MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health and Family Welfare)

NOTIFICATION

New Delhi, the 28th December, 2023

G.S.R. 922(E).—Whereas, a draft of certain rules further to amend the Drugs Rules, 1945 was published as required under sub-section (1) of section 12 and sub-section (1) of section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940) (thereafter referred to as the said Act) *vide* notification of the Government of India in the Ministry of Health and Family Welfare (Department of Health and Family Welfare), number G.S.R. 999(E), dated the 5th October, 2018, published in the Gazette of India, Extraordinary, Part II, Section 3, Sub-section (i), inviting objections and suggestions from persons likely to be affected thereby, before the expiry of a period of thirty days from the date on which the copies of the said Official Gazette containing the said notification were made available to the public;

And, whereas, copies of the said Gazette were made available to the public on 9th October, 2018;

And, whereas, objections or suggestions received from the public on the said rules were considered by the Central Government;

Now, therefore, in exercise of the powers conferred by sections 12 and 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board constituted under section 5 of the said Act, hereby makes the following rules further to amend the Drugs Rules, 1945, namely:-

1. Short title and commencement.- (1) These rules may be called the Drugs (….. Amendment) Rules, 2023.

(2) They shall come into force from the date of their publication in the Official Gazette.

2. In the Drugs Rules, 1945 (hereinafter referred to as the principal rules), in rule 74, in clause (o), for the words "Good Manufacturing Practices", the words "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products" shall be substituted.

3. In the principal rules, in rule 76, in clause (8), for the words "Good Manufacturing Practices", the words "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products" shall be substituted.

4. In the principal rules, in rule 78, in clause (p), for the words "Good Manufacturing Practices", the words "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products" shall be substituted.

5. In the principal rules, for Schedule M, the following Schedule shall be substituted, namely:-

SCHEDULE M

[See rules 71, 74, 76 and 78]

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.

PART I

GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS:

MAIN PRINCIPLES

1. Pharmaceutical Quality System (PQS):

1.1. The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the licence and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in different departments and at all levels within the company, the company's suppliers and the distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented pharmaceutical quality system incorporating Good Manufacturing Practices (GMP) and Quality Risk Management (QRM).

1.2. Senior management has the ultimate responsibility to ensure that an effective pharmaceutical quality system is in place, is adequately resourced, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the pharmaceutical quality system is essential. This shall ensure the support and commitment of staff at all levels and sites within the organisation to the pharmaceutical quality system.

1.3. Quality management is a wide-ranging concept covering 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 pharmaceutical products are of the quality required for their intended use. Quality management, therefore, incorporates Good Manufacturing Practices and other factors, including those outside the scope of this Part, such as product design and development.

1.4. Good Manufacturing Practices applies to the life-cycle stages from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, until the product discontinuation. The product quality system can extend to the pharmaceutical development life-cycle stages and shall facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. All parts of the product quality system shall be adequately resourced and maintained, including being provided with sufficient competent personnel, suitable premises, equipment and facilities.

1.5. The product quality system appropriate to the manufacture of pharmaceutical products shall ensure that—

(a) product realisation is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

(b) product and process knowledge is managed throughout all lifecycle stages;

(c) pharmaceutical products are designed and developed in a way that takes into account, the requirements of GMP and other GXPs such as those of Good Laboratory Practices (GLP) and Good Clinical Practices (GCP);

(d) production and quality control operations shall be clearly specified in a written form and GMP requirements are adopted;

(e) managerial responsibilities are clearly specified in the job descriptions;

(f) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;

(g) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out;

(h) the finished product is correctly processed and checked, according to the defined procedures;

(i) pharmaceutical products are not sold or supplied before the authorised persons have certified that each production batch has been produced and controlled in accordance with the requirements of the licence and other applicable regulations relevant to the production, control and release of pharmaceutical products;

(j) processes are in place to ensure the management of outsourced activities;

(k) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;

(l) there is a procedure for self-inspection or quality audit that regularly appraises the effectiveness and applicability of the product quality system;

(m) product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviations occurring in the future;

(n) arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to their implementation, taking into account regulatory notification and approval where required. After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;

(o) regular reviews of the quality of pharmaceutical products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;

(p) a state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;

(q) continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;

(r) there is a system for QRM; and

(s) deviations, suspected product defects and other problems are reported, investigated and recorded. An

appropriate level of root cause analysis is applied during such investigations. The most likely root causes shall be identified and appropriate corrective and preventive actions shall be identified and taken. The effectiveness of corrective and preventive actions shall be monitored.

1.6. There shall be periodic management reviews, with the involvement of senior management, of the operation of the product quality system to identify opportunities for continual improvement of products, processes and the system itself. Unless otherwise justified, such reviews shall be conducted at least annually.

1.7. The product quality system shall be defined and documented. A quality manual or an equivalent documentation shall be established and shall contain a description of the quality management system including management responsibilities.

2. Quality Risk Management (QRM):

2.1. Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

2.2. Quality Risk Management shall ensure that the-

(a) evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

(b) level of effort, formality and documentation of the QRM process is commensurate with the level of risk.

2.3. Product quality review-

2.3.1. Regular, periodic or rolling quality reviews of all pharmaceutical products, including products for export only, shall be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

2.3.2. Such reviews shall normally be conducted and documented annually, taking into account previous reviews, and shall include at least,-

(a) review of starting materials and packaging materials used for the product, especially those from new sources and in particular the review of supply chain traceability of active substances;

(b) a review of critical in-process controls, and finished product results;

(c) a review of all batches that failed to meet established specifications and their investigation;

(d) a review of all significant deviations or non-conformity, the related investigations and the effectiveness of resultant corrective and preventive actions taken;

(e) a review of all changes made to the processes or analytical methods;

(f) a review of dossier variations submitted, granted or refused;

(g) a review of the results of the stability monitoring programme and any adverse trends;

(h) a review of all quality related returns, complaints and recalls and the investigations performed at the time;

(i) a review of adequacy of any other previous corrective actions on product processes or equipment;

(j) post marketing commitments for new dossiers and variations to the dossiers;

(k) the qualification status of relevant equipment and utilities, e.g., heating, ventilation and air conditioning, water or compressed gases and a review of the results of monitoring the output of such equipment and utilities; and

(l) a review of technical agreements to ensure that they are up to date.

2.3.3. The manufacturer shall evaluate the results of the review and an assessment shall be made as to whether corrective and preventive actions or any revalidation shall be undertaken, under the product quality system. Corrective and preventive actions shall be completed in a timely and effective manner, according to documented procedures. There shall be procedures for the on-going management and review of these actions, and the effectiveness of these procedures shall be verified during self-inspection. Quality reviews may be grouped by product type e.g., solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified. There shall be a

technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorised person responsible for final batch certification shall ensure that the quality review is performed in a timely manner and is accurate.

3. Good manufacturing practices for pharmaceutical products:

3.1. Good manufacturing practices 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 as required by the conditions of licence, clinical trial permission or product specifications. Good manufacturing practices are concerned with both production and quality control. Good manufacturing practices are aimed primarily at managing and minimising the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products. Under Good manufacturing practices—

(1) 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;

(2) qualification and validation are performed;

(3) all necessary resources are provided, including the following, namely-

(a) sufficient and appropriately qualified and trained personnel;

(b) adequate premises and space;

(c) suitable equipment and services;

(d) appropriate materials, containers and labels;

(e) approved procedures and instructions;

(f) suitable storage and transport;

(g) adequate personnel, laboratories and equipment are in process controls; and

(h) books necessary for ensuring compliance with the requirements relating to product development, manufacturing and quality control testing such as the Drugs and Cosmetics Act, 1940, the Drugs Rules, 1945, the Indian Pharmacopoeia (Current Edition) and other relevant books and guidance documents officially issued by the Ministry of Health and Family Welfare, Government of India;

(4) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;

(5) procedures are carried out correctly and personnel are trained to do so;

(6) records are made (manually or by recording instruments or by both) 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;

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

(8) the proper storage and distribution of the products which minimises any risk to their quality;

(9) a system is available to recall any batch of product from sale or supply; and

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

4. Sanitation and hygiene:

A high level of sanitation and hygiene shall be practiced in every aspect of the manufacture of drugs. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection and anything that could become a source of contamination to the product. Potential sources of contamination shall be eliminated through an integrated comprehensive programme of sanitation and hygiene.

5. Qualification and validation:

5.1. In accordance with GMP, each pharmaceutical company shall identify what qualification and validation work

is required to prove that the critical aspects of their particular operation is controlled.

5.2. The key elements of a qualification and validation programme of a company shall be clearly defined and documented in a validation master plan.

5.3. Qualification and validation shall establish and provide documentary evidence that—

(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for good manufacturing practices [design qualification (DQ)];

(b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications [installation qualification (IQ)];

(c) the premises, supporting utilities and equipment operate in accordance with their design specifications [operational qualification (OQ)];

(d) a specific process shall consistently produce a product meeting its predetermined specifications and quality attributes [process validation (PV), also called performance qualification (PQ)].

5.4. Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, shall be qualified and validated.

5.5. Qualification and validation shall not be considered as one-off exercises. An on-going programme shall follow their first implementation and shall be based on a periodic review.

5.6. The commitment to maintain continued validation status shall be stated in the relevant company documentation, such as the quality manual or validation master plan.

5.7. The responsibility for performing validation shall be clearly defined.

5.8. Validation studies are an essential part of good manufacturing practices and shall be conducted in accordance with predefined and approved protocols.

5.9. A written report summarising the results recorded and the conclusions reached shall be prepared and stored.

5.10. Processes and procedures shall be established on the basis of the results of the validation performed.

5.11. Particular attention shall be paid to the validation of analytical test methods, automated systems and cleaning procedures.

5.12. The premises, equipment or process system, facility qualification and validation shall be carried out.

6. Complaints and adverse reaction:

6.1. All complaints and other information concerning potentially defective products shall be carefully reviewed according to the written procedures and corrective action shall be taken.

6.2. A person responsible for handling the complaints and deciding the measures to be taken shall be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorised person, the latter shall be made aware of any complaint, investigation or recall.

6.3. There shall be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

6.4. Special attention shall be given to establishing that the product that gave rise to a complaint was defective.

6.5. Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control (QC) shall normally be involved in the review of such investigations.

6.6. If a product defect is identified or suspected in a batch, consideration shall be given as to whether other batches shall be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch shall be investigated.

6.7. Where necessary, appropriate follow-up action, possibly including product recall, shall be taken after investigation and evaluation of the complaint.

6.8. All decisions made and measures taken as a result of a complaint shall be recorded and referenced to the corresponding batch records.

6.9. Complaint records shall be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

6.10. The licensing authorities shall be informed if a manufacturer is considering action following the faulty manufacture, product deterioration, a suspect product or any other serious quality problems with a product.

6.11. The licensee shall have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the adverse drug reactions emerging from the use of drugs manufactured or marketed by the licensee.

7. Product recalls:

7.1. There shall be a system to recall from the market, products known or suspected to be defective.

7.2. The authorised person shall be responsible for the execution and coordination of recalls. He or she shall have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

7.3. There shall be established written procedures, which are regularly reviewed and updated, for the organisation of any recall activity. Recall operations shall be capable of being initiated at the required level in the distribution chain.

7.4. An instruction shall be included in the written procedures to store recalled products in a secure segregated area.

7.5. The licensing authorities shall be informed of any intention to recall the product because it is, or is suspected of being, defective.

7.6. The distribution records shall be readily available to the authorised person, and they shall contain sufficient information on wholesalers and directly supplied customers to permit an effective recall.

7.7. The progress of the recall process shall be monitored and recorded. Records shall include the disposition of the product. A final report shall be issued, including reconciliation between the delivered and recovered quantities of the products.

7.8. The effectiveness of the arrangements for recall shall be tested and evaluated from time to time.

7.9. A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard.

7.10. There shall be an established written procedure in the form of Standard Operating Procedure for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated, so as to effectively reach at the level of each distribution channel.

7.11. The distribution records shall be readily made available to the persons designated for recall.

7.12. The designated person shall record a final report issued, including reconciliation between the delivered and the recovered quantities of the products.

7.13. The effectiveness of the arrangements for recall shall be evaluated from time to time.

7.14. The recalled products shall be stored separately in a secured segregated area pending final decision on them.

8. Change control:

8.1. A formal change control system shall be established to evaluate all changes that may affect the production and control of the product.

8.2. Written procedures shall cover the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

8.3. Any proposals for relevant changes to GMP shall be drafted, reviewed and approved by the appropriate organisational units and reviewed and approved by the quality units.

8.4. The potential impact of the proposed change on the quality of the intermediate or Active Pharmaceutical Ingredient (API) or finished product shall be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on their nature and extent and the effect of these changes may have on the process. Scientific judgement shall be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.

8.5. When implementing the approved changes, measures shall be taken to ensure that all the documents are affected by the changes as revised.

8.6. After the change has been implemented there shall be an evaluation of the first batch produced or tested under the change.

8.7. The potential for critical changes to affect established retest or expiry dates shall be evaluated. If necessary,

samples of the intermediate or API or finished product produced by the modified process can be placed on an accelerated stability programme or can be added to the stability monitoring programme or both.

9. Production under loan licence or contract and contract analysis and other activities:

9.1. **Principle-** Production under loan licence or contract and contract analysis and any other activity covered by good manufacturing practices must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

9.2. **General-**

9.2.1. All arrangements for production under loan licence or contract and analysis, including technology transfer and any proposed changes in technical or other arrangements, shall be in accordance with the licence for the product concerned.

9.2.2. The contract shall permit the loan licensee or contract giver to audit the facilities and activities of the manufacturing facility provider or contract acceptor or mutually agreed sub-contractors.

9.2.3. In the case of contract analysis, the final approval for release must be given by the authorised person in accordance with good manufacturing practices and the licence as specified in the contract.

9.3. **Loan licensee or contract giver-**

9.3.1. The product quality system of the loan licensee or contract giver shall include the control and review of any outsourced activities. The contract giver is responsible for assessing the legality, suitability and competence of the manufacturing facility provider or contract acceptor to successfully carry out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of good manufacturing practices incorporating quality risk management principles are followed.

9.3.2. The loan licensee or contract giver shall provide the manufacturing facility provider or contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the licence and any other legal requirements. The loan licensee or contract giver shall ensure that the manufacturing facility provider or contract acceptor is fully aware of any hazards associated with the product, work or tests that might pose a risk to premises, equipment, personnel, other materials or other products.

9.3.3. The loan licensee or contract giver shall review and assess the records and results related to the outsourced activities. The contract giver shall ensure that all the products and materials delivered by the manufacturing facility provider or contract acceptor have been processed in accordance with good manufacturing practices and the licence; comply with their specifications and that the product has been released by the authorised person in accordance with good manufacturing practices and the licence.

