Garments with damaged zips shall not be used.

Only clean, sterilized and protective garments shall be used at each work session where aseptic filtration and filling operations are undertaken and at each work shift for products intended to be sterilized, post-filling. The mask and gloves shall be changed at every work session in both instances.

In the case of manufacture of solid dosage forms like tablets and capsules, the processing of dry materials and products creates problems of dust control and cross-contamination. Special attention is therefore, needed in the design, maintenance and use of premises and equipment in order to overcome these problems. Wherever required, enclosed dust control manufacturing systems shall be employed. Suitable environmental conditions for the products handled shall be maintained by installation of air-conditioning wherever necessary. Effective air extraction systems, with discharge points situated to avoid contamination of other products and professes shall be provided. Filters shall be installed to retain dust and protect the factory and local environment.

Special care shall be taken to protect against subsequent contamination of the product by particles of metal or wood. The use of metal detector is recommended. Wooden equipment should be avoided. Screens, sieves, punches and dies shall be examined for wear and tear or for breakage before and after each use.

SAQ 2

What are GMP requirements?

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13.4 GOOD CLINICAL PRACTICES (GCP)

13.4.1 Origin of the Concept of GCP

The history of Good Clinical Practice (GCP) statute traces back to one of the oldest enduring traditions in the history of medicine – the Hippocratic Oath. As a guiding ethical code, the Hippocrates Oath is primarily known for its edict to do no harm to the patient. However, the complexities of modern medicine research necessitate a more elaborate set of norms and guidelines. A physician has to comply with some ethical and scientific responsibilities such as obtaining informed consent or disclosing risk while involved in biomedical research.

13.4.2 Definition

Good Clinical Practice is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the study subject.

It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek to establish two cardinal principles – protection of the rights of human subjects and authenticity of biomedical data generated. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India.

13.4.3 Principles of GCP

The main principles of GCP are given below:

i) Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (which you will study better in this unit) and that are consistent with GCP and the applicable regulatory requirement.

ii) 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.

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

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

v) Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

vi) 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.

vii) 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.

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

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

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

xi) 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).

xii) 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.

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

13.4.4 Helsinki Declaration

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects include research on identifiable human material or identifiable data. The Declaration was originally adopted in June 1964 in Helsinki, Finland, and has since undergone five revisions (1975, 1983, 1989, 1996, 2000) and two clarifications.

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects include research on identifiable human material or identifiable data.

Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

13.4.5 Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical trails on patients in different countries are approved and monitored by different regulatory agencies. In India it is governed by the Drug Controller General of India (DCGI) office through its subsidiary known as Central Drug Control Organisation CDSCO). In UK it is monitored by the Medicine and Healthcare products Regulatory Agency (MHRA), as advised by the committee on Safety of Medicines (SCM) while in USA the Food and Drug Administration (FDA) is in charge of the clinical trials.

13.4.6 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Composition: The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

a) At least five members.
b) At least one member whose primary area of interest is in a non-scientific area.
c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter. A list of IRB/IEC members and their qualifications should be maintained.

An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects. IRB/IEC should obtain the various necessary documents-trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities. The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed.

The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any

other relevant documentation the IRB/IEC requests. The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

Functions and Operations

The function and operations of IRB/IEC are given below:

- The IRB/IEC should perform its functions according to written operating procedures. It should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).
- An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.
- Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.
- The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.
- An IRB/IEC may invite non-members with expertise in special areas for assistance

Investigator

Investigator is an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations. For protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of drugs under investigation, an investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered.

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. He 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.

The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's brochure, in the product information and in other information sources provided by the sponsor. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority/ies. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

Sponsor

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

13.4.7 Contract Research Organization (CRO)

A Contract Research Organization (CRO) is an organization that offers clients a wide range of pharmaceutical research services. A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing. Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor. All references to a sponsor in this guidance document also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

Monitoring

The purposes of trial monitoring are to verify that:

a) The rights and well-being of human subjects are protected.

b) The reported trial data are accurate, complete, and verifiable from source documents.

c) The conduct of the trial is in compliance with the currently approved protocol / amendment(s), with GCP, and with the applicable regulatory requirement.

Schedule Y of Drug and Cosmetics Act

Schedule Y deals with regulations relating to clinical trial requirements for import, manufacture and obtaining marketing approval for a new drug in India. The procedure for applying for marketing approval depends on the status of the new drug, which can be broadly classified into three categories viz. new drug substances discovered which are already approved/marketed in other countries, new drug substances discovered which are not approved/ marketed in other countries and new drug substances discovered in India.

