SHAMBHUNATH INSTITUTE OF PHARMACY, JHALWA, ALLAHABAD

LECTURE NOTES
ON

GOOD MANUFACTURING PRACTICES

UNIT –I

(BOP-485(B))

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BY

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UNIT I

INTRODUCTION TO GOOD MANUFACTURING PRACTICES

GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and QC. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products. Under GMP:

a) All manufacturing processes are clearly defined, systematically reviewed for associated risks in the light of scientific knowledge and experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
b) Qualification and validation are performed;
c) All necessary resources are provided, including: sufficient and appropriately qualified and trained personnel, adequate premises and space,

(iii) Suitable equipment and services,
(iv) Appropriate materials, containers and labels,
(v) Approved procedures and instructions,
(vi) Suitable storage and transport,
(vii) Adequate personnel, laboratories and equipment for in-process controls;

d) Instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
e) Procedures are carried out correctly and personnel are trained to do so;

f) **Records** are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive action is implemented;

g) **Records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;**

h) The proper storage and distribution of the products minimizes any risk to their quality and takes account of good distribution practices (GDP);

i) A system is available to recall any batch of product from sale or supply;

j) Complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products to prevent recurrence.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation: Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

Good manufacturing practices for pharmaceutical products

GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and QC. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products. Under GMP:

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Principle

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must 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.

Premises

General

1. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

2. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

4. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

5. Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Weighing areas

The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

Production Area

Cross- contamination should be avoided for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. Risk assessment should include among other parameters a toxicological evaluation of the products being manufactured (see Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities).

Dedicated facilities are required for manufacturing when a medicinal product presents a risk:

a) Which cannot be adequately controlled by operational and/ or technical measures or
b) Scientific data does not support threshold values (e.g. allergenic potential from highly sensitizing materials such as beta lactams) or

c) Threshold values derived from the toxicological evaluation are below the levels of detection

1. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
2. The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

4. Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

5. Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

6. Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

7. Weighing of starting materials usually should be carried out in a separate weighing room designed for such use.

8. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross contamination and facilitate cleaning.

9. Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

10. Production areas should be well lit, particularly where visual on-line controls are carried out.

11. In-process controls may be carried out within the production area provided they do not carry any risk to production.

Storage Areas

1. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

2. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3. Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

4. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

5. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

6. Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

7. Highly active materials or products should be stored in safe and secure areas.

8. Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

1. Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

2. Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

4. Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

1. Rest and refreshment rooms should be separate from other areas.

2. Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3. Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

4. Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

Equipment

1. Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

2. Repair and maintenance operations should not present any hazard to the quality of the products.

3. Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

4. Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

5. Equipment should be installed in such a way as to prevent any risk of error or of contamination.

6. Production equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

7. Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

8. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

9. Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

10. Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

11. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

Training

1. The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

2. Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.

3. Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

4. The concept of QA and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

5. Visitors or untrained personnel should preferably not be taken into the production and QC areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

6. Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

Personal hygiene

1. All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

2. All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions complied with.

3. Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or medicines until the condition is no longer judged to be a risk.

4. All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.

5. Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

6. To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

7. Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.

8. Personal hygiene procedures, including the wearing of protective clothing, should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g. contractors' employees, visitors, senior managers and inspectors.

Master formulae

A formally authorized master formula should exist for each product and batch size to be manufactured.

The master formula should include:

(a) the name of the product, with a product reference code relating to its specification;
(b) a description of the dosage form, strength of the product and
(c) batch size;
(d) a list of all starting materials to be used (if applicable with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);

(e) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
(f) a statement of the processing location and the principal equipment to be used;
(g) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
(h) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
(i) the instructions for any in-process controls with their limits;
(j) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
(k) any special precautions to be observed.
(l) Packaging instructions
(m) Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to: the name of the product;
(n) a description of its pharmaceutical form, strength and, where applicable, method of application;
(o) the pack size expressed in terms of the number, weight or volume of the product in the final container;
(p) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
(q) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the
(r) batch number and expiry date of the product have been marked;
(s) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
(t) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
(u) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

a) A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended.
b) Transcribing from approved documents should be avoided.)
c) Before any processing begins a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

d) During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:
   - the name of the product;
   - the number of the batch being manufactured;
   - dates and times of commencement, of significant intermediate stages, and of completion of production;
   - the name of the person responsible for each stage of production;
   - the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
   - the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
   - any relevant processing operation or event and the major equipment used;
   - the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
   - the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
   - notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

(a) A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

(b) Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

(c) The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:
   - the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
   - the date(s) and time(s) of the packaging operations;
   - the name of the responsible person carrying out the packaging operation;
   - the initials of the operators of the different significant steps;
   - the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

Standard operating procedures and records

(a) SOPs and associated records of actions taken or, where appropriate, conclusions reached should be available for:
(b) equipment assembly and validation;
(c) analytical apparatus and calibration;
(d) maintenance, cleaning and sanitization;
(e) personnel matters including qualification, training, clothing and hygiene;
(f) environmental monitoring;
(g) pest control;
(h) complaints;
(i) recalls;
(j) returns.