9.3.4. The loan licensee or contract giver shall monitor and review the performance of the manufacturing facility provider or contract acceptor including the implementation of any needed improvements and their effectiveness.

9.3.5. The loan licensee or contract giver is responsible for ensuring that the manufacturing facility provider or contract acceptor understands that his or her activities may be subject to inspection by the competent authorities.

9.4. **Manufacturing facility provider or contract acceptor-**

9.4.1. The manufacturing facility provider or contract acceptor must have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work ordered by the loan licensee or contract giver. Contract manufacture shall be undertaken only by a manufacturer who holds a valid manufacturing licence.

9.4.2. The manufacturing facility provider or contract acceptor shall not pass to a third party any of the work entrusted to him or her under the contract without the loan licensee or contract giver's prior evaluation and approval of the arrangements. Arrangements made between the manufacturing facility provider or contract acceptor and any third party shall ensure that information and knowledge, including that from assessments of the suitability of the third party, are made available in the same way as between the original loan licensee or contract giver and contract acceptor.

9.4.3. The manufacturing facility provider or contract acceptor shall refrain from any activity (including unauthorised changes outside the terms of the contract) that may adversely affect the quality of the product manufactured oranalysed or both for the loan licensee or contract giver.

9.5. **Contract-**

9.5.1. There must be a written contract between the loan licensee or contract giver and the manufacturing facility provider or contract acceptor which clearly establishes the responsibilities of each party, covering the outsourced activities, the products or operations to which they are related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it.

9.5.2. The contract must clearly state the way in which the authorised person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the licence.

9.5.3. Technical aspects of the contract shall be drawn up by competent persons with suitable knowledge of pharmaceutical technology, analysis and good manufacturing practices.

9.5.4. All arrangements for production and analysis must be in accordance with the licence and agreed by both parties.

9.5.5. The contract shall clearly describe who is responsible for contracted activities e.g., knowledge management, technology transfer, supply chain, sub-contracting, testing and releasing materials and undertaking production and quality control, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract shall state whether or not the manufacturing facility provider or contract acceptor shall take samples at the premises of the manufacturer.

9.5.6. Manufacturing, analytical and distribution records, and reference samples, shall be kept by, or be available to, the loan licensee or contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect, or to investigating a suspected product or laboratory fraud, must be accessible and specified in the procedures of the loan licensee or contract giver.

9.5.7. The contract shall describe the handling of starting materials, intermediate, bulk and finished products, if they are rejected. It shall also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

10. Self-inspection, quality audits and suppliers' audits and approval:

10.1. The purpose of self-inspection is to evaluate the manufacturer's compliance with good manufacturing practices in all aspects of production and QC. The self-inspection programme shall be designed to detect any shortcomings in the implementation of good manufacturing practices and to recommend the necessary corrective actions. Self-inspections shall be performed routinely, and may be, in addition, performed on special occasions e.g., in the case of product recall or repeated rejections, or when an inspection by the regulatory authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of good manufacturing practices objectively. All recommendations for corrective action shall be implemented. The procedure for self-inspection shall be documented and there shall be an effective follow-up programme.

10.2. **Items for self-inspection-**Written instructions for self-inspection shall be established to provide a minimum and uniform standard of requirements. These may include questionnaires on good manufacturing practices requirements covering at least the following items, namely:-

(a) personnel;

(b) premises including personnel facilities;

(c) maintenance of buildings and equipment;

(d) storage of starting materials and finished products;

(e) equipment;

(f) production and in-process controls;

(g) quality control (QC);

(h) documentation;

(i) sanitation and hygiene;

(j) validation and revalidation programmes;

(k) calibration of instruments or measurement systems;

(l) recall procedures;

(m) complaints management;

(n) labels control; and

(o) results of previous self-inspections and any corrective steps taken.

10.3. **Self-inspection team-** Management shall appoint a self-inspection team consisting of experts in their respective fields who are familiar with GMP. The members of the team may be appointed from inside or outside the company.

10.4. **Frequency of self-inspection-** The frequency with which self-inspections are conducted may depend on company requirements but shall be at least once in a year. The frequency shall be stated in the procedure.

10.5. **Self-inspection report-** A report shall be made at the completion of a self-inspection. The report shall include the following, namely:-

(a) self-inspection results;

(b) evaluation and conclusions; and

(c) recommended corrective actions.

10.6. **Follow-up action-** There shall be an effective follow-up programme. The company management shall evaluate both the self-inspection report and the corrective actions as necessary.

10.7. **Quality audit-** It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

10.8. **Suppliers' audits and approval-**

10.8.1. The person responsible for quality control shall have responsibility, together with other relevant departments, for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

10.8.2. Before suppliers are approved and included in the approved suppliers' list or specifications, they shall be evaluated. The evaluation shall take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it shall determine the supplier's ability to conform with good manufacturing practices standards.

11. Personnel:

11.1. Principle-The establishment and maintenance of a satisfactory system of Quality Assurance (QA) and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities shall be clearly defined and understood by the persons concerned and recorded as written descriptions.

11.2. General-

11.2.1. The manufacturer shall have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual shall not be so extensive as to present any risk to quality.

11.2.2. Responsible staff shall have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities. Its duties may be delegated to designated deputies with a satisfactory level of qualifications. There shall be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of good manufacturing practices. The manufacturer shall have an organisation chart.

11.2.3. All personnel shall be aware of the principles of good manufacturing practices that affect them and receive initial and continuing training, including hygiene instruction, relevant to their needs. All personnel shall be motivated to support the establishment and maintenance of high quality standards.

11.2.4. Steps shall be taken to prevent unauthorised people from entering production, storage and QC areas. Personnel who do not work in these areas shall not use them as a passageway.

11.3. Key personnel-

11.3.1. Key personnel include the heads of production, the heads of quality units and the authorised person. The quality units typically comprise the QA and QC functions. In some cases, these could be combined in one department. The authorised person may also be responsible for one or more of these quality units. Normally, key posts shall be occupied by full-time personnel. The heads of production and quality units shall be independent of each other. In large organisations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

11.3.2. Key personnel responsible for supervising the production and quality units for pharmaceutical products shall possess the qualifications and experience as specified under the rules. Their education shall include the study of an appropriate combination of the following, namely:-

(a) chemistry (analytical or organic) or biochemistry;

(b) chemical engineering;

(c) microbiology;

(d) pharmaceutical sciences and technology;

(e) pharmacology and toxicology;

(f) physiology; or

(g) other related sciences.

They shall also have adequate practical experience in the manufacture and QA of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they shall perform their duties under professional guidance. The scientific education and practical experience of experts shall be such, so as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and QC of pharmaceutical products.

11.3.3. The heads of the production and the quality units shall have shared, or jointly exercised, responsibilities relating to quality. They may include the following, namely:-

(a) authorisation of written procedures and other documents, including amendments;

(b) monitoring and control of the manufacturing environment;

(c) plant hygiene;

(d) process validation and calibration of analytical apparatus;

(e) training, including the application and principles of QA;

(f) approval and monitoring of suppliers of materials;

(g) approval and monitoring of contract manufacturers;

(h) designation and monitoring of storage conditions for materials and products;

(i) performance and evaluation of in-process controls;

(j) retention of records;

(k) monitoring of compliance with good manufacturing practices requirements; and

(l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.

11.3.4. The head of production has the following responsibilities, namely:-

(a) to ensure that products are produced and stored in accordance with the appropriate documentation in order to obtain the required quality;

(b) to approve the instructions relating to production operations, including the in-process controls and to ensure their strict implementation;

(c) to ensure that the production records are evaluated and signed by a designated person;

(d) to check the maintenance of the department, premises and equipment;

(e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports are made available; and

(f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

11.3.5. The heads of the quality units generally have the following responsibilities, namely:-

(a) to approve or reject starting materials, packaging materials and intermediate, bulk and finished products in relation to their specifications;

(b) to evaluate batch records;

(c) to ensure that all necessary testing is carried out;

(d) to approve sampling instructions, specifications, test methods and other QC procedures;

(e) to approve and monitor analysis carried out under contract;

(f) to check the maintenance of the department, premises and equipment;

(g) to ensure that the appropriate validations, including those of analytical procedures and calibrations of control equipment are carried out;

(h) to ensure that the required initial and continuing training of quality unit personnel is carried out and adapted according to need;

(i) establishment, implementation and maintenance of the quality system;

(j) supervision of the regular internal audits or self-inspections;

(k) participation in external audit (vendor audit); and

(l) participation in validation programmes.

11.3.6. The authorised person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval for the release of finished product for sale or supply.

11.3.7. Assessment of finished products shall embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product and an examination of the finished pack.

11.3.8. No batch of product is to be released for sale or supply prior to certification by the authorised persons.

11.3.9. The authorised person responsible for approving a batch for release shall always ensure that the following requirements have been met:-

(a) the licence and the approval requirements for the product have been met for the batch concerned;

(b) the principles and guidelines of GMP, as laid down in this Part, have been followed;

(c) the principal manufacturing and testing processes have been validated;

(d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;

(e) any planned changes or deviations in manufacturing or QC have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification and approval by the licensing authority;

(f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;

(g) all necessary production and QC documentation has been completed and endorsed by supervisors trained in appropriate disciplines;

(h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;

(i) approval has been given by the head of quality control; and

(j) all relevant factors have been considered, including the factor associated with the output batch directly under review (e.g., sub-division of output batches from a common input, factors associated with continuous production runs).

11.3.10. The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

11.4. Training-

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

11.4.2. Besides basic training on the theory and practice of good manufacturing practices, newly recruited personnel shall receive training appropriate to the duties assigned to them. Continuous training shall also be given, and its practical effectiveness be assessed periodically. Approved training programmes shall be available. Training records shall be kept.

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

11.4.4. The concept of quality assurance and all the measures which aid its understanding and implementation shall be fully discussed during the training sessions.

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

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

11.5. Personal hygiene-

11.5.1. All personnel, prior to and during employment, as appropriate, shall undergo health checkups. Personnel conducting visual inspections shall also undergo periodic eye checkups.

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

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

11.5.4. All employees shall 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.

11.5.5. Direct contact shall be avoided between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk products.

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

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

11.5.8. Personal hygiene procedures, including the wearing of protective clothing, shall 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.

12. Premises:

12.1. **Principle-** Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. They shall conform to the conditions as laid down in the Factories Act, 1948 (63 of 1948).

12.2. **General-**

12.2.1. The layout and design of premises must 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.

12.2.2. Where dust is generated (e.g., during sampling, weighing, mixing and processing operations or packaging of powder), measures shall be taken to avoid cross-contamination and facilitate cleaning.

12.2.3. Premises shall be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.2.4. Premises used for the manufacture of finished products shall be suitably designed and constructed to facilitate good sanitation.

12.2.5. Premises shall be carefully maintained, and it shall be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.2.6. Premises shall be cleaned and, where applicable, disinfected according to detailed written procedures and records shall be maintained.

12.2.7. Electrical supply, lighting, temperature, humidity and ventilation shall be appropriate and they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage or the accurate functioning of equipment.

12.2.8. The design, installation, qualification and maintenance of the Heating, Ventilation, Air Conditioning (HVAC) systems of the manufacturing plant shall be carried out.

12.2.9. Premises shall be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There shall be a procedure for rodent and pest control.

12.2.10. Premises shall be designed to ensure the logical flow of materials and personnel.

12.3. **Ancillary areas-**

12.3.1. Rest and refreshment rooms shall be separate from manufacturing and control areas.

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

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

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

12.4. **Storage areas-**

12.4.1. Storage areas shall be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation; starting and packaging materials, intermediates, bulk and finished products, products in quarantine and released, rejected, returned or recalled products.

12.4.2. Storage areas shall be designed or adapted to ensure good storage conditions. In particular, they shall be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature, humidity) they shall be provided, controlled, monitored and recorded, where appropriate.

12.4.3. Receiving and dispatch bays shall be separated and shall protect the materials and products from the weather. Receiving areas shall be designed and equipped to allow containers of incoming materials to be cleaned, if necessary, before storage.

12.4.4. 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 shall give equivalent security.

12.4.5. Segregation shall be provided for the storage of rejected, recalled or returned materials or products.

12.4.6. Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion shall be stored in safe and secure areas.

12.4.7. Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention shall be paid to sampling and the safe and secure storage of these materials.

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

12.5. **Weighing areas**-The weighing of starting materials and the estimation of yield by weighing shall 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.

12.6. **Production areas-**

12.6.1. In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitising materials (e.g., penicillins) or biological preparations (e.g., live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and non-pharmaceutical products, shall not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, shall not be allowed in premises used for the manufacture of pharmaceutical products.

12.6.2. Premises shall preferably be laid out in such a way so 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.

12.6.3. The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different pharmaceutical 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.

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

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

12.6.6. Drains shall be of adequate size and designed and equipped to prevent back-flow. Open channels shall be avoided where possible, but if they are necessary they shall be shallow to facilitate cleaning and disinfection.

12.6.7. Production areas shall be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas shall be regularly monitored during both production and non-production periods so as to ensure compliance with their design specifications.

12.6.8. Premises for the packaging of pharmaceutical products shall be specifically designed and laid out so as to avoid mix ups, contamination or cross-contamination.

12.6.9. Production areas shall be well lit, particularly where visual online controls are carried out.

12.7. **Quality Control (QC) areas-**

12.7.1. QC laboratories shall be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed shall be separated from each other.

12.7.2. QC laboratories shall be designed to suit the operations to be carried out in them. Sufficient space shall be given to avoid mix ups and cross-contamination. There shall be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

12.7.3. The design of the laboratories shall take into account the suitability of construction materials, prevention of fumes, and ventilation. There shall be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

12.7.4. A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors or where it is necessary to isolate the instruments.

13. Equipment:

13.1. Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of equipment must 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.

13.2. Equipment shall be installed in such a way so as to minimise any risk of error or of contamination.

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

13.4. All service pipework and devices shall be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

13.5. Balances and other measuring equipment of an appropriate range and precision shall be available for production and control operations and shall be calibrated according to a fixed schedule.

13.6. Production equipment shall be thoroughly cleaned according to a fixed schedule.

13.7. Laboratory equipment and instruments shall be suited to the testing procedures undertaken.

13.8. Washing, cleaning and drying equipment shall be chosen and used so as not to be a source of contamination.

13.9. Production equipment shall not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to an extent that would affect the quality of the product.

13.10. Defective equipment shall be removed from production and QC areas. If this is not possible, it shall be clearly labelled as defective to prevent use.

13.11. Closed equipment shall be used whenever appropriate. Where open equipment is used or equipment is opened, precautions shall be taken to minimize the contamination.