Recommendations for carrying out Clinical Trials in India:

- The clinical trials required to be carried out in the country before a new drug is approved for marketing depend on the status of the drug in other countries.
- Phase III trials are usually required for the drugs which are already approved/marketed in the country of origin.
- If the drug is not approved /marketed, trials are generally allowed to be initiated at one phase earlier to the phase of trials in other countries.
- For new drug substances (IND) discovered in other countries phase I trials are not usually allowed to be initiated in India unless phase I data from other countries are available. If the is of unmet therapeutic need, such trials may be permitted even in the absence of phase I data from other countries.
- For new drugs having potential for use in children, permission for clinical trials in the paediatric age group is normally given after phase III trials in adults are completed. However, if the drug is of value primarily in a disease of children, early trials in the paediatric age group may be allowed.

SAQ 3

What is meant by Good Clinical Practice (GCP)?

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13.5 SUMMARY

GLP is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental studies are planned, performed, monitored, recorded, archived and reported. GLP applies to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals. . GMP takes the holistic approach of regulating the manufacturing process and laboratory testing during the process itself. GMP gives much significance for the documentation of every aspect of the process, activities, and operations involved with drug and medical device manufacture. The Guidelines that govern the conduct of clinical trials in India include GCP 2001, Schedule Y, Ethical Guidelines for Biomedical Research on Human Subjects. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Clinical research is done in four phases (I, II, III and IV), each designed to address different questions.

13.6 TERMINAL QUESTIONS

1. Give the full form of the following:
   i) OECD; ii) QAP; iii) SOP; iv) IRB; v) IEC; vi) IB; vii) CRO
2. What are the purposes of trial monitoring?
3. Who chair the meeting of APEX body of nation GLP?
4. What are the functions of GLP inspectors?
5. Discuss the role of CRO in GCP.

13.7 ANSWERS

Self Assessment Questions

1. Good Laboratory Practice (GLP) embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, cosmetics, food and feed additives and contaminants, novel foods and biocides. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

2. GMP gives much significance for the documentation of every aspect of the process, activities, and operations involved with drug and medical device manufacture. Apart from the general GMP requirements, specific regulations are prescribed for various dosage forms injections, tablets, capsules and oral liquid items. Additionally, GMP requires that all manufacturing and testing equipment has been qualified as suitable for use, and that all operational methodologies and procedures (such as manufacturing, cleaning, and analytical testing) utilized in the drug manufacturing process have been validated (according to predetermined specifications), to demonstrate that they can perform their purported functions.

3. Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance 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, and that the clinical trial data are credible.

Terminal Questions

1. i) OECD: Organizations for Economic Co-operation and Development; ii) QAP: Quality Assurance Programme; iii) SOP: Standard Operating Procedures; iv) IRB: Institutional Review Board; v) IEC: Independent Ethics Committee; vi) IB: Investigator's Brochure; vii) CRO: Contract Research Organization

2. The purposes of trial monitoring are to verify that:

   a) The rights and well-being of human subjects are protected.
   b) The reported trial data are accurate, complete, and verifiable from source documents.
   c) The conduct of the trial is in compliance with the currently approved protocol / amendment(s), with GCP, and with the applicable regulatory requirement.

3. Chairman: Secretary, Department of Science and Technology, Ministry of Science and Technology, Govt. of India.

4. Please see subsection 13.2.5.

5. Refer to 13.4.7.

GLOSSARY

Good Laboratory Practice (GLP) : A set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived.

Contract : A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Contract Research Organization (CRO) : A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Ethics Committee : An independent review board or committee comprising of medical / scientific and non-medical / non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the “Protocol”, the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting “Informed Consent” of the study subjects and adequacy of confidentiality safeguards.

Investigator : A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Protocol : A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.

Sponsor : An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Standard Operating Procedures (SOPs) : Detailed, written instructions to achieve uniformity of the performance of a specific function.

Suggested Readings

1. OECD Principles of Good Laboratory Practice (as revised).
2. Schedule M of the Drugs and Cosmetic Act Rules.
3. Sharma P.P. (2004) How to practice GMPs. 4th ed. Vandana Publications.
4. ICH Quality Guidance's.Q10 - Pharmaceutical Quality System, Q8- Pharmaceutical Management.
5. ICH Guidelines for Good Clinical Practice, 1997.
6. Ethical Guidelines for Biomedical Research on Human Subjects, India Council of Medical Research, 2000.
7. Good Clinical Practice, Guidelines from Clinical Trials on Pharmaceutical Products I India, CDSCO, DGHS, Ministry of Health& Family Welfare, Government of India, 2001.