GOOD CLINICAL PRACTICES

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.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (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. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

THE PRINCIPLES OF ICH GCP

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 requirement(s).

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 nonclinical 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.

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

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 requirement(s).

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.

INVESTIGATOR'S BROCHURE

1. Introduction The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.
2. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitors procedures.
3. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.
4. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.
5. This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary.
6. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator.
7. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information.
8. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.
9. **Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for**

providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer.

10. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

Guideline for Good Clinical Practice

General Considerations

The IB should include:

1. **Title Page: This** should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

2. Confidentiality Statement The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

3. Contents of the Investigator's Brochure The IB should contain the following sections, each with literature references where appropriate:

4. Summary A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

5. Introduction A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

6. Physical, Chemical, and Pharmaceutical Properties and Formulation A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and

justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given. Any structural similarities to other known compounds should be mentioned. 35 Guideline for Good Clinical Practice

7. Nonclinical Studies Introduction: The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form.

8. Nonclinical Pharmacology A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

9. 36 Guideline for Good Clinical Practice (b) Pharmacokinetics and Product Metabolism in Animals A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given.

Medical Care of Trial Subjects

1) A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
2) During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
3) It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
4) Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

Investigational Product(s)

1) Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.
2) Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution’s duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

3) The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s).
4) These **records** should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.
5) The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
6) The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
7) The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly. 14 Guideline for Good Clinical Practice

Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

Informed Consent of Trial Subjects

1) In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.
2) The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.
3) The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4) Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
5) Those records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

GOOD LABORATORY PRACTICES (GLP)

THE FUNDAMENTAL POINTS OF GLP

The GLP regulations set out the rules for good practice and help researchers perform their work in compliance with their own pre-established plans and standardized procedures.

The regulations are not concerned with the scientific or technical content of the research programmes. Nor do they aim to evaluate the scientific value of the studies. All GLP texts, irrespective of their origin, stress the importance on the following points five points:

1. Resources: organization, personnel, facilities and equipment
2. Characterization: test items and test systems
3. Rules: study plans (or protocols) and written procedures
4. Results: raw data, final report and archives
5. Quality Assurance.

1. Resources Organization and personnel

GLP regulations require that the structure of R&D organizations and the responsibilities of R&D personnel be clearly defined. GLP also stresses that there should be sufficient staff to perform the tasks required. The qualifications and the training of staff must also be defined and documented. Facilities and equipment The regulations emphasize the need for sufficient facilities and equipment to perform the studies. All equipment must be in working order. To ensure this, a strict programme of qualification, calibration and maintenance must be adopted.

2. Characterization

In order to perform a study correctly, it is essential to know as much as possible about the materials used during the study. For studies that evaluate the properties of pharmaceutical compounds during non-clinical studies, it is a prerequisite to have details about the test item and the test system (often an animal or plant) to which the test item is to be administered.

3.Protocols and written procedures

The main steps of research studies are prescribed in the study plan or protocol. Being able to repeat studies and obtain similar results is a sine qua non of mutual acceptance of data and,

indeed, a central tenet of the scientific method, so the details of routine procedures must also be available to scientists involved in the study. However, the protocol, which provides the experimental design and timeframe for the study, does not contain all the technical detail necessary to conduct the study. These details are found in written standard operating procedures (SOPs). With the protocol and the SOPs it should be possible to repeat the study exactly, if necessary.

4. Results

Raw data All studies generate raw data. These are the outcome of research and form the basis for establishing scientific interpretations and arriving at conclusions. The raw data must also reflect the procedures and conditions of the study. Final Report The study report contains an account of the way in which the study was performed, incorporates the study results and includes the scientific interpretation of the data. The report is provided to regulatory authorities as part of the submission for registration and marketing approval. Archives Storage of records must ensure safekeeping for many years and allow for prompt retrieval.

5. Quality Assurance Quality assurance (QA)

As defined by GLP, is a team of persons (often called the Quality assurance unit – QAU) charged with assuring management that GLP compliance has been attained within the laboratory. QA must be independent from scientists involved in the operational aspects of the study being performed. QA functions as a witness to the whole non-clinical research process.