13.12. Non-dedicated equipment shall be cleaned according to validated cleaning procedures between being used for production of different pharmaceutical products to prevent cross-contamination.

13.13. Current drawings of critical equipment and support systems shall be maintained.

14. Materials:

14.1. The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2. Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

14.3. No materials used for operations such as cleaning, lubrication of equipment and pest control shall come into direct contact with the product. Where possible, such materials shall be of a suitable grade (e.g., food grade) to minimise health risks.

14.4. All incoming materials and finished products shall be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5. All materials and products shall be stored under the appropriate conditions established by the manufacturer, and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule.

14.6. Water used in the manufacture of pharmaceutical products shall be suitable for its intended use. There shall be validated system for treatment of water drawn from own or any other source to render it potable in accordance with the 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 the operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf. Good manufacturing practices regarding the design, installation and operation of pharmaceutical water systems including guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients and dosage forms, shall be ensured.

14.7. The purchase of starting materials is an important operation that shall involve staff who has a particular and thorough knowledge of the products and suppliers.

14.8. Starting materials shall be purchased only from the approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is beneficial for all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, to be contractually agreed between the manufacturer and the supplier.

14.9. For each consignment, at a minimum, the containers shall be checked at least for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10. All incoming materials shall be checked to ensure that the consignment corresponds to the order. Containers shall be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information shall not be lost.

14.11. Damage to containers and any other problem that might adversely affect the quality of a material shall be recorded and reported to the QC Department and investigated.

14.12. If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

14.13. Starting materials in the storage area shall be appropriately labelled. Labels shall bear at least the following information, namely:—

(a) the designated name of the product and the internal code reference where applicable;

(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;

(c) the status of the contents (e.g., in quarantine, on test, released, rejected, returned or recalled); and

(d) where appropriate, an expiry date or a date beyond which retesting is necessary. When fully validated computerised storage systems are used, not all of the above information need be in a legible form on the label.

14.14. Only raw materials which have been released by the QC Department and which are within their shelf-life shall be used.

14.15. The raw materials other than APIs, if released by QC Department without specific batch testing, for use in manufacturing, it shall be based on vendor approval and statistical data analysis of earlier test results of such material for release.

14.16. There shall be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn shall be identified.

14.17. Only starting materials released by the QC Department and within their shelf-life shall be used.

14.18. Starting materials shall be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

14.19. Each dispensed material and its weight or volume shall be independently checked and recorded.

14.20. Materials dispensed for each batch of the final product shall be kept together and conspicuously labelled as such.

14.21. The purchase, handling and control of primary and printed packaging materials shall as for starting materials.

14.22. Particular attention shall be paid to printed packaging materials. They shall be stored in secure conditions so as to exclude the possibility of unauthorised access. Roll feed labels shall be used wherever possible. Cut labels and other loose printed materials shall be stored and transported in separate closed containers so as to avoid mix ups. Packaging materials shall be issued for use only by designated personnel following an approved and documented procedure.

14.23. Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.

14.24. Out-dated or obsolete primary packaging material or printed packaging material shall be destroyed and its disposal shall be recorded.

14.25. All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

14.26. All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validated test methods, sample sizes, specifications, cleaning procedure and sterilisation 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.

14.26.1. Whenever bottles are being used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, they shall be rinsed with purified water or water for injection, as the case may be.

14.26.2. The requirements mentioned in this Part do not include requirements of machinery, equipment and premises required for preparation of containers and closures for different dosage forms and categories of drugs. The suitability and adequacy of the machinery, equipment and premises shall be examined taking into consideration the requirements of each licensee in this respect.

14.26.3. Packaging material to be used for pharmaceutical products shall be in accordance with the requirements prescribed in Indian Pharmacopoeia (IP).

14.27. Intermediate and bulk products shall be kept under appropriate conditions.

14.28. Intermediate and bulk products purchased shall be handled on receipt as they were starting materials.

14.29. Finished products shall be held in quarantine until their final release, after which they shall be stored as usable stock under conditions established by the manufacturer.

14.30. The evaluation of finished products and the documentation necessary for release of a product for sale are described in paragraph 19.

14.31. Rejected materials and products shall be clearly marked and stored separately in restricted areas. They shall either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken shall be approved by the authorised personnel and recorded.

14.32. The reworking or recovery of rejected products shall be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. A record shall be kept of the reworking or recovery. A reworked batch shall be given a new batch number.

14.33. The introduction of all or part of earlier batches, conforming to the required quality standards, into a batch of the same product at a defined stage of manufacture shall be authorised beforehand. This recovery shall be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery shall be recorded.

14.34. The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, shall be considered by the QC Department.

14.35. Recalled products shall be identified and stored separately in a secure area until a decision is taken and the decision shall be made as soon as possible.

14.36. Products returned from the market shall be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they

have been critically assessed by the QC function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued shall be taken into account in the assessment. Where any doubt arises over the quality of the product, it shall not be considered suitable for reissue or reuse. Any action taken shall be appropriately recorded.

14.37. There shall be records for the receipt and preparation of reagents and culture media.

14.38. Reagents made up in the laboratory shall be prepared according to the written procedures and appropriately labelled. The label shall indicate the concentration, standardisation factor, shelf-life, the date when re-standardisation is due and the storage conditions. The label shall be signed and dated by the person preparing the reagent.

14.39. Both positive and negative controls shall be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls shall be appropriate to the sensitivity required.

15. Reference Standards:

15.1. Whenever official reference standards exist, they shall be used.

15.2. Indian Pharmacopoeia reference standards shall be procured from Indian Pharmacopoeia Commission.

15.3. Official reference standards shall only be used for the purpose described in the appropriate monograph.

15.4. Reference standards prepared by the manufacturer shall be tested, released and stored in the same way as official standards. They shall be kept under the responsibility of a designated person in a secure area.

15.5. Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardisation.

15.6. Reference standards shall be properly labelled with at least the following information, namely-

(a) name of the material;

(b) batch or lot number and control number;

(c) date of preparation;

(d) shelf-life;

(e) potency; and

(f) storage conditions.

15.7. All in-house working standards or secondary standards shall be standardised against an official reference standard, when available, initially and at regular intervals thereafter.

15.8. All reference standards shall be stored and used in a manner that will not adversely affect their quality.

16. Waste materials:

16.1. Provision shall be made for the proper and safe storage of waste materials waiting disposal. Toxic substances and flammable materials shall be stored in suitably designed, separate, enclosed cupboards.

16.2. Waste material shall not be allowed to accumulate. It shall be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

16.3. The disposal of sewage and effluents (solid, liquid and gas) from the manufacturing area shall be in conformity with the requirements of the guidelines issued by the Environmental Pollution Control Board.

16.4. All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 2016.

16.5. Rodenticides, insecticides, fumigating agents and sanitising materials shall not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

17. Documentation:

17.1. **Principle**-Good documentation is an essential part of the quality assurance system and, as such, shall exist for all aspects of good manufacturing practices. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel

concerned with manufacture know what to do and when to do it; to ensure that authorised persons have all the information necessary to decide whether or not to release a batch of a drug for sale; to ensure the existence of documented evidence, traceability and to provide records and an audit trial that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described in this paragraph may be brought together, but they will usually be separate.

17.2. **General-**

17.2.1. Documents shall be designed, prepared, reviewed and distributed with care. They shall comply with the relevant Parts of the manufacturing and licences.

17.2.2. Documents shall be approved, signed and dated by the responsible persons. No document shall be changed without authorisation and approval.

17.2.3. Documents shall have unambiguous contents; the title, nature and purpose shall be clearly stated. They shall be laid out in an orderly manner and be easy to check. Reproduced documents shall be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

17.2.4. Documents shall be regularly reviewed and kept up to date. When a document has been revised, a system shall exist to prevent inadvertent use of the superseded version. Superseded documents shall be retained for a specific period of time.

17.2.5. Where documents require the entry of data, these entries shall be clear, legible and indelible. Sufficient space shall be provided for such entries.

17.2.6. Any alteration made to a document shall be signed and dated; the alteration shall be done in such a way so as to permit the reading of the original information. Where appropriate, the reason for the alteration shall be recorded.

17.2.7. Records shall be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records shall be retained for at least one year after the expiry date of the finished product.

17.2.8. Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed SOPs relating to the system in use shall be available and the accuracy of the records shall be checked. If documentation is handled by electronic data-processing methods, only authorised persons shall be able to enter or modify data in the computer system, and there shall be a record of changes and deletions; access shall be restricted by passwords or other means and the entry of critical data shall be independently checked. Batch records stored electronically shall be protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is particularly important that, during the period of retention, the data are readily available.

17.2.9 The site master file shall be prepared and maintained up to date as per the Appendix-I this Part.

17.3. **Documents Required:**

17.3.1. **Labels-**

17.3.1.1. Labels applied to containers, equipment or premises shall be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g., quarantined, accepted, reject0ed and clean).

17.3.1.2. All finished drugs shall be identified by labelling bearing at least the following information, namely:-

(a) the name of the drugs;

(b) a list of the active ingredients [if applicable, with the International Nonproprietary Names (INN)], showing the amount of each present and a statement of the net contents (e.g., number of dosage units, weight and volume);

(c) the batch number assigned by the manufacturer;

(d) the expiry date and date of manufacture in an uncoded form;

(e) any special storage conditions or handling precautions that may be necessary;

(f) directions for use, and warnings and precautions that may be necessary; and

(g) the name and address of the manufacturer or the company and the person responsible for placing the product on the market.

17.3.1.3. For reference standards, the label or accompanying document or both shall indicate potency or concentration, date of manufacture, expiry date, date the closure if it is first opened, storage conditions and control number, as appropriate.

17.3.2. **Specifications and testing procedures**

17.3.2.1. Testing procedures described in documents shall be validated in the context of available facilities and equipment before they are adopted for routine testing.

17.3.2.2. There shall be appropriately authorised and dated specifications, including tests on identity, content, purity and quality for starting and packaging materials and for finished products; where appropriate, they shall also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g., acids and bases) used in production shall be included.

17.3.2.3. Each specification shall be approved, signed and dated, and maintained by the QC or QA units. Specifications for starting materials, intermediates, bulk, finished products and packaging materials.

17.3.2.4. Periodic revisions of the specifications may be necessary to comply with new editions of the Indian pharmacopoeia or other official pharmacopoeia.

17.3.2.5. Pharmacopoeias, reference standards, reference spectra and other reference materials shall be available in the QC laboratory.

17.3.3. **Specifications for starting and packaging materials-**

17.3.3.1. Specifications for starting, primary and printed packaging materials shall provide, if applicable, a description of the materials, including—

(a) the designated name (if applicable, the INN) and internal code reference;

(b) the reference, if any, to a pharmacopoeial monograph; and

(c) qualitative and quantitative requirements with acceptance limits.

17.3.3.2. Depending on the company's practice other data may be added to the specification, namely:-

(a) the supplier and the original producer of the materials;

(b) a specimen of printed materials;

(c) directions for sampling and testing, or a reference to procedures;

(d) storage conditions and precautions; and

(e) the maximum period of storage before re-examination.

17.3.3.3. Packaging material shall conform to the specifications and shall be compatible with the material or with the drugs or both it contains. The material shall be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

17.3.3.4. Documents describing testing procedures shall state the required frequency for re-assaying each starting material, as determined by its stability.

17.3.4. **Specifications for intermediate and bulk products-** Specifications for intermediate and bulk products shall be available. The specifications shall be similar to specifications for starting materials or for finished products, as appropriate.

17.3.5. **Specifications for finished products-** Specifications for finished products shall include the following, namely:—

(a) the designated name of the product and the code reference, where applicable;

(b) the designated names of the active ingredients (if applicable, with the INNs);

(c) the formula or a reference to the formula if provided in any pharmacopoeia;

(d) a description of the dosage form and package details;

(e) directions for sampling and testing or a reference to procedures;

(f) the qualitative and quantitative requirements, with acceptance limits;

(g) the storage conditions and precautions, where applicable; and

(h) the shelf-life.

17.3.6. **Master formula records-**

17.3.6.1. A formally authorised master formula shall exist for each product and batch size to be manufactured.

17.3.6.2. The master formula records shall include the following, namely:-

(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 batch size;

(c) 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 shall be made of any substance that may disappear in the course 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 and operating the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilising, use;

(g) detailed step-wise processing instructions (e.g., checks on materials, pre-treatments, sequence for adding materials, mixing times and temperatures);

(h) the instructions for any in-process controls with their limits;

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

(j) any special precautions to be observed; and

(k) the hold time permitted for intermediate and in process material.

17.3.7. **Packaging instructions-** Formally authorised packaging instructions shall exist for each product, pack size and type. These shall normally include or make reference to the following, namely:—

(a) the name of the product;

(b) a description of its pharmaceutical form, strength and, where applicable, method of application;

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

(d) 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;

(e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;

(f) 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;

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

(h) details of in-process controls with instructions for sampling and acceptance limits.

17.3.8. **Batch processing records-**

17.3.8.1. A batch processing record shall be kept for each batch processed. It shall be based on the relevant Parts of the currently approved specifications on the record. The method of preparation of such records shall be designed to avoid errors. (copying or validated computer programmes are recommended. Transcribing from approved documents shall be avoided.)

17.3.8.2. Before any processing begins a check shall 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 shall be recorded.

17.3.8.3. During processing, the following information shall be recorded at the time each action is taken, and after completion of the record shall be dated and signed by the person responsible for the processing operations, namely:-

(a) the name of the product;

(b) the number of the batch being manufactured;

(c) dates and time of commencement of significant intermediate stages and of completion of production;

(d) the name of the person responsible for each stage of production;

(e) the initials of the operators of different significant steps of production and, where appropriate, of the persons who checked each of these operations (e.g., weighing);

(f) the batch number or analytical control number or both and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

(g) any relevant processing operation or event and the major equipment used;

(h) the hold time permitted for intermediate and in process material;

(i) the in-process controls performed, the initials of the persons carrying them out, and the results obtained;

(j) 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; and

(k) notes on special problems including details, with signed authorisation for any deviation from the master formula.

17.3.9. **Batch packaging records-**

17.3.9.1. A batch packaging record shall be kept for each batch or part batch processed. It shall be based on the relevant Parts of the approved packaging instructions and the method of preparing such records shall be designed to avoid errors. (copying or validated computer programmes are recommended. Transcribing from approved documents shall be avoided.)

17.3.9.2. Before any packaging operation begins, checks shall 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 shall be recorded.