RESOURCES This section on resources is divided into three parts:

1. Management
2. Personnel
3. Facilities: buildings and equipment

Managerial aspects are therefore critical for GLP implementation in a laboratory. Laboratory management responsibilities and organizational requirements take up about 15% of the GLP text, clearly demonstrating that the regulators also consider these points as important. **Management has the overall responsibility for the implementation of both good science and good organization within their institution**

Good Science

- Careful definition of experimental design and study parameters.
- Science based on known scientific principles.
- Control and documentation of experimental and environmental variables.
- Careful and complete evaluation and reporting of results.
- Results becoming part of accepted scientific knowledge.

Good Organization

- Proper planning of studies and allocation of resources.
- Provision of adequate facilities, infrastructure and qualified staff.
- Definition of staff responsibilities and provision of staff training.
- Establishment of procedures to ensure proper conduct of studies.
- Good record keeping and organized archives.

• Implementation of verification procedures for study conduct and results.

• GLP Training Manual These organizational aspects of studies can be met by complying with GLP.

Planning (Master Schedule)

The need for a system of organising the allocation of resources and time for studies is self evident.

GLP requires that Management ensures allocation of sufficient personnel and other resources to specific studies and support areas.

The record of planning/resource allocation required by GLP is called the master schedule. The format of the master schedule is not stipulated. However, the general rules are: • All studies (contracted and in-house) must be included in the schedule.

• A change control procedure is in place to reflect shifts in dates and workload.

• Time-consuming activities such as protocol review and report preparation should also be included.

• The schedule is "official" (i.e. there should not be two or more competing systems for the same purpose).

• The system is described in an approved SOP.

• Responsibilities for its maintenance and updating are defined by management.

• Various versions of the master schedule are approved and maintained in the archive as data. • Distribution is adequate and key responsibilities are identified. Typically, once the protocol is signed and issued, the study is entered into the master schedule. Often responsibility for the master schedule rests with project management and the schedule is computerized for efficiency and ease of cross-indexing. The master schedule system is described in an SOP.

FACILITIES: BUILDINGS AND EQUIPMENT

1) GLP requires that test facilities be of appropriate size, construction and location to meet the requirements of the study and minimize disturbances that would interfere with the validity of the study.
2) They should be designed to provide an adequate degree of separation between the various activities of the study. The purpose of these requirements is to ensure that the study is not compromised because of inadequate facilities. It is important to remember that fulfilling the requirements of the study does not necessarily mean providing "state of the art" constructions, but carefully considering the objectives of the study and how to achieve them. It is up to the facility management to define what is adequate; this will depend on the kind of studies being performed.
3) Separation ensures that different functions or activities do not interfere with each other or affect the study. Minimizing disturbance by separation can be achieved by:

• Physical separation: this can be achieved by walls, doors or filters, or by the use of isolators. In new buildings or those under transition or renovation, separation will be part of the design.

• Separation by organization, for example by the establishment of defined work areas within a laboratory carrying out different activities in the same area at different times, allowing for cleaning and preparation between operations or maintaining separation of staff, or by the establishment of defined work areas within a laboratory.

As an illustration of the principles involved we have chosen two examples that are often found in laboratories.

These are

(A) The Dose Mixing Unit: the zone used for the preparation of the dosage form and

(B) Animal House Facilities. Example A: Dose Mixing Unit

(A)The Dose Mixing Unit is a laboratory area dealing with the work flow of test items, vehicles and control items: receipt, storage, dispensing, weighing, mixing, dispatch to the animal house and waste disposal. (Note: Most of the points which follow would equally apply to other laboratory areas such as analytical or histopathology areas

(B)Animal House Facility To minimize the effects of environmental variables on the animal, the facility should be designed and operated to control selected parameters (such as temperature, humidity and light). In addition, the facility should be organized in a way that prevents the animals from coming into contact with disease, or with a test item other than the one under investigation.

Requirements will be different depending upon the nature and duration of the studies being performed in the facility.

Risks of contamination can be reduced by a "barrier" system, where all supplies, staff and services cross the barrier in a controlled way. A typical animal house should have separations maintained by provision of areas for:

- different species
- different studies
- quarantine • changing rooms
- receipt of materials
- storage of materials – bedding and diet – test doses – cages – cleaning equipment
- necropsy
- waste disposal. The building and rooms should provide sufficient space for animals and studies, allowing the operators to work efficiently.

The environment control system should maintain the temperature, humidity and airflow constantly at the defined levels for the species concerned. Design should allow easy and thorough cleaning of surfaces of walls, doors, floors and ceilings. There should be no gaps or ledges where dirt and dust can accumulate. Water should not accumulate on uneven floors i.e. floors should be smooth and even and without crevices.