17.3.9.3. The following information shall be recorded at the time each action is taken, and the date and the person responsible shall be clearly identified by signature or electronic password, namely:-

(a) 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;

(b) the date and time of packaging operations;

(c) the name of the responsible person carrying out the packaging operation;

(d) (d) the initials of the operators of the different significant steps;

(e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product if it is unpacked or a record of returning product that has not been packaged to the storage area;

(g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;

(h) notes on any special problems, including the details of any deviation from the packaging instructions, with written authorisation by an appropriate person; and

(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

17.3.10. **Standard operating procedures and records:**

17.3.10.1. Standard Operating Procedures (hereinafter to be referred as SOPs) and associated records of actions taken or, where appropriate, conclusions reached shall be available for the following, namely-

(a) equipment assembly and validation;

(b) analytical apparatus and calibration;

(c) maintenance, cleaning and sanitisation;

(d) personnel matters including qualifications, training, clothing and hygiene;

(e) environmental monitoring;

(f) pest control;

(g) complaints;

(h) recalls; and

(i) returns.

17.3.10.2. There shall be SOPs and records for the receipt of each delivery of starting material and primary and printed packaging material.

17.3.10.3. The records of the receipts shall include the following, namely-

(a) the name of the material on the delivery note and the containers;

(b) the "in-house" name or code or both of material, if different from clause (a);

(c) the date of receipt;

(d) the supplier's name and, if possible, manufacturer's name;

(e) the manufacturer's batch or reference number;

(f) the total quantity and number of containers received;

(g) the batch number assigned after receipt; and

(h) any relevant comment (e.g. state of the containers).

17.3.10.4. There shall be SOPs for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

17.3.10.5. SOPs shall be available for each instrument and piece of equipment (e.g., use, calibration, cleaning and maintenance) and placed in close proximity to the equipment.

17.3.10.6. There shall be SOPs for sampling, which specify the persons authorised to take samples.

17.3.10.7. The sampling instructions shall include-

(a) the method of sampling and the sampling plan;

(b) the equipment to be used;

(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;

(d) the amount of samples to be taken;

(e) instructions for any required sub-division of the sample;

(f) the type of sample containers to be used, and whether they are for aseptic sampling or for normal sampling and labelling; and

(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

17.3.10.8. There shall be an SOPs describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

17.3.10.9. The SOPs for batch numbering that are applied to the processing stage and to the respective packaging stage shall be related to each other.

17.3.10.10. The SOPs for batch numbering shall ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

17.3.10.11. Batch-number allocation shall be immediately recorded, e.g. in a logbook. The record shall include at least the date of allocation, product identity and size of batch.

17.3.10.12. There shall be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed shall be recorded.

17.3.10.13. Analysis records shall include at least the following data, namely-

(a) the name of the material or product and, where applicable, dosage form;

(b) the batch number and, where appropriate, the manufacturer and supplier;

(c) references to the relevant specifications and testing procedures;

(d) test results, including observations and calculations, and reference to any specifications (limits);

(e) date and reference number of testing;

(f) the initials of the persons who performed the testing;

(g) the date and initials of the persons who verified the testing and the calculations, where appropriate; and

(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated person.

17.3.10.14. Written release and rejection procedures shall be available for materials and products and in particular for the release for sale of the finished product by an authorised person.

17.3.10.15. Records shall be maintained regarding the distribution of each batch of a product in order, for example, to facilitate the recall of the batch, if necessary.

17.3.10.16. Records shall be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning or repair operations, including dates and the identity of the people who carried out these operations.

17.3.10.17. The use of major and critical equipment and the areas where products have been processed shall be appropriately recorded in chronological order.

17.3.10.18. There shall be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned and such written procedures shall be followed.

18. Good practices in production:

18.1. **Principle-** Production operations must follow clearly defined procedures in accordance with manufacturing and licences, with the objective of obtaining products of the requisite quality.

18.2. **General-**

18.2.1. All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution shall be done in accordance with written procedures or instructions and, where necessary, recorded.

18.2.2. Deviation from instructions or procedures shall be avoided as far as possible. If deviations occur, they shall be in accordance with an approved procedure. The authorisation of the deviation shall be approved in writing by a designated person, with the involvement of the QC Department, when appropriate.

18.2.3. Checks on yields and reconciliation of quantities shall be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

18.2.4. Operations on different products shall not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix up or cross-contamination.

18.2.5. At all times during processing, all materials, bulk containers, major items of equipment, and, where appropriate, the rooms and packaging lines being used, shall be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication shall also mention the stage of production. In some cases, it may be useful to also record the name of the previous product that has been processed.

18.2.6. Access to production premises shall be restricted to authorised personnel.

18.2.7. Non-medicinal products shall not be produced in areas or with equipment destined for the production of pharmaceutical products.

18.2.8. In-process controls are usually performed within the production area. The performance of such in-process controls shall not have any negative effect on the quality of the product or another product (e.g., cross-contamination or mix up).

18.3. **Prevention of cross-contamination and bacterial contamination during production-**

18.3.1. When dry materials and products are used in production, special precautions shall be taken to prevent the generation and dissemination of dust. Provision shall be made for proper air control (e.g., supply and extraction of air of suitable quality).

18.3.2. Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitising materials, biological preparations such as living organisms, certain hormones, cytotoxic substances and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses or over a long time or both. Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure areas. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authorities.

18.3.3. Cross-contamination shall be avoided by taking appropriate technical or organisational measures, namely:-

(a) carrying out production in dedicated and self-contained areas (which may be required for

products such as penicillins, cytotoxic, sex hormones, spore forming, live vaccines, live bacterial preparations and certain other biologicals);

(b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;

(c) providing appropriately designed airlocks, pressure differentials and air supply and extraction systems;

(d) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

(e) wearing protective clothing where products or materials are handled;

(f) using cleaning and decontamination procedures of known effectiveness;

(g) using a closed system in production;

(h) testing for residues; and

(i) using cleanliness status labels on equipment.

18.3.4. 1Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to SOPs.

18.3.5. Production areas where susceptible products are processed shall undergo periodic environmental monitoring (e.g., for microbiological and particulate matter, where appropriate).

18.4. **Processing operations-**

18.4.1. Before any processing operation is started, steps shall be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

18.4.2. Any necessary in-process controls and environmental controls shall be carried out and recorded.

18.4.3. Means shall be instituted of indicating failures of equipment or of services (e.g., water and gas) to equipment. Defective equipment shall be withdrawn from use until the defect has been rectified. After use, production equipment shall be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

18.4.4. Time limits for storage of process materials and equipment, after cleaning and before use, shall be stated and based on relevant data.

18.4.5. Containers for filling shall be cleaned before filling. Attention shall be given for avoiding and removing any contaminants such as glass fragments and metal particles.

18.4.6. Any significant deviation from the expected yield shall be recorded and investigated.

18.4.7. Checks shall be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another area are connected in the correct manner.

18.4.8. Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes shall be sanitised and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

18.4.9. Measuring, weighing, recording and control equipment and instruments shall be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments shall be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due shall be clearly indicated on a label attached to the instrument.

18.4.10. Repair and maintenance operations shall not present any hazard to the quality of the products.

18.5. **Packaging operations:**

18.5.1. When the programme for packaging operations is being set up, particular attention shall be given to minimising the risk of cross-contamination, mix ups or substitutions. Different products shall not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

18.5.2. Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance shall be performed according to an appropriate procedure and checklist and shall be recorded.

18.5.3. The name and batch number of the product being handled shall be displayed at each packaging station or line.

18.5.4. Normally, filling and sealing shall be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures shall be applied to ensure that no mix ups or mislabelling can occur.

18.5.5. The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging shall be checked and recorded. Attention shall be paid to printing by hand, which shall be rechecked at regular intervals.

18.5.6. Special care shall be taken when cut labels are used and when overprinting is carried out off-line and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix ups. Online verification of all labels by automated electronic means can be helpful in preventing mix ups, but checks shall be made to ensure that any electronic code readers, label counters or similar devices are operating correctly. When labels are attached manually, in-process control checks shall be performed more frequently.

18.5.7. Printed and embossed information on packaging materials shall be distinct and resistant to fading or erasing.

18.5.8.1. Regular online control of the product during packaging shall include at a minimum checks on—

(a) the general appearance of the packages;

(b) whether the packages are complete;

(c) whether the correct products and packaging materials are used;

(d) whether any overprinting is correct; and

(e) the correct functioning of line monitors.

18.5.8.2. Samples taken away from the packaging line shall not be returned.

18.5.9. Products that have been involved in an unusual event during packaging shall be reintroduced into the process only after special inspection, investigation and approval by the authorised personnel. A detailed record shall be kept of this operation.

18.5.10. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated, satisfactorily accounted for and recorded before release.

18.5.11. Upon completion of a packaging operation, any unused batch-coded packaging materials shall be destroyed and the destruction shall be recorded. A documented procedure requiring checks to be performed before returning unused materials shall be followed, if uncoded printed materials are returned back to the stock.

18.5.12. Production records shall be reviewed as part of the approval process of batch release before transfer to the authorised person. Any divergence or failure of a batch to meet production specifications shall be thoroughly investigated. The investigation shall, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusion and follow-up action.

19. Good practices in quality control:

19.1. Quality control is the part of good manufacturing practices concerned with sampling, specifications and testing and with the organisation and documentation which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the requirements. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

19.2. The independence of QC from production is considered fundamental.

19.3. Each manufacturer shall have a QC function. The QC function shall be independent of other Departments

and under the authority of a person with appropriate qualifications and experience. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out. The basic requirements for QC are as follows—

(a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials and intermediate, bulk and finished products and where appropriate for monitoring environmental conditions for good manufacturing practices purposes;

(b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved by the QC Department;

(c) qualification and validation;

(d) records must be made (manually or by recording instruments or both) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;

(e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the licence; the ingredients must be of the required purity, in their proper container and correctly labelled;

(f) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

(g) sufficient samples of starting materials and products must be retained to permit future examination of the product, if necessary; the retained product must be kept for the appropriate time in its final pack unless the pack is exceptionally large, in which case one that is equivalent to the marketed packaging system may be used.

19.4.1. Other QC responsibilities include the following, namely:-

(a) establishing, validating and implementing all QC procedures;

(b) evaluating, maintaining and storing reference standards for substances;

(c) ensuring the correct labelling of containers of materials and products;

(d) ensuring that the stability of the active pharmaceutical ingredients and products are monitored;

(e) participating in the investigation of complaints related to the quality of the product;

(f) participating in environmental monitoring; and

(g) participation in quality risk management programme.

19.4.2. These activities shall be carried out in accordance with written procedures and, where necessary, recorded.

19.5. Quality control personnel shall have access to the production areas for sampling and investigation as appropriate.

19.6. **Control of starting materials and intermediate, bulk and finished products-**

19.6.1. All tests shall follow the instructions given in the relevant written test procedure for each material or product. The result shall be checked by the supervisor before the material or product is released or rejected.

19.6.2. Samples shall be representative of the batches of material from which they are taken in accordance with the approved written procedure.

19.6.3. Sampling shall be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled shall be marked accordingly and carefully resealed after sampling.

19.6.4. Care shall be taken during sampling to guard against contamination or mix up of, or by, the material being sampled. All sampling equipment that comes into contact with the material shall be clean. Hazardous or potent materials may require special precautions.

19.6.5. Sampling equipment shall be cleaned and, if necessary, sterilised before and after each use and stored separately from other laboratory equipment.

19.6.6. Each sample container shall bear a label indicating-

(a) the name of the sampled material;

(b) the batch or lot number;

(c) the number of the container from which the sample has been taken;

(d) the number of the sample;

(e) the signature of the person who has taken the sample; and

(f) the date of sampling.

19.6.7. Out-of-specification results obtained during testing of materials or products shall be investigated in accordance with an approved procedure and record shall be maintained.

19.7. **Test requirements-**

19.7.1. Before releasing a starting or packaging material for use, the QC in-charge shall ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

19.7.2. An identity test shall be conducted on a sample from each container of starting material. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.

19.7.2.1. The above validation shall take account of at least the following aspects, namely:-

(a) the nature and status of the manufacturer and of the supplier and their understanding of the good manufacturing practices requirements;

(b) the QA system of the manufacturer of the starting material;

(c) the manufacturing conditions under which the starting material is produced and controlled; and

(d) the nature of the starting material and the medicinal products in which it will be used.

19.7.2.2. Under such a system it is possible that a validated procedure for exemption from the requirement for identity testing of each incoming container of starting material could be accepted for the following, namely-

(a) starting materials coming from a single product manufacturer or plant; or

(b) starting materials coming directly from a manufacturer, or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's QA system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

19.7.2.3. It is improbable that such a procedure could be satisfactorily validated for either-

(a) starting materials supplied by intermediaries, such as brokers, where the source of manufacture is unknown or not audited; or

(b) starting materials for use in parenteral products.

19.7.3. Each batch (lot) of printed packaging materials shall be examined following its receipt.

19.7.4. In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities. Certificates must be originals and not photocopies or otherwise have their authenticity assured. Certificates must contain at least the following information, namely:—

(a) identification (name and address) of the issuing supplier;

(b) signature of the competent official and statement of his or her qualifications;

(c) the name of the material tested;

(d) the batch number of the material tested;

(e) the specifications and methods used;

(f) the test results obtained; and

(g) the date of testing.

19.7.5. In-process control records shall be maintained and form part of the batch records.

19.7.6. For each batch of drugs, there shall be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to its release.

19.7.7. Products failing to meet the established specifications or any other relevant quality criteria shall be rejected.

19.8. **Batch record review:**

19.8.1. Quality control records shall be reviewed as part of the approval process of batch release before transfer to the authorised person. Any divergence or failure of a batch to meet its specifications shall be thoroughly investigated. The investigation shall, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusion and follow-up action.

19.8.2. Retention samples from each batch of finished product shall be kept for at least one year after the expiry date. Finished products shall usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials shall be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases and water) shall be retained for a minimum of two years, if their stability allows. Retention samples of materials and products shall be of a size sufficient to permit at least two full re-examinations.

19.9. **Stability studies-**

19.9.1. QC shall evaluate quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

19.9.2. QC shall establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

19.9.3. A written programme for on-going stability determination shall be developed and implemented to include elements such as —

(a) a complete description of the drug involved in the study;

(b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;

(c) provision for the inclusion of a sufficient number of batches;

(d) the testing schedule for each drug;

(e) provision for special storage conditions;

(f) provision for adequate sample retention; and

(g) a summary of all the data generated, including the evaluation and the conclusion of the study.

19.9.4. Stability shall be determined prior to marketing and following any significant changes, for example, in processes, equipment or packaging materials.

20. Computerised systems:

20.1. GMP-related computerised systems shall be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.

20.2. Appropriate installation qualification and operational qualification shall demonstrate the suitability of computer hardware and software to perform assigned tasks.

20.3. Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at the time of installation, a retrospective validation could be conducted, if appropriate documentation is available.

20.4. Computerised systems shall have sufficient controls to prevent unauthorised access or changes to data. There shall be controls to prevent omissions in data (e.g., the system being turned off and data not captured). There shall be a record of any data change made, the previous entry, the person who made the change and when the change was made.

20.5. Written procedures shall be available for the operation and maintenance of computerised systems.

20.6. Where critical data are being entered manually, there shall be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.

20.7. Incidents related to computerised systems that could affect the quality of products or the reliability of records or test results shall be recorded and investigated.

20.8. Changes to the computerised system shall be made according to a change procedure and shall be formally authorised, documented and tested. Records shall be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records shall demonstrate that the system is maintained in a validated state.

20.9. A back-up system shall be provided so that there is no permanent loss of records due to system breakdown or failure. Means of ensuring data protection shall be established for all computerised systems.

20.10. Data may be recorded by other means in addition to the computer system.

Appendix-I

Site Master File

The licensee shall prepare a succinct document in the form of 'Site Master File' containing specific and factual Good Manufacturing Practices about the production or control or both of pharmaceutical manufacturing preparations carried out at the licensed premises. It shall contain the following, namely-

1. General information:-

(a) brief information of the firm;

(b) pharmaceutical manufacturing activities as permitted by the licensing authority;

(c) other manufacturing activities, if any, carried out in the premises;

(d) type of products licensed for manufacture with flow charts mentioning procedure and process flow;

(e) number of employees engaged in the production, quality control, storage and distribution;

(f) use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;

(g) products details registered with foreign countries.

(h) short description of the Quality Management System of the firm;

(i) pharmaceutical Quality System; and

(j) quality risk assessment.

2. Personnel:-

(a) organisational chart showing the arrangement for quality assurance including production and quality control;

(b) qualifications, experience and responsibilities of key personnel;

(c) outline for arrangements for basic and in-service training and how the records are maintained;

(d) health requirements for personnel engaged in production; and

(e) personnel hygiene requirements, including clothing.

3. Premises:-

(a) simple plan or description of manufacturing areas drawn to scale;

(b) nature of construction and fixtures or fittings;

(c) brief description of ventilation systems. More details shall be given for critical areas with potential risk of airborne contamination (schematic drawing of systems). Classification of the rooms used for the manufacture of sterile products shall be mentioned;

(d) special areas for the handling of the highly toxic, hazardous and sensitising materials;

(e) brief description of water system (schematic drawings of systems), including sanitation; and

(f) description of planned preventive maintenance programmes for premises and of the recording system.

4. Equipment:-

(a) brief description of major equipment used in production and Quality Control Laboratories (a list of equipment required);

(b) description of planned preventive maintenance programmes for equipment and of the recording system; and

(c) qualification and calibration including the recording systems and arrangements for computerised systems validation.

5. Sanitation:-availability of written specifications and procedures for cleaning manufacturing areas and equipment.

6. Documentation:-

(a) arrangements for the preparation, revision and distribution of;

(b) necessary documentation for the manufacture; and

(c) any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls about air and water).

7. Production:-

(a) brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters;

(b) arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage;

(c) arrangements for the handling of rejected materials and products; and

(d) brief description of general policy for process validation.

8. Quality Assurance and Control:-

(a) documentation system;

(b) change control;

(c) master validation plan and validation policy;

(d) product quality review; and

(e) description of the quality control system and of the activities of the QC Department. Procedures for the release of the finished products.

9. Manufacture under loan licence and licensee:- description of the way in which compliance of GMP by the loan licensee shall be assessed.

10. Distribution, complaints and product recall:-

(a) arrangements and recording system for distribution; and

(b) arrangements for the handling of complaints and product recalls.

11. Self-inspection:- short description of the self-inspection system indicating whether an outside, independent and experienced external expert was involved in evaluating the manufacturer's compliance with GMP in all aspects of production.

12. Export of drugs:-

(a) products exported to different countries; and

(b) complaints and product recall, if any.

Note.-The guidelines published by the World Health Organization (WHO) on following aspects relating to GMP through their Technical Report Series from time to time may be considered for general guidance purposes:-

(1) Guidelines on the principles of airflow directions, air filtration standards, temperature, humidity and related parameters.

(2) GMP guidelines regarding the design, installation and operation of pharmaceutical water systems including guidance about which quality of water to use for specific applications, such as the manufacture of APIs and dosage forms.

(3) Guidelines on design, installation, qualification and maintenance of the HVAC systems of the manufacturing plant.

(4) GMP guidelines for validation.

(5) Guidelines on packaging of pharmaceutical products.

PART II

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF STERILE PRODUCTS, PARENTERAL PREPARATIONS (SMALL VOLUME INJECTABLES AND LARGE VOLUME PARENTERALS) AND STERILE OPHTHALMIC PREPARATIONS

Note.-Good Manufacturing Practices for pharmaceutical products:- Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of sterile products, parenteral preparations (small volume injectables and large volume parenterals) and sterile ophthalmic preparations. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General considerations:-

1.1. The production of sterile preparations shall be carried out in clean areas, entry shall be through airlocks for personnel or for equipment and materials or both. Clean areas shall be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2. The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilisation shall be carried out in separate areas within the clean area. These areas are classified into four grades as described in paragraph of this Part.

1.3. Manufacturing operations are divided here into two categories, namely:-

(I) those, where the product is terminally sterilised; and

(II) those, which are conducted aseptically at some or all stages.

2. Quality control:-

2.1. The sterility test applied to the finished product shall only be regarded as the last in a series of control measures by which sterility is assured. The test shall be validated for the product concerned.

2.2. Samples taken for sterility testing shall be representative of the whole of the batch but shall, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example-

(i) for products that have been filled aseptically, samples shall include containers filled at the beginning and end of the batch and after any significant interruption of work;

(ii) for products that have been heat sterilised in their final containers, consideration shall be given to taking samples from that part of the load that is potentially the coolest.

2.3. The sterility of the finished product is assured by validation of the sterilisation cycle in the case of terminally sterilised products, and by "media simulation" or "media fill" runs for aseptically processed products. Batch-processing records and, in the case of aseptic processing, environmental quality records, shall be examined in conjunction with the results of the sterility tests. The sterility test procedure shall be validated for a given product. Pharmacopoeial methods shall be used for the validation and performance of the sterility test. In those cases where parametric release has been authorised in place of sterility testing, special attention shall be paid to the validation and the monitoring of the entire manufacturing process.

2.4. For injectable products, the water for injection and the intermediate, if appropriate and finished products shall be monitored for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume parenterals, such monitoring of water or intermediates shall always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of the failure shall be investigated and necessary action shall be taken.

2.5. The use of rapid microbiological methods to replace the traditional microbiological methods, and to obtain earlier results on the microbiological quality of, for example, water, the environment or bio burden, could be considered if appropriately validated and a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method.

3. Sanitation:-

3.1. The sanitation of clean areas is particularly important. They shall be cleaned frequently and thoroughly in accordance with an approved written programme. Where disinfectants are used, more than one type shall be employed. Monitoring shall be regularly undertaken to detect contamination or the presence of an organism against which the cleaning procedure is ineffective. Interactions between different cleaning materials shall be validated. Appropriate cleaning validation shall be carried out to ensure disinfectant residuals can be detected and are removed by the cleaning process.

3.2. Disinfectants and detergents shall be monitored for microbial contamination; dilutions shall be kept in previously cleaned containers and shall only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grade A and B areas shall be sterile before use.

3.3. A disinfectant programme shall also include a sporicidal agent since many common disinfectants are ineffective against spores. The effectiveness of cleaning and disinfectant procedures shall be demonstrated.

3.4. Fumigation of clean areas may be useful for reducing microbial contamination in inaccessible places.

4. Manufacture of sterile preparations:-

4.1. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate level of environmental cleanliness in the operational state to minimise the risk of particulate or microbial contamination of the product or materials being handled.

4.2. Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc., is not given in this Part. International Organization for Standardisation (ISO) standards shall be used for classification of cleanliness according to concentration of airborne particles (determination of number of sample locations, calculation of sample size and evaluation of classification from the data obtained). Table 1 shall also be used to define the levels to be used as the basis for monitoring clean areas for airborne particles.

4.3. For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:-

Grade A: The local zone for high-risk operations, e.g., filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems shall provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level shall not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow shall be demonstrated by undertaking airflow visualisation tests.

Grade B: In aseptic preparation and filling, this is the background environment for the Grade A zone.

Grades C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e., aseptic connection with aseptic connectors and operations in a closed system).

A unidirectional airflow and lower velocities may be used in closed isolators and glove boxes.

Explanation.- For the purpose of classification of grade C and grade D clean areas, the parameters provided in paragraph 4.6, 4.7, 4.9, and 4.11of this Part shall be applied.

4.4. In order to reach the B, C and D air grades the number of air changes shall be appropriate for the size of the room and the equipment and personnel present in it.

4.5. High-efficiency particulate air (hereinafter to be referred as HEPA) filters shall be subjected to an installed filter leakage test in accordance with ISO standards at a recommended interval of every six months, but not exceeding twelve months. The purpose of performing regular leak tests is to ensure the filter media, filter

frame and filter seal are free from leaks. The aerosol selected for HEPA leak testing shall not support microbial growth and shall be composed of a sufficient number or mass of particles. HEPA filter patching is allowed at the filter manufacturer and in situ operation provided that the patch sizes and procedures follow the recommendations of ISO standards.

4.6. Clean rooms and clean-air devices shall be classified in accordance with ISO standards.

4.6.1. Classification shall be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each Grade is given in Table 1 below.

Table 1

Maximum permitted airborne particle concentrate

Grade	Maximum permitted number of particles per m^3 greater than or equal to the tabulated size			
	At rest		In operation	
	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3 520000	29000	Not defined	Not defined

The "at rest" state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

The "in operation" state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems shall be designed to achieve both the "at rest" and "in operation" states.

4.6.2. For classification purposes in Grade A zones, a minimum sample volume of 1 m^3 shall be taken per sample location. Referring to Table 1, for Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥ 5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both particle sizes considered. For Grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8, respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes ISO standards methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest particle size considered and the method of evaluation of the data collected. The sample volume shall be determined according to ISO standards. However, for lower grades (Grade C in operation and Grade D at rest) the sample volume per location shall be at least two litres and the sample time per location shall be not less than one minute.

4.6.3. Portable particle counters with a short length of sample tubing shall be used for classification purposes to avoid the loss of particles ≥ 5.0 µm. Isokinetic sample heads shall be used in unidirectional airflow systems.

4.6.4. "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. ISO standards provide information on testing to demonstrate continued compliance with the assigned cleanliness classification.

4.7. Clean rooms and clean-air devices shall be routinely monitored while in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms or clean-air devices or both.

4.7.1. For Grade A zones, particle monitoring shall be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards. In such cases monitoring during routine equipment set-up operations shall be undertaken before exposure to the risk. Monitoring during simulated operations shall also be performed. The Grade A zone shall be monitored at a frequency and sample size such that all

interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 μm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

4.7.2. It is recommended that a similar system be used for Grade B zones, although the sample frequency may be decreased. The importance of the particle monitoring system shall be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone shall be monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded.

4.7.3. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or multiple small particle counters located near monitoring points and networked to a data acquisition system. Combination of systems can also be used. The system selected shall be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing shall be considered in the context of particle losses in the tubing. The selection of the monitoring system shall take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.

4.7.4. The sizes of samples taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean-air devices.

4.7.5. The airborne particle conditions given in Table 1 for the "at rest" state shall be achieved in the absence of the operating personnel after a short "clean-up" or "recovery" period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 1 for Grade A "in operation" shall be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. The "clean-up" or "recovery" test shall demonstrate a change in particle concentration by a factor of 100 within the prescribed time as per the ISO standards.

4.7.6. In order to demonstrate control of the cleanliness of the various clean areas during operation, they shall be monitored for airborne particles and microbial contamination. In addition to "at rest" and "in operation" classification, airborne particles shall be monitored periodically "in operation" at critical locations. The sampling plan need not be the same as that used for classification. Locations and sample sizes shall be determined based on an assessment of the process and contamination risk.

4.7.7. The monitoring of Grade C and D areas in operation shall be performed in accordance with the principles of QRM. The requirements and alert or action limits will depend on the nature of the operations carried out, but the recommended "clean-up period" shall be attained.

4.7.8. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters shall not interfere with the defined cleanliness standard.

4.7.9. Examples of operations to be carried out in the various Grades are given in the Table 2 below:

Table 2

Examples of operations to be carried out in the various Grades

Grade	Examples of operations for terminally sterilised products
A	Filling of products, which are unusually at risk
C	Placement of filling and sealing machines, preparation of solutions, when (usually at risk). Filling of product when usually at risk.
D	Moulding, blowing (pre forming) operations of solutions and components for subsequent filling.

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
B	Background room conditions for activities requiring Grade A
C	Preparation of solutions to be filtered
D	Handling of components after washing

4.8. To control the microbiological cleanliness of Grades A to D in-operation, the clean areas shall be monitored. Where aseptic operations are performed, monitoring shall be frequent using methods such as settle plates, volumetric air and surface sampling (e.g., swabs and contact plates). Sampling methods used in operation shall not interfere with zone protection. Results from monitoring shall be considered when reviewing batch documentation for finished product release. Surfaces and personnel shall be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g., after validation of systems, cleaning and sanitisation.

4.9. Levels of detection of microbial contamination shall be established for the purpose of setting alert and action limits and for monitoring the trends in environmental cleanliness in the facility. Limits expressed in Colony-Forming Units(CFU) for the microbiological monitoring of clean areas in operation are given in Table 3 below. The sampling methods and numerical values included in the said Table are not intended to represent specifications, but are for information only.

Table

Recommended limits for microbial contamination

Grade	Air sample (CFU/m3)	Settle plates (diameter 90 mm)(CFU/4 hours)	Contact plates (diameter 55 mm)(CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

These are average values.

Individual settle plates may be exposed for less than four hours.

4.10. Appropriate alert and action limits shall be set for the results of particulate and microbiological monitoring. If the action limits are exceeded or a trend is identified in the alert limits, investigation shall be initiated and the appropriate corrective actions shall be taken, as prescribed in the operating procedures.

4.11. The area Grades specified in this Part shall be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g., aseptic media fills or others types of process simulations) are used to establish processing hold times and a maximum fill duration. The determination of an appropriate process area environment and a time limit shall be based on the microbial contamination (bio burden) found.

4.11.1. **Terminally sterilised products**

4.11.1.1. Components and products shall be prepared in at least a Grade D zone to ensure low microbial bio burden and particulate counts prior to filtration and sterilisation. Where the product is at unusual risk of microbial contamination (e.g., because it actively supports microbial growth, must be held for a long period before sterilisation, or is necessarily processed mainly in open vessels), the preparation shall generally be done in a Grade C zone.