Whatever the capabilities or needs of the laboratory, sensible working procedures can reduce the damage from outside influences. Such procedures may include:

- minimising the number of staff allowed to enter the building;
- restricting entry into animal rooms;
- organising work flow so that clean and dirty materials are moved around the facility at different times of the day and ensuring that corridors are cleaned between these times;
- requiring staff to put on different clothing for different zones within the animal facility;
- ensuring that rooms are cleaned between studies.

Equipment Suitability and Calibration

To perform a study properly, adequate equipment must be available. All equipment should be suitable for its intended use. The equipment that is suitable for a given study depends on the type of the study and the study objectives. Suitability can only be assessed by consideration of the performance of the equipment. For example, there is no need to have a balance capable of weighing to decimals of a milligram to obtain the weekly weight of a rat; however a balance with this precision may be required in the analytical laboratory.

Whether formally qualified or not, all equipment must be calibrated and maintained to ensure accurate performance. Most frequently, the calibration depends on the use of standards used. For example, in the case of a balance, the standards are the weights that have been certified by a national or international standards authority as being within specified limits. Frequently the laboratory will have a set of certified weights. These "primary standards" are only used to qualify "secondary standards", which are then used on a routine basis.

Another example is standard chemicals which are used to test/calibrate equipment, like pH meters, to ensure accurate performance. Standards may also be compound samples of known concentration used to ensure that analytical equipment is functioning as expected and providing a basis for the calculation of the final result. The laboratory must decide the acceptable frequency for calibration; this will depend on the type of equipment and its use.

The calibration programme should be included in the SOPs of the institution. Proof that equipment is performing to specifications is essential, whether generating data (e.g. analytical equipment or balances) or maintaining standard conditions (e.g. refrigerators or air conditioning equipment). This can be done by periodic checking at a frequency that allows action to be taken in time to prevent any adverse effect on the study should the equipment be faulty.

Logbooks are often used to record these regular verifications. Full documentation of all tests for suitability and for all calibration must be kept within the laboratory to allow scientists to assess the accuracy of measurements taken during studies. These data should be archived so that they are readily available should it become necessary to investigate the results of a study, or during regulatory inspections. Records of repairs and routine maintenance, and any non-routine work should be kept. The purpose of these GLP requirements is to ensure the reliability of data generated and to ensure that data are not lost as a result of inaccurate, inadequate or faulty equipment.

Maintenance Facilities - Buildings and Equipment

GLP requirements that equipment should be maintained are based on the assumption that this reduces the likelihood of an unexpected breakdown and consequent loss of data. Maintenance may be carried out in two distinct ways:

- Preventive or planned, whereby a regular check is made irrespective of the performance of the equipment;
- Curative or reparative, when the piece of equipment is not functioning according to specification or when the equipment or system has broken down. Planned routine maintenance is a useful precaution for equipment that does not have a suitable backup or alternative. However, some pieces of equipment, such as modern computer driven analyzers or electronic balances, do not lend themselves to routine maintenance.

A better approach may be to check them regularly and ensure that suitable contingencies are available if any problem occurs. The contingencies may include having duplicate equipment,

having immediate access to an engineer, or having immediate access to a contract laboratory with equivalent equipment. Back-up for vital equipment as well as back-up for power failure should be available whenever possible. A laboratory should have the ability to continue with essential services to prevent the loss of animals or data. For example, a laboratory carrying out animal studies may need a stand-by generator capable of maintaining at least the animal room environment to prevent the loss of the animals that would irretrievably affect the study. Meanwhile, samples could be stored for a period until power is restored.

Documentation Facilities – Buildings and Equipment

Staff must be sure that that the equipment they use is suitable for use, has been adequately calibrated and maintained and is not outside its service interval.

Records of equipment suitability, calibration, checking and maintenance demonstrate that the laboratory SOPs have been followed and that the equipment used in any study is adequate for the job and performing to its specification. Records should also demonstrate that required actions have been taken as a result of the checks made. Documents and records should also show that that staff are well instructed in the use of equipment and are able to take appropriate action when problems arise.

The following section lists documents that should be present in a GLP compliant institution.

SOP: SOPs for instructions in the routine use, cleaning, calibration etc. of the facility or equipment. SOP for the regular verifications or services performed on buildings or equipment.

Qualification documents: When formal qualification is required, each phase of the qualification process should be documented. Each phase should have a protocol defining the tests to be conducted, data resulting from these tests, a report including the test results and a conclusion. When no formal qualification is required, the study director or the management of the institution should define, usually in an SOP, the purpose of the equipment. For example, a balance with a precision to the nearest gram will be suitable for weighing in an animal house but not in the analytical laboratory.