4.11.1.2. The filling of products for terminal sterilisation shall generally be done in at least a Grade C environment.

4.11.1.3. Where the product is at unusual risk of contamination from the environment (e.g., because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling shall be done in a Grade A zone with at least a Grade C background.

4.11.1.4. The preparation and filling of ointments, creams, suspensions and emulsions shall generally be done in a Grade C zone before terminal sterilisation.

4.11.2. **Aseptic preparation-**

4.11.2.1. Components after washing shall be handled in at least Grade D zone. The handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a microorganism-retaining filter later in the process, shall be undertaken in a Grade A zone with Grade B background.

4.11.2.2. The preparation of solutions which are to be sterile-filtered during the process shall be undertaken in Grade C zone (unless a closed system is used, in which Grade D zone may be justifiable). If not sterile-filtered (therefore an aseptic manipulation) the preparation of materials and products shall be undertaken in Grade A zone with Grade B background.

4.11.2.3. The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, shall be undertaken in Grade A zone with Grade B background.

4.11.2.4. The transfer of partially closed containers, as used in freeze-drying, before stoppering is completed, shall be undertaken either in Grade A zone with Grade B background or in sealed transfer trays in Grade B zone.

4.11.2.5. The preparation and filling of sterile ointments, creams, suspensions and emulsions shall be undertaken in Grade A zone with Grade B background when the product is exposed and is not subsequently filtered.

5. Processing:

5.1. Precautions to minimise contamination shall be taken during all processing stages, including the stages before sterilisation.

5.2. In general, preparations containing live micro-organisms shall not be made, nor shall containers be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live micro-organisms, the use of multi-product facilities may be justifiable. Vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers in the same premises as other sterile pharmaceutical products, provided that the inactivation procedure has been properly validated. When multi-product facilities are used to manufacture sterile preparations containing live microorganisms and other sterile pharmaceutical products, the manufacturer shall demonstrate and validate the effective decontamination of the live micro-organisms, in addition to precautions taken to minimise contamination.

5.3. Validation of aseptic processing shall include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium shall be based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.

5.4. The process simulation test shall imitate as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.

5.5. Process simulation tests shall be performed as part of validation by running three consecutive satisfactory simulation tests. These tests shall be repeated at defined intervals and after any significant modification to the HVAC system, equipment or process. Process simulation tests shall incorporate activities and interventions known to occur during normal production as well as in the worst-case situations. The process simulation tests shall be representative of each shift and shift changeover to address any time-related and operational features.

5.6. The number of containers used for media fills shall be sufficient to enable a valid evaluation. For small batches the number of containers for media fills shall at least equal to the size of the product batch. The target shall be zero growth and the following shall apply:

(a) when filling fewer than 5000 units, no contaminated units shall be detected;

(b) when filling 5000–10000 units -

(i) one contaminated unit shall result in an investigation, including consideration of a repeat media fill;

(ii) two contaminated units are considered cause for revalidation following investigation;

(c) when filling more than 10000 units -

(i) one contaminated unit shall result in an investigation;

(ii) two contaminated units are considered cause for revalidation following investigation.

5.7. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that shall be investigated. Investigation of gross failures shall include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

5.8. Care shall be taken to ensure that any validation does not compromise the processes.

5.9. Water sources, water-treatment equipment and treated water shall be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records shall be maintained of the results of the monitoring and of any action taken.

5.10. Activities in clean areas, especially when aseptic operations are in progress, shall be kept to a minimum and the movement of personnel shall be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. As far as possible, personnel shall be excluded from Grade A zones. The ambient temperature and humidity shall not be uncomfortably high because of the nature of the garments worn and to reduce the risk of contamination liberated from the personnel.

5.11. The presence of containers and materials liable to generate fibres shall be minimised in clean areas and avoided completely when aseptic work is in progress.

5.12. Components, bulk-product containers and equipment shall be handled after the final cleaning process in such a way so as to ensure that they are not re-contaminated. The stage of processing of components as well as the bulk-product containers and equipment shall be properly identified.

5.13. The interval between the washing and drying and the sterilisation of components, bulk-product containers and equipment, as well as between sterilisation and use, shall be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

5.14. The time between the start of the preparation of a solution and its sterilisation or filtration through a bacteria-retaining filter shall be as short as possible. A maximum permissible time shall be set for each product that takes into account its composition and the prescribed method of storage.

5.15. Any gas that is used to purge a solution or blanket a product shall be passed through a sterilising filter.

5.16. The bio burden shall be monitored before sterilisation. There shall be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bio burden assay shall be performed on each batch for both aseptically filled products and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bio burden might be monitored only at suitable scheduled intervals. For parametric release systems, bio burden assay shall be performed on each batch and considered as an in-process test. Where appropriate, the level of endotoxins shall be monitored. All solutions, in particular large-volume infusion fluids, shall be passed through a microorganism-retaining filter, if possible sited immediately before filling.

5.17. Components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress, shall be sterilised and wherever possible passed into the area through double-ended sterilisers sealed into the wall. Other procedures that prevent the introduction of contamination may be acceptable in some circumstances.

5.18. The efficacy of any new processing procedure shall be validated and the validation shall be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

6. Sterilisation:

6.1. Whenever possible products intended to be sterile shall be terminally sterilised by heat in their final container. Where it is not possible to carry out terminal sterilisation by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g., plastic eye-dropper bottles), a decision shall be taken to use an alternative method of terminal sterilisation following filtration or aseptic processing or both.

6.2. Sterilisation can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilisation), by ethylene oxide (or other suitable gaseous sterilising agents), or by filtration with subsequent aseptic filling of sterile final containers. Each method has its advantages and disadvantages. Where possible and practicable, heat sterilisation is the method of choice. In any case the sterilisation process shall be in accordance with the

marketing and manufacturing authorisations.

6.3. The microbial contamination of starting materials shall be minimal and their bio burden shall be monitored before sterilisation. Specifications shall include requirements for microbiological quality when the need for this has been indicated by monitoring.

6.4. All sterilisation processes shall be validated. Particular attention shall be paid when the adopted sterilisation method is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions.

6.5. Before any sterilisation process is adopted, its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed shall be demonstrated by physical measurements and by biological indicators, where appropriate. The validity of the process shall be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records shall be kept of the results.

6.6. For effective sterilisation the whole of the material shall be subjected to the required treatment and the process shall be designed to ensure that it is achieved.

6.7. Biological indicators shall be considered only as an additional method of monitoring the sterilisation process. They shall be stored and used according to the manufacturer's instructions and their quality checked by positive controls. If they are used, strict precautions shall be taken to avoid any transfer of microbial contamination from them.

6.8. There shall be a clear means of differentiating products that have not been sterilised from those which have. Each basket, tray, or other carrier of products or components shall be clearly labelled with the name of the material, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the batch is in fact sterile.

6.9. Validated loading patterns shall be established for all sterilisation processes.

6.10. Sterilisation records shall be available for each sterilisation run. They shall be approved as part of the batch-release procedure.

6.11.1. **Terminal sterilisation-**

6.11.1.1. Each heat-sterilisation cycle shall be recorded by means of appropriate equipment of suitable accuracy and precision, e.g., on a time or temperature chart with a suitably large scale. The temperature shall be recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature shall preferably be checked against a second independent temperature probe located at the same position. Sterilisation records shall be available for each sterilisation run and shall be approved as part of the batch release procedure. Chemical or biological indicators may also be used but shall not take the place of physical controls.

6.11.1.2. Sufficient time shall be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time is started. This time shall be determined for each type of load to be processed.

6.11.1.3. After the high-temperature phase of a heat sterilisation cycle, precautions shall be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product shall be sterilised.

6.11.1.4. Both temperature and pressure shall be used to monitor the process. Control instrumentation shall normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they shall be validated to ensure that critical process requirements are met. System and cycle faults shall be registered by the system and observed by the operator. The reading of the independent temperature indicator shall be routinely checked against the reading on the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilisation period. There shall be regular leak tests on the chamber when a vacuum phase is part of the cycle.

6.11.1.5. The items to be sterilised, other than products in sealed containers, shall be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilisation. Specially designed autoclavable stainless steel containers, that allow steam to enter and air to leave, can also be used. All parts of the load shall be in

contact with water or saturated steam at the required temperature for the required time.

6.11.1.6. Care shall be taken to ensure that the steam used for sterilisation is of suitable quality chemical, microbiological and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat and non-condensable gases) and does not contain additives at a level that could cause contamination of the product or equipment. Steam used for sterilisation shall be tested regularly.

6.11.1.7. Sterilisation by dry heat may be suitable for non-aqueous liquids or dry-powder products. The process used shall include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied it shall be passed through a microorganism-retaining filter (e.g., a HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins are required as part of the validation.

6.11.1.8. Sterilisation by radiation is used mainly for heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilisation.

6.11.1.9. If sterilisation by radiation is done by an outside contractor, the manufacturer is responsible for ensuring that the requirements of paragraph 6.8 are met and that the sterilisation process is validated.

6.11.1.10. During the sterilisation procedure the radiation dose shall be measured. The dosimeters used for this purpose shall be independent of the dose rate and shall provide a quantitative measurement of the dose received by the product itself. Dosimeters shall be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used they shall be used within the time-limit of their calibration. Dosimeter absorbance shall be read shortly after exposure to radiation. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilisation. The information obtained shall constitute part of the batch record.

6.11.1.11. Validation procedures shall ensure that consideration is given to the effects of variations in the density of the packages.

6.11.1.12. Material-handling procedures shall prevent any mix-up of irradiated and non-irradiated materials. Each package shall carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

6.11.1.13. The total radiation dose shall be administered within a predetermined period.

6.11.1.14. Sterilisation by gases and fumigants shall only be used for finished products where there is no suitable alternative.

6.11.1.15. Various gases and fumigants may be used for sterilisation (e.g., ethylene oxide and hydrogen peroxide vapour). Ethylene oxide shall be used only when no other method is practicable. During process validation, it shall be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits shall be incorporated in the specifications.

6.11.1.16. Direct contact between gas and microorganisms is essential; precautions shall, therefore, be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

6.11.1.17. Before exposure to the gas, materials shall be brought into equilibrium with the humidity and temperature required by the process. This requirement shall be balanced against the need to minimise the waiting time before sterilisation.

6.11.1.18. Each sterilisation cycle shall be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information thus obtained shall form part of the batch record.

6.11.1.19. Biological indicators shall be stored and used according to the manufacturer's instructions and their performance checked by positive controls.

6.11.1.20. For each sterilization cycle, records shall be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration. The pressure and temperature shall be recorded on a chart throughout the cycle. The records shall form part of the batch record.

6.11.1.21. After sterilisation, the load shall be stored in a controlled manner in ventilated conditions to allow concentration of residual gas and reaction products to fall to their prescribed levels. This process shall be validated.

6.11.2. **Aseptic processing and sterilisation by filtration:-**

6.11.2.1. The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilised by one of the above methods.

6.11.2.2. The operating conditions shall be to prevent microbial contamination.

6.11.2.3. In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to the following namely:-

(a) the environment;

(b) personnel;

(c) critical surfaces;

(d) container or closure sterilisation and transfer procedures;

(e) the maximum holding period of the product before filling into the final container; and

(f) the sterilising filter.

6.11.2.4. Certain solutions and liquids that cannot be sterilised in the final container can be filtered through a sterile filter of nominal pore size 0.22 µ (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilised container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration shall be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilisation in the final container is possible. Of the methods currently available, steam sterilisation is preferred.

6.11.2.5. Owing to the potential additional risks of the filtration method as compared with other sterilisation processes, a double-filter layer or second filtration through a further sterilised microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration shall be carried out as close as possible to the filling point.

6.11.2.6. The fibre-shedding characteristics of filters shall be minimal (virtually zero). Asbestos-containing filters shall not be used under any circumstances.

6.11.2.7. The integrity of the sterilised filter shall be verified before use and shall be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter shall be determined during validation and any significant difference from these during routine manufacturing shall be noted and investigated. Results of these checks shall be included in the batch record. The integrity of critical gas and air vent filters shall be confirmed after use. The integrity of other filters shall be confirmed at appropriate intervals. Consideration shall be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g., the circulation of high-temperature air.

6.11.2.8. The same filter shall not be used for more than one working day unless such use has been validated.

6.11.2.9. The filter shall not affect the product either by removing ingredients from it or by releasing substances into it.

6.11.3. **Isolator technology-**

6.11.3.1. The use of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbial contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment shall be designed so that the required air quality for each zone can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from single-door to double-door designs to fully-sealed systems incorporating sterilisation mechanisms.

6.11.3.2. The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high-risk manipulations, although it is recognised that unidirectional airflow may not exist in the working zone of all isolators and transfer devices.

Explanation.- For the purpose of this paragraph "local zone" means an area inside the isolator for high risk manipulation.

6.11.3.3. The air classification required for the background environment depends on the design of the isolator and its application. It shall be controlled, and for aseptic processing it shall be at least Grade D.

6.11.3.4. Isolators shall be introduced only after appropriate validation. Validation shall take into account all critical factors of isolator technology, for example, the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.

6.11.3.5. Monitoring shall be done routinely and shall include frequent leak testing of the isolator and the glove or sleeve system.

6.11.4. **Blow, Fill-Seal technology-**

6.11.4.1. Blow, Fill-Seal units are purpose-built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow, Fill-Seal equipment used for aseptic production which is fitted with an effective Grade A air shower may be installed in at least a Grade C zone, provided that Grade A or B clothing is used. The environment shall comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow, Fill-Seal equipment used for the production of products which are terminally sterilised shall be installed in at least a Grade D zone.

6.11.4.2. Because of this special technology, particular attention shall be paid to at least the following, namely:-

(a) equipment design and qualification;

(b) validation and reproducibility of cleaning-in-place and sterilisation-in-place;

(c) background clean room environment in which the equipment is located;

(d) operator training and clothing; and

(e) interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

7. Personnel:-

7.1. Only the minimum number of personnel required shall be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls shall be conducted from outside such areas.

7.2. All personnel (including those concerned with cleaning and maintenance) employed in such areas shall receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g., building or maintenance contractors) need to be brought in, particular care shall be taken over their instruction and supervision.

7.3. Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process shall not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

7.4. High standards of personal hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations shall be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbial hazards shall be decided by a designated competent person.

7.5. Changing and washing shall follow a written procedure designed to minimise the contamination of clean-area clothing or the carry-through of contaminants to clean areas. The clothing and its quality shall be appropriate for the process and the grade of the working area. It shall be worn in such a way so as to protect the product from contamination.