Logbook: Logbooks are kept to record the use of equipment (e.g. HPLC column used for product "x" – with dates, then for product "y" – with dates). They are also used for recording regular checks (e.g. regular use of check-weight for balances, temperature record for refrigerator, etc.).

Service report: Service reports and equipment labels indicate which instrument was serviced, when and by whom. The date of the next service is usually recorded on the equipment label. In the case of routine servicing the actual service procedure would be included in the SOP concerning the apparatus or facility.

Fault action report: These reports are made when something goes wrong. This is not routine work and an SOP may not be available for the person who deals with this problem. Therefore the fault action report should include the work performed on the equipment, the date of the work and the person who carried out the job. It is important that the person signs off with a statement indicating whether the equipment is fit or unfit for use.

SCHEDULE M

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR PHARMACEUTICAL PRODUCTS.

Note: - To achieve the objectives listed below, each licensee shall evolve appropriate methodology, systems and procedures which shall be documented and maintained for inspection and reference; and the manufacturing premises shall be used exclusively for production of drugs and no other manufacturing activity shall be undertaken therein.

GOOD MANUFACTURING PRACTICES FOR PREMISES AND MATERIALS.

1. GENERAL REQUIREMENTS

1.1. Location and surroundings.- The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environmental including open sewage, drain, public lavatory or any factory which product disagreeable or obnoxious odour, fumes, excessive soot, dust, smoke, chemical or biological emissions.

1.2. Building and premises.- The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948) the premises used for manufacturing, processing, warehousing, packaging labeling and testing purposes shall be
(i) compatible with other drug manufacturing operations that may be carried out in the same or adjacent area / section;
(ii) adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to:

(a) avoid the risk of mix-up between different categories of drugs or with raw materials, intermediates and in-process material;

(b) avoid the possibilities of contamination and cross- contamination by providing suitable mechanism;

(iii) designed / constructed / maintained to prevent entry of insects, pests, birds, vermins, and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection;

(iv) air-conditioned, where prescribed for the operations and dosage froms under production. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units (wherever applicable) 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. These shall also be suitable to the comforts of the personnel working with protective clothing, products

handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications;

(v) Provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back flow and/or prevent insets and rodents entering the premises. Open channels shall be avoided in manufacturing areas and, where provided, these shall be shallow to facilitate cleaning and disinfection;
(vi) The walls and floors of the areas where manufacture of drugs is carried out shall be free from cracks and open joints to avoid accumulation of dust. These shall be smooth, washable, covered and shall permit easy and effective cleaning and dis-infection. The interior surfaces shall not shed particles. A periodical record of cleaning and painting of the premises shall be maintained.

1.3 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.

1.4. Disposal of waste. - (i) 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. (ii) All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 1996.

Hazardous,toxic substances and flammable materials shall be stored in suitably designed and segregated, enclosed areas in conformity with Central and State Legislations.

2. Warehousing Area. –

2.1 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.

2.2 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), these shall be provided, monitored and recorded. Storage areas shall have appropriate house-keeping and rodent, pests and vermin control procedures and records maintained. Proper racks, bins and platforms shall be provided for the storage of materials.

2.3 Receiving and dispatch bays shall protect materials and products from adverse weather conditions.

2.4. Where quarantine status is ensured by warehousing in separate earmarked areas in the same warehouse or store, these areas shall be clearly demarcated. Any system replacing the physical quarantine, shall give equivalent assurance of segregation. Access to these areas shall be restricted to authorized persons

3. Production area.

3.1. The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.

3.2. In order to avoid the risk of corss-contamination, separate dedicated and self-contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live microorganisms. Separate dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as Beta-Lactum, sex hormones and cytotoxic substances.

3.3. 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.

4. Ancillary Areas.

4.1 Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.

4.2 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.

5. Quality Control Area

5.1. Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio-isotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis.

5.2 Quality Control Laboratories shall be designed appropriately for the operations to be carried out in them. Adequate space shall be provided to avoid mix-ups and cross-contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.

5.3. 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.

5.4. Quality Control Laboratory shall be divided into separate sections i.e. for chemical, microbiological and wherever required, biological testing.

6. Personnel.

6.1. The manufacture 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.

6.2 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.

6.3. Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced.

7. Health, clothing and sanitation of workers.

7.1 The personnel handling Beta-lactum antibiotics shall be tested for Penicillin sensitivity before employment and those handling sex hormones, cytotoxic substances and other potent drugs shall be periodically examined for adverse effects. These personnel should be moved out of these sections (except in dedicated facilities), by rotation, as a health safeguard.