7.6. Outdoor clothing shall not be brought into changing rooms leading to Grade B and C rooms. For every worker in a Grade A or B area, clean sterile (sterilised or adequately sanitized) protective garments shall be provided at each work session. Gloves shall be regularly disinfected during operations. Masks and gloves shall be changed at least every working session. Operators working in Grade A and B zone shall wear sanitised goggles.

7.7. Wrist-watches, cosmetics and jewellery shall not be worn in clean areas.

7.8. The clothing required for each grade is as follows:

(i) Grade D: The hair and, where relevant, beard and moustache shall be covered. Protective clothing and appropriate shoes or overshoes shall be worn. Appropriate measures shall be taken to avoid any contamination from outside the clean area.

(ii) Grade C: The hair and, where relevant, beard and moustache shall be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes shall be worn. The clothing shall shed virtually no fibres or particulate matter.

(iii) Grades A and B: Entry of personnel into Grade A zone shall be minimised. Headgear shall totally enclose the hair and, where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and with a high neck, shall be worn. The headgear shall be tucked into the neck of the suit. A facemask shall be worn to prevent the shedding of droplets. Sterilised, non-powdered gloves of appropriate material and sterilised or disinfected footwear shall be worn. Trouser bottoms shall be tucked inside the footwear and garment sleeves into the gloves. The protective clothing shall shed virtually no fibres or particulate matter and shall retain particles shed by the body.

7.9. Clothing used in clean areas shall be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilisation, there may be an increased risk of shedding particles. Washing and sterilisation operations shall follow standard operating procedures.

8. Premises:

8.1. All premises shall as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A and B zone shall be designed so that all operations can be observed from outside.

8.2. In clean areas all exposed surfaces shall be smooth, impervious and unbroken to minimise the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

8.3. To reduce the accumulation of dust and to facilitate cleaning, there shall be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors shall be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors shall open to the high pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements.

8.4. False ceilings shall be sealed to prevent contamination from the void space above them.

8.5. Pipes and ducts and other utilities shall be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings shall be used and threaded pipe connections shall be avoided.

8.6. Sinks and drains shall be avoided wherever possible and shall be excluded from Grade A and B zone where aseptic operations are carried out. Where installed they shall be designed, located and maintained so as to minimise the risks of microbial contamination; they shall be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels shall be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants.

8.7. Changing rooms shall be designed as airlocks and used to provide physical separation of the different stages of changing tominimise microbial and particulate contamination of protective clothing. They shall be flushed

effectively with filtered air. The final stage of the changing room shall, in the at rest state, be the same Grade as the zone into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities shall be provided only in the first stage of the changing rooms. There shall not be a change of more than one Grade between airlocks or passages and changing rooms, i.e., a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads to a Grade B clean room. Changing rooms shall be of a sufficient size to allow for ease of changing. Changing rooms shall be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room.

8.8. Airlock doors shall not be opened simultaneously. An interlocking system and a visual or audible or both warning system shall be operated to prevent the opening of more than one door at a time.

8.9. A filtered air supply shall be used to maintain a positive pressure and the airflow relative to surrounding areas of a lower Grade under all operational conditions; it shall flush the area effectively. Adjacent rooms of different Grades shall have a pressure differential of approximately 10 to 15 Pascal (guidance value). Particular attention shall be paid to the protection of the zone of greatest risk, i.e., the immediate environment to which the product and the cleaned components in contact with it are exposed. The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

8.10. It shall be demonstrated that airflow patterns do not present a contamination risk; for example, care shall be taken to ensure that particles from a particle generating person, operation or machine are not conveyed to a zone of higher product risk.

8.11. A warning system shall be operated to indicate failure in the air supply. Indicators of pressure differentials shall be fitted between areas where this difference is important, and the pressure differentials shall be regularly recorded and failure alarmed.

8.12. Consideration shall be given to restricting unnecessary access to critical filling areas e.g., Grade A filling zones, by means of a physical barrier.

9. Equipment:

9.1. A conveyor belt shall not pass through a partition between a Grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilised (e.g., in a sterilising tunnel).

9.2. Whenever possible, equipment used for processing sterile products shall be chosen so that it can be effectively sterilised by steam or dry heat or other methods.

9.3. As far as possible, equipment fittings and services shall be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance shall be re-sterilised after complete reassembly, wherever possible.

9.4. When equipment maintenance is carried out within a clean area, clean instruments and tools shall be used and the area shall be cleaned and disinfected again, where appropriate, before processing recommences, if the required standards of cleanliness or asepsis or both have not been maintained during the maintenance work.

9.5. All equipment such as sterilisers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems shall be subject to validation and planned maintenance; their return to use shall be approved.

9.6. Water-treatment plants and distribution systems shall be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They shall not be operated beyond their designed capacity. Consideration shall be given to include a testing programme in the maintenance of a water system. Water for injection shall be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g., by constant circulation at a temperature above 70 °C or not more than 4 °C.

10. Finishing of sterile products:-

10.1. Containers shall be closed by appropriately validated methods. Containers closed by fusion, e.g., glass or plastic ampoules, shall be subject to 100 percent integrity testing. Samples of other containers shall be checked for integrity according to appropriate procedures.

10.2. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap shall, therefore, be performed as soon as possible after stopper insertion.

10.3. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment shall be located at a separate station equipped with adequate air extraction.

10.4. Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials shall be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials shall be protected with a Grade A air supply until the cap has been crimped.

10.5. Vials with missing or displaced stoppers shall be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology shall be used to prevent direct contact with the vials and to minimise microbial contamination.

10.6. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.

10.7. Containers sealed under vacuum shall be tested for maintenance of that vacuum after an appropriate, predetermined period.

10.8. Filled containers of parenteral products shall be inspected individually for extraneous contamination or other defects. When inspection is carried out visually this shall be done under suitable and controlled conditions of illumination and background. Operators doing the inspection shall pass regular eyesight checks, using personal corrective lenses (e.g., spectacles or contact lenses) as required, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process shall be validated and the performance of the equipment shall be checked at intervals. Results shall be recorded.

PART III

SPECIFIC REQUIREMENTS FOR MANUFACTURING OF PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES SUCH AS SEX HORMONES, STEROIDS (ANABOLIC, ANDROGENIC) OR CYTOTOXIC SUBSTANCES

Note.-Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I Schedule shall be complied with, *mutatis mutandis*, for the manufacture of hazardous substances such as certain sex hormones, steroids (anabolic, androgenic) or cytotoxic substances. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Introduction:-

The areas to which this Part applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. Wherever possible products shall be manufactured in closed systems.

1.1. Facilities shall be designed and operated in accordance with the main good manufacturing practices principles, as follows:-

(a) to ensure quality of product;

(b) to protect the operators from possible harmful effects of products containing hazardous substances; and

(c) to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

1.2. The production of certain products containing hazardous substances shall generally be conducted in separate, dedicated, self-contained facilities. These self-contained facilities may be in the same building as another facility but shall be separated by a physical barrier and have e.g., separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services shall be determined by risk assessment.

1.3. In general these manufacturing facilities shall be regarded as containment facilities.

1.4. The effective operation of a facility may require the combination of some or all of the following, namely:-

(a) appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;

(b) manufacturing process controls including adherence to SOPs;

(c) appropriately designed Environmental Controls Systems (ECS) or HVAC;

(d) extraction systems;

(e) Personal Protective Equipment (PPE);

(f) appropriate de-gowning and decontamination procedures;

(g) industrial hygiene (monitoring staff exposure levels);

(h) medical surveillance (monitoring staff exposure levels); and

(i) administrative controls.

2. Risk assessment:-

2.1. Not all products containing hazardous substances are equally potent and risk assessments shall be carried out to determine the potential hazards to operators and to the environment. The risk assessment shall also determine which phase of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment shall include airborne contamination as well as liquid effluent contamination.

2.2. Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators or to the public or to the environment, the guidelines to be followed for the design and operation of the facility shall be as detailed in this Schedule.

2.3. The toxicological data available, such as permissible occupational exposure levels (OEL) for the product, shall be taken into account when conducting the risk assessment.

2.4. The risk assessment shall take into account occupational health and safety requirements for OELs in the work environment.

3. Product protection:- The requirement for producing quality products, with respect to protection from contamination and cross-contamination, clean room class of air, temperature and humidity shall be as for other pharmaceutical products.

4. Personal Protection Equipment and breathing air systems:-

4.1. The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. In case of the facility and equipment design is not providing adequate product containment, operator protection shall be provided. If facility and equipment design are adequate, a spillage or non-routine incident could cause a hazardous situation, in which case PPE shall be available. Unless otherwise specified in the material safety data sheet, operators shall be protected from exposure with an appropriate method, such as by wearing-

(a) flash-spun, high-density polyethylene fibre material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;

(b) flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;

(c) suitable single-use, disposable gloves. Double gloves shall be worn where direct active contact with the product cannot be avoided. Gloves shall be taped or sealed on to the protective suit sleeves; and

(d) respirator eye and face protection with associated breathing air systems.

4.2. Where breathing air systems are used, these shall be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel shall be appropriately trained and assessed in the use of these systems before they enter the area. The breathing air systems shall comprise a protective face mask, which shall form an integral part of a protective suit. The breathing air systems could be any of the systems described below-

(a) a central air supply system which connects to the operator's facemask by means of flexible hoses and quick coupling sockets, also called an Airline Respirator (AR). The air connection shall incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply shall be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it shall be of the oil-free type or have suitable oil removal filters fitted;

(b) a Self-Contained Breathing Apparatus (SCBA) or Powered Air Purifying Respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;

(c) for zones with lower contamination levels, a half-mask High Efficiency Particulate Air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.

4.3. The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified Protection Factor (PF).

4.4. The air supplies shall be filtered through a final filter, which shall be a HEPA filter rated as an H13 filter according to European norms. The supply of breathing air in to the face mask or protective suit or both shall result in the interior of the mask and suit being at a positive pressure relative to the facility environment.

4.5. Central breathing air supply systems shall have a one hundred percent back-up system in the event of the main system failing. This could be in the form of a gas bottle system with atleast five minutes supply. Change over from the normal supply to the back-up supply shall be automatic. The system shall have a monitoring system and send alarm signals to a permanently manned location in the following situations, namely:-

(i) failure of main air supply;

(ii) temperature out of specification (OOS);

(iii) humidity OOS;

(iv) carbon dioxide (CO_2) OOS;

(v) carbon monoxide (CO) OOS; and

(vi) sulfur dioxide (SO_2) OOS.

4.6. Breathing air shall be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO standards and European norms.

4.7. Where air is delivered through a central system the piping shall not cause any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters shall be as close as possible to the operator connection points. The operator hose connection to the air supply shall be a dedicated connection specific to the breathing air system to avoid inadvertent connection to a different gas system.

5. Environmental protection:-

5.1. Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues shall be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

5.2. The external atmosphere and the public in the vicinity of the facility shall be protected from possible harm from hazardous substances.

5.3. If liquid effluent poses a safety or contamination risk, the effluent shall be treated before being discharged to a municipal drain.

5.4. Exhaust air filtration to ensure environmental protection shall be as per paragraph 11.

6. Facility layout:-

6.1. The premises shall be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention shall be paid to the level of containment provided by the equipment.

6.2. The link between the interior and exterior of the premises shall be through airlocks [Personnel Airlock (PAL), Material Airlock (MAL)], changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel shall have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

6.3. The changing rooms shall have an arrangement with a step-over- bench. The facilities on the exit side shall incorporate showers for the operators.

6.4. The premises shall be laid out and designed so as to facilitate the required pressure cascades and containment.

6.5. The premises and equipment shall be appropriately designed and installed to facilitate cleaning and decontamination.

6.6. The manufacturing site and buildings shall be described in sufficient detail by means of plans and written explanations to ensure that the designation and conditions of use of all the rooms are correctly shown.

6.7. The flow of people and products shall be clearly marked on the layouts and plans.

6.8. The activities carried out in the vicinity of the site shall be indicated.

6.9. Plans shall describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

6.10. The facility shall be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

6.11. Areas of the facility where exposed product presents a risk shall be maintained at a negative air pressure relative to the environment.

7. Air-handling systems:-

7.1. The HVAC system shall be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.

7.2. Facilities and premises dealing with hazardous substances shall have the following basic air-handling characteristics, namely:-

(i) there shall be no direct venting of air to the outside;

(ii) air-conditioning or ventilation shall result in a negative pressure relative to the outside. Air pressure differentials shall be such that there is no uncontrolled flow of air between the work area and the external environment;

(iii) appropriate air pressure alarm systems shall be provided to warn of any pressure cascade reversal or loss of design pressure status. The appropriate design, alert and action limits shall be in place. System redundancies shall be in place to respond appropriately to pressure cascade failure;

(iv) the starting and stopping of the supply and exhaust air fan shall be synchronized so that the premises remain at a negative pressure during start-up and shut-down;

(v) the air pressure cascade within the facility, shall comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection;

(vi) visual indication of the status of room pressures shall be provided in each room;

(vii) air shall be exhausted to the outside through HEPA filters and not be re-circulated except to the same area, and provided that a further HEPA filtration stage is applied to the return air. Where HEPA filters are mentioned in the Schedule, this refers to HEPA filters with a minimum rating of H13 according to European norms;

(viii) where possible, single-pass air-handling systems with no recirculation shall be provided;

(ix) exhaust air or return air shall be filtered through a safe-change or bag- in-bag-out filter housing. The filter housing shall contain pre-filters and HEPA filters, both of which shall be removable with the safe bagging system;

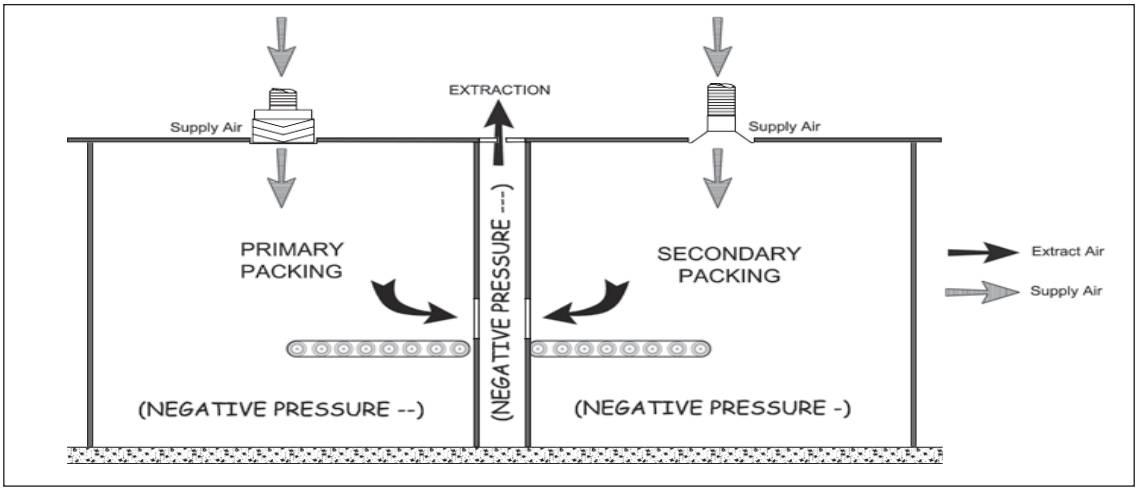
(x) changing rooms shall be supplied with air filtered to the same standard as that for the work area they serve;

(xi) airlocks, pass-through hatches, etc., shall have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, airlock or pass-through hatch bordering on an external or non-good manufacturing practices area shall be at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility;

(xii) if the facility provides insufficient containment, and operators' garments are contaminated with dust, the operators leaving the containment area shall pass through a decontamination system e.g., air showers or a mist shower system, to assist with removing or controlling dust particles on their garments. Operators shall follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering shall be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities shall be in place.

7.3. If required, appropriate measures shall be taken to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area.

Note.- This could be overcome by having a pass-through chamber over the "mouse hole" which is maintained at a negative pressure to both primary and secondary packing. This typical arrangement is illustrated in Figure below. This principle can be applied to other situations where containment from two sides is required. The typical airflow pattern for contaminant shall be as specified in the figure below–



7.4. Where possible, HEPA filters in the supply air system shall be terminally mounted to provide protection against back-flow cross-contamination in the event of failure in the supply airflow.

7.5. In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection.

7.6. There shall be a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications. These shall be available for inspection.

7.7. There shall be an indication of pressure gradients that are monitored by means of digital or analogue pressure indicators.

7.8. Consideration shall be given to providing an emergency power supply, e.g., diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

7.9. The principles of airflow direction, air filtration standards, temperature, humidity and related parameters shall be ensured and the filtration shall be consistent with the zone concepts and product protection required.

8. Air-Handling Units (AHU):-

8.1. The decision to use return air or re-circulated air shall be made on the basis of a risk assessment.

8.2. Where a full fresh-air or single-pass system is used, an energy recovery wheel could be considered. In such cases, there shall not be any potential for air leakage between the supply air and exhaust air as it passes through the wheel. The relative pressures between supply and exhaust air systems shall be such that the exhaust-air system operates at a lower pressure than the supply system. (Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)

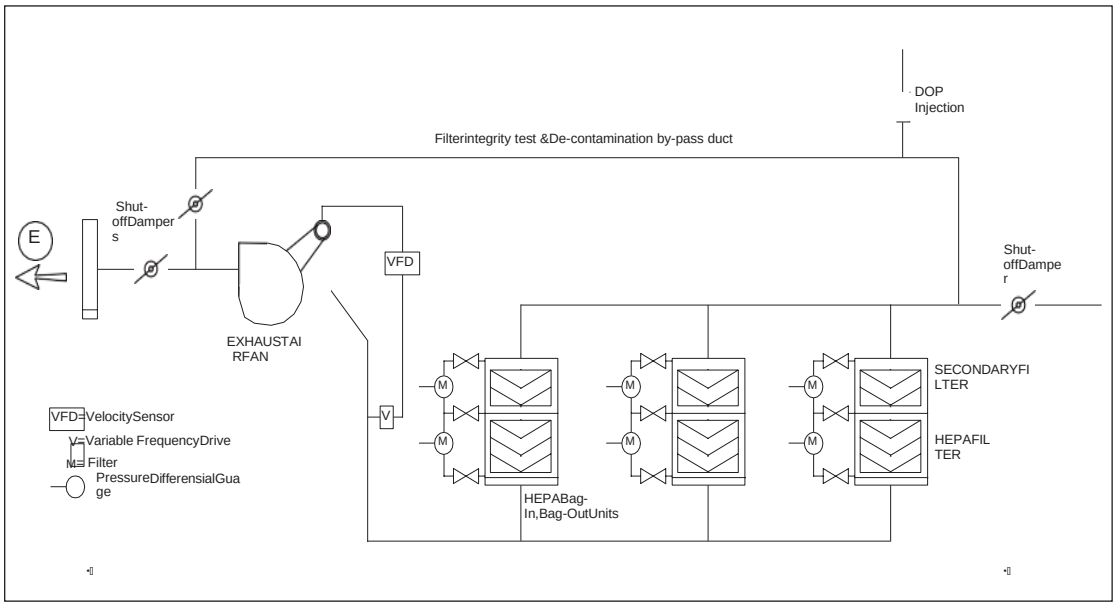
8.3. Risk management principles shall be applied to address the potential of cross-contamination where energy wheels are used.

8.4. If return air is to be re-circulated it shall pass through a safe change filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU; however, the safe change filter shall be a dedicated unit. With this arrangement the return air passes through two sets of HEPA filters in series, i.e., the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.

8.5. The starting and stopping of the supply and exhaust air fans and associated system ventilation fans shall be synchronised such that the premises retain their design pressure and flow relationships during start-up and shut-down. Processing shall stop when the fans are not running. This fan interlock sequence shall also apply if any fan shall fail, to ensure that there is no airflow reversal in the system.

9. Safe change filter housings:-

9.1. Safe change or bag-in-bag-out filter housings shall be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed. The Safe change filter bypass arrangement shall be as specified in the figure below–



9.2. The final filters on the safe change unit shall be HEPA filters with at least an H13 classification according to European norms filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters shall also be removable through the bag-in-bag-out method.

9.3. For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series shall be considered to provide additional protection the first filter fail.

9.4. All filter banks shall be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges shall be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing shall be provided with stopcocks, for safe removal or calibration of gauges.

9.5. Monitoring of filters shall be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

9.6. Computer based data monitoring systems may be installed to monitor filter condition.

9.7. Filter pressure gauges shall be marked with the clean filter resistance and the change-out filter resistance.

9.8. Installed filter leakage tests shall be performed in accordance with ISO standards. Injection ports (upstream) and access ports (downstream) shall, therefore, be provided for this purpose.

9.9. The exhaust air fan on a safe change filter system shall be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests and for this reason a bypass damper system shall be provided, as illustrated in figure at paragraph 9.1, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively, an independent booster fan system can be used, with appropriate shut-off dampers.

9.10. The bypass arrangement as shown in figure at paragraph 9.1also permits decontamination of the filters by means of circulation of a sanitising agent.

9.11. All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, shall be passed through safe change filter housings before being exhausted to the atmosphere.

9.12. All exhaust points outside the building shall be located as far as possible from air entry points and exit points shall be at a high level to minimise the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions shall be taken into account when positioning exhaust and supply points.

9.13. Where excessively dust-laden air is handled, a dust collector or bag house shall be considered with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, PPE and breathing air systems shall then be provided to protect the operators during removal of dust from the collector bins.

9.14. Portable vacuum cleaners and portable dust collectors shall be fitted with H13 HEPA filters. These types of units shall be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel shall be provided with suitable PPE.

9.15. Records of the safe disposal of all contaminated filters and dust shall be kept.

10. Personnel decontamination systems:-

10.1. If required, a means of preventing contaminants from leaving the facility on the garments of personnel shall be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.

10.2. An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g., from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g., at low level) shall draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note.- When air showers are used these shall be correctly designed to effectively extract dust. Air filtration of the supply air and return or exhaust air shall comply with the same filtration standards as used in the manufacturing facility. Normally the fan shall be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

10.3. Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.

10.4. Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operators' garments or causing contaminants to adhere to the garments so that they are not easily liberated.

10.5. Personnel shall change into clean garments after having taken a shower.

11. Effluent treatment:-

11.1. Liquid and solid waste effluent shall be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.

11.2. All effluent shall be disposed of in a safe manner and the means of disposal shall be documented. Where external contractors are used for effluent disposal they shall have certification authorising them to handle and treat hazardous products.

12. Maintenance:- The efficient and safe operation of a facility handling hazardous materials is reliant on regular maintenance being carried out, to ensure that all parameters remain within specified tolerances.

13. Qualification and validation:-

System qualification and validation shall be carried out.

PART IV

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF BIOLOGICAL PRODUCTS

Note.—Good Manufacturing Practices for pharmaceutical products: main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Biological products. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Principles and general considerations:-

1.1. Biological products can be defined according to their source material and method of manufacture. The source materials and methods employed in the manufacture of biological products for human use therefore represent critical factors in shaping their appropriate regulatory control. Biological products are derived from cells, tissues or microorganisms and reflect the inherent variability characteristic of living

materials. The active substances in biological products are often too complex to be fully characterised by utilising physicochemical testing methods alone and may show a marked heterogeneity from one preparation or batch or both. Consequently, special considerations are needed when manufacturing biological products in order to maintain consistency in product quality.

1.2. The guidance provided in this Part applies to the manufacture, control and testing of biological products for human use from starting materials and preparations (including seed lots, cell banks and intermediates) to the finished product.

1.3. Manufacturing procedures within the scope of this Schedule includes-

(a) growth of strains of microorganisms and eukaryotic cells;

(b) extraction of substances from biological tissues, including human, animal and plant tissues, and fungi;

(c) recombinant DNA (rDNA) techniques;

(d) hybridoma techniques; and

(e) propagation of microorganisms in embryos or animals.

1.4. Medicinal products of biological origin manufactured by these procedures include allergens, antigens, vaccines, certain hormones, cytokines, monoclonal antibodies (mAbs), enzymes, animal immune sera, products of fermentation (including products derived from rDNA), biological diagnostic reagents for in-vivo use and Advanced Therapy Medicinal Products (ATMPs) used for example in gene therapy and cell therapy.

1.5. The manufacture, control and administration of biological active substances and finished products require certain specific considerations and precautions arising from the nature of these products and their processes. Unlike conventional pharmaceutical products which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and finished products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. As these biological processes may display inherent variability, the range and nature of by-products may also be variable. As a result, QRM principles are particularly important for this class of materials and shall be used to develop the control strategy across all stages of manufacture so as to minimise variability and reduce the opportunity for contamination and cross-contamination.

1.6. Materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of target cells and microorganisms. Therefore, extraneous microbial contaminants have the opportunity to grow. Furthermore, many biological products have limited ability to withstand certain purification techniques, particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations in minimising such contamination events. Manufacturing shall be consistent with other specifications set out in the product summary files, marketing authorisation or clinical trial approvals [for example, number of generations (expressed as doublings or passages) between the seed lot or cell bank and the finished product].

1.7. Many biological materials (such as live-attenuated bacteria and viruses) cannot be terminally sterilised by heat, gas or radiation. In addition, some products, such as certain live and adjuvant vaccines [for example, Bacilli Calmette Guerin (BCG) or Cholera], may not be sterilised by filtration processes. For these axenic products, processing shall be conducted aseptically to minimise the introduction of contaminants from the point where a potential contamination cannot be removed from the manufacturing process. The validation of specific and critical manufacturing steps such as virus removal or inactivation shall be carried out. Robust environmental controls and monitoring and, wherever feasible, *in situ* cleaning and sterilisation systems, together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.

1.8. Control usually involves biological analytical techniques, which typically have a greater variability than physicochemical determinations. The combination of variability in starting materials and the potential for subtle changes during the manufacturing process of biological products also requires an emphasis on production consistency. This is of particular concern because of the need to link consistency to original clinical trials documenting the product's safety and efficacy. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

1.9. Because of the risks inherent in producing and manipulating pathogenic and transmissible microorganisms during the production and testing of biological materials, GMP shall prioritise the safety

of the recipient to whom the biological product is administered, the safety of personnel during operation and the protection of the environment.

1.10 Biosafety considerations shall follow the guidelines issued by the Central Government in this regard. In the context of manufacturing pathogenic biological products of Biosafety Risk Group 3 and 4, close collaboration between such institutions is especially required to assure that both product contamination and environmental contamination levels are controlled within the acceptable limits.

2. Pharmaceutical quality system and quality risk management:-

2.1. Biological products, like any pharmaceutical product, shall be manufactured in accordance with the requirements of a pharmaceutical quality system (product quality system) based on a life-cycle approach, good manufacturing practices for pharmaceutical products. Main principles- This approach facilitates innovation and continual improvement and also strengthens the link between pharmaceutical development and manufacturing activities.

2.2. QRM principles shall be used to develop the control strategy across all manufacturing and control stages including materials sourcing and storage, personnel and materials flow, manufacture and packaging, quality control, quality assurance, storage and distribution activities, as described in this Part. Due to the inherent variability of biological processes and starting materials, ongoing trend analysis and periodic review are particularly important elements of product quality system. Thus, special attention shall be paid to starting material controls, change control, trend analysis and deviation management in order to ensure production consistency. Monitoring systems shall be designed so as to provide early detection of any unwanted or unanticipated factors that may affect the quality, safety and efficacy of the product. The effectiveness of the control strategy in monitoring, reducing and managing such risks shall be regularly reviewed and the systems updated as required taking into account scientific and technical progress.

3. Personnel:-

3.1. Personnel responsible for production and control shall have an adequate background in relevant scientific disciplines such as microbiology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology, biotechnology and veterinary medicine, together with sufficient practical experience to enable them to perform their duties.

3.2. The health status of personnel shall be taken into consideration as part of ensuring product safety. Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) shall be vaccinated with appropriate specific vaccines and have regular health checks. Any changes in the health status of personnel which could adversely affect the quality of the product shall preclude their working in the production area, and appropriate records kept. The scope and frequency of health monitoring shall be commensurate with the risk to the product and personnel.

3.3. Training in cleaning and disinfection procedures, hygiene and microbiology shall emphasise the risk of microbial and adventitious contamination and the nature of the target microorganisms and growth media routinely used.

3.4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control, maintenance and cleaning staff) shall be defined on the basis of quality risk management principles. In general, all personnel including those not routinely involved in the production operation (such as management, engineering staff and validation staff or auditors) shall not pass from areas with exposure to live microorganisms, genetically modified microorganisms, animal tissue, toxins, venoms or animals, to areas where other products (inactivated or sterile) or different organisms are handled. If such passage is unavoidable during a working day, then contamination control measures (for example, clearly defined decontamination measures such as a complete change of appropriate clothing and shoes and showering, if applicable) shall be followed by all personnel visiting any such production area unless otherwise justified on the basis of QRM.

3.5. Because the risks are difficult to manage, personnel working in an animal facility shall be restricted from entering production areas where potential risks of cross-contamination exist.

3.6. Staff