7.2 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.

8. Manufacturing Operations and Controls.

8.1 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 labeled with the name of the product, batch number, batch size and stage of manufacture. Each label should be initialled and dated by the auhorised technical staff.

Products not prepared under aseptic conditions are required to be free from pathogens like Salmonella, Escherichia coli, Pyocyanea, etc.

8.2. Precautions against mix-up and cross-contamination-
8.2.1. The licensee shall prevent mix-up and cross-contamination of drug material and drug product (from environmental dust) by proper air-handling system, pressure differential, segregation, status labeling and cleaning. Proper records and Standard Operating Procedures thereof shall be maintained.
8.2.2 The licensee shall ensure processing of sensitive drugs like Beta-Lactum antibiotics, sex hormones and cytotoxic substances in segregated areas or isolated production areas within the building with independent air-handling unit and proper pressure differential. The effective segregation of these areas shall be demonstrated with adequate records of maintenance and services.
8.2.3 To prevent mix-ups during production stages, materials under process shall be conspicuously labeled to demonstrate their status. All equipment used for production shall be labeled with their current status.

9. Sanitation in the Manufacturing Premises.

9.1 The manufacturing premises shall be cleaned 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.

9.2 The manufacturing areas shall not be used for storage of materials, except for the material being processed. It shall not be used as a general throughfare.

10. Raw Materials.

10.1 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.

10.2 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 ëfirst in/first expiryí ñ ëfirstoutí principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed.

11. Equipment. –

11.1 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 minimise 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.

11.2 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.

12. 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.

12.1 Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.

12.2 Documents shall be approved, signed and dated by appropriate and authorized persons.

12.3 Documents shall specify the title, nature and purpose. They shall be laid out in an orderly fashion and be easy to check. Reproduced documents shall be clear and legible. Documents shall be regularly reviewed and kept up to date. Any alteration made in the entry of a document shall be signed and dated.

13. 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.

13.1 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).

13.2 To avoid chance mix-up of printed packaging materials, product leaflets, relating to different products, shall be stored separately.

13.3 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

14. 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.

14.1 The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that: -

(a) the pharmaceutical products are designed and developed in a way that takes account of the requirement of Good Manufacturing Practices (herein referred as GMP) and other associated codes such as those of Good Laboratory Practices (hereinafter referred as GLP) and Good Clinical Practices (herein after referred as GCP);

(b) adequate arrangements are made for manufacture, supply and use of the correct starting and packaging materials.

(c) adequate controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.

(d) the finished product is correctly processed and checked in accordance with established procedures;

(e) the pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch as been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of pharmaceutical products.

15. Self Inspection and Quality audit -

It may be useful to constitute a selfinspection team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it.

15.1 To evaluate the manufacturerís compliance with GMP in all aspects of production and quality control, concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results; evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.

15.2 The program shall be designed to detect shortcomings in the implementation of Good Manufacturing Practice and to recommend the necessary corrective actions. Self-inspections shall be performed routinely and on specific occasions, like when product recalls or repeated rejections occur or when an inspection by the licensing authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of Good Manufacturing Practice objectively; all recommendations for corrective action shall be implemented.

16. 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.

17. Specification

17.1 For raw materials and packaging materials. - They shall includea) the designated name and internal code reference; b) reference, if any, to a pharmacopoeial monograph; c) qualitative and quantitative requirements with acceptance limits; d) name and address of manufacturer or supplier and original manufacturer of the material; e) specimen of printed material; f) directions for sampling and testing or reference to procedures; g) storage conditions; and h) maximum period of storage before re-testing.

17.2 For product containers and closures. –

17.2.1 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.
17.2.2 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

18. 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 the competent technical staff i.e. 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 ëdisappearí 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.

19. Packing Records. –

There shall be authorised packaging instructions for each product, pack size and type. These shall include or have a reference to the following: -

(a) name of the product;

(b) description of the dosage form, strength and composition;

(c) the pack size expressed in terms of the number of doses, weight or volume of the product in the final container;

(d) complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types with the code of reference number relating to the specifications of each packaging material.

(e) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied;

(f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin.

(g) description of the packaging operation, including any significant subsidiary operations and equipment to be used;

20. Batch Packaging Records.

20.1 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.
20.2 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.

21. Batch Processing Records
21.1 There shall be Batch Processing Record for each product. It shall be based on the relevant parts of the currently approved Master Formula. The method of preparation of such records included in the Master Formula shall be designed to avoid transcription errors.
21.2 Before any processing begins, check shall be performed and recorded to ensure that the equipment and work station are clear of previous products, documents or materials not required for the planned process are removed and the equipment is clean and suitable for use.

22. Standard Operating Procedures (SOPs) and Records, regarding. –

22.1 Receipt of materials:
22.1.1 there shall be written Standard Operating Procedures and records for the receipt of each delivery of raw, primary and printed packaging material.
22.1.2 the records of the receipts shall include; (a) the name of the material on the delivery note and the number of containers; (b) the date of receipt; (c) the manufacturerís and/ or supplierís name; (d) the manufacturerís batch or reference number; (e) the total quantity, and number of containers, quantity in each container received; (f) the control reference number assigned after receipt; (g) any other relevant comment or information.
22.1.3 There shall be written standard operating procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

23. Reference Samples. –

23.1 Each lot of every active ingredient, in a quality sufficient to carryout all the tests, except sterility and pyrogens / Bacterial Endotoxin Test, shall be retained for a period of 3 months after the date of expiry of the last batch produced from that active ingredient.

23.2. Samples of finished formulations shall be stored in the same or simulated containers in which the drug has been actually marketed.

STANDARD OPERATING PROCEDURE (SOP)

INTRODUCTION

A Standard Operating Procedure (SOP) is a set of written instructions that document a routine or repetitive activity followed by an organization. The development and use of SOPs are an integral part of a successful quality system as it provides individuals with the information to perform a job properly, and facilitates consistency in the quality and integrity of a product or end-result. The term “SOP” may not always be appropriate and terms such as protocols,

instructions, worksheets, and laboratory operating procedures may also be used. For this document “SOP” will be used.

Purpose

SOPs detail the regularly recurring work processes that are to be conducted or followed within an organization. They document the way activities are to be performed to facilitate consistent conformance to technical and quality system requirements and to support data quality. They may describe, for example, fundamental programmatic actions and technical actions such as analytical processes, and processes for maintaining, calibrating, and using equipment. SOPs are intended to be specific to the organization or facility whose activities are described and assist that organization to maintain their quality control and quality assurance processes and ensure compliance with governmental regulations.

If not written correctly, SOPs are of limited value. In addition, the best written SOPs will fail if they are not followed. Therefore, the use of SOPs needs to be reviewed and re-enforced by management, preferably the direct supervisor. Current copies of the SOPs also need to be readily accessible for reference in the work areas of those individuals actually performing the activity, either in hard copy or electronic format, otherwise SOPs serve little purpose.

SOP Preparation

The organization should have a procedure in place for determining what procedures or processes need to be documented. Those SOPs should then be written by individuals knowledgeable with the activity and the organization's internal structure. These individuals are essentially subject-matter experts who actually perform the work or use the process.

A team approach can be followed, especially for multi-tasked processes where the experiences of a number of individuals are critical, which also promotes “buy-in” from potential users of the SOP.

SOPs should be written with sufficient detail so that someone with limited experience with or knowledge of the procedure, but with a basic understanding, can successfully reproduce the procedure when unsupervised.

The experience requirement for performing an activity should be noted in the section on personnel qualifications. For example, if a basic chemistry or biological course experience or additional training is required that requirement should be indicated.

SOP Review and Approval

SOPs should be reviewed (that is, validated) by one or more individuals with appropriate training and experience with the process. It is especially helpful if draft SOPs are actually tested by individuals other than the original writer before the SOPs are finalized. The finalized SOPs should be approved as described in the organization’s Quality Management

Plan or its own SOP for preparation of SOPs. Generally the immediate supervisor, such as a section or branch chief, and the organization’s quality assurance officer review and approve each SOP. Signature approval indicates that an SOP has been both reviewed and approved by management.

Frequency of Revisions and Reviews SOPs need to remain current to be useful. Therefore, whenever procedures are changed, SOPs should be updated and re-approved. If desired, modify only the pertinent section of an SOP and indicate the change date/revision number for that

section in the Table of Contents and the document control notation. SOPs should be also systematically reviewed on a periodic basis, e.g. every 1-2 years, to ensure that the policies and procedures remain current and appropriate, or to determine whether the SOPs are even needed. The review date should be added to each SOP that has been reviewed. If an SOP describes a process that is no longer followed, it should be withdrawn from the current file and archived. The review process should not be overly cumbersome to encourage timely review. The frequency of review should be indicated by management in the organization's Quality Management Plan.

That plan should also indicate the individual(s) responsible for ensuring that SOPs are current.

Checklists

Many activities use checklists to ensure that steps are followed in order. Checklists are also used to document completed actions. Any checklists or forms included as part of an activity should be referenced at the points in the procedure where they are to be used and then attached to the SOP.

In some cases, detailed checklists are prepared specifically for a given activity. In those cases, the SOP should describe, at least generally, how the checklist is to be prepared, or on what it is to be based. Copies of specific checklists should be then maintained in the file with the activity results and/or with the SOP.

Remember that the checklist is not the SOP, but a part of the SOP.

2.6 SOP Document Tracking and Archival

The organization should maintain a master list of all SOPs. This file or database should indicate the SOP number, version number, date of issuance, title, author, status, organizational division, branch, section, and any historical information regarding past versions.

The QA Manager (or designee) is generally the individual responsible for maintaining a file listing all current quality-related SOPs used within the organization. If an electronic database is used, automatic "Review SOP" notices can be sent. The Quality Management Plan should indicate the individual(s) responsible for assuring that only the current version is used. That plan should also designated where, and how, outdated versions are to be maintained or archived in a manner to prevent their continued use, as well as to be available for historical data review. Electronic storage and retrieval mechanisms are usually easier to access than a hard-copy document format. For the user, electronic access can be limited to a read-only format, thereby protecting against unauthorized changes made to the document.

SOP GENERAL FORMAT

SOPs should be organized to ensure ease and efficiency in use and to be specific to the organization which develops it. There is no one "correct" format; and internal formatting will vary with each organization and with the type of SOP being written. Where possible break the information into a series of logical steps to avoid a long list.

The level of detail provided in the SOP may differ based on, e.g., whether the process is critical, the frequency of that procedure being followed, the number of people who will use the SOP, and where training is not routinely available.

A generalized format is discussed next.

1 Title Page

The first page or cover page of each SOP should contain the following information: a title that clearly identifies the activity or procedure, an SOP identification (ID) number, date of issue and/or revision, the name of the applicable agency, division, and/or branch to which this SOP applies, and the signatures and signature dates of those individuals who prepared and approved the SOP. Electronic signatures are acceptable for SOPs maintained on a computerized database.

2. Table of Contents

A Table of Contents may be needed for quick reference, especially if the SOP is long, for locating information and to denote changes or revisions made only to certain sections of an SOP.

3. Text Well-written SOPs should first briefly describe the purpose of the work or process, including any regulatory information or standards that are appropriate to the SOP process, and the scope to indicate what is covered.

Define any specialized or unusual terms either in a separate definition section or in the appropriate discussion section. Denote what sequential procedures should be followed, divided into significant sections; e.g., possible interferences, equipment needed, personnel qualifications, and safety considerations (preferably listed in bold to capture the attention of the user).

Finally, describe next all appropriate QA and quality control (QC) activities for that procedure, and list any cited or significant references.

VALIDATION OF SOP's

Definition of Validation

Validation is a systematic approach to gathering and analyzing sufficient data which will give reasonable assurance (documented evidence), based upon scientific judgment, that a process, when operating within specified parameters, will consistently produce results within predetermined specifications.

Type of Validation

Retrospective Validation
Prospective Validation
Concurrent Validation
Revalidation

1. **Retrospective Validation**

   Validation of a process for a product already in distribution, based on accumulated production, testing, and control dates. Summary of existing historical data.
2. **Prospective Validation**

   Validation conducted prior to distribution either of a new product, or a product made under a revised manufacturing process. Validation is completed and the results are approved prior to any product release.
3. **Concurrent Validation**

A combination of retrospective and prospective validation. Performed against an approved protocol but product is released on a lot-by-lot basis. Usually used on an existing product not previously validated or insufficiently validated.

4. **Revalidation**

   To validate change in equipment, packaging, formulation operating procedure, or process that could impact product safety, efficacy, or potency. It is important to establish a revalidation program for critical equipment to maintain validity.

Importance of Validation

1) Increased throughput
2) Reduction in rejections and reworking
3) Reduction in utility costs
4) Avoidance of capital expenditures
5) Fewer complaints about process-related failures
6) Reduced testing in-process and in finished goods
7) More rapid and reliable start-up of new equipment
8) Easier scale-up from development work
9) Easier maintenance of equipment
10) Improved employee awareness of processes
11) More rapid automation

The Basic Concept of Process Validation

1. Requalification or revalidation
2. Calibration, verification, and maintenance of process equipment
3. Establishing specifications and performance characteristics
4. Selection of methods, process, and equipment to ensure the product meets specifications
5. Qualification or validation of process and equipment
6. Testing the final product, using validated analytical methods, in order to meet specifications
7. Challenging, auditing, monitoring, or sampling the recognized critical and key steps of the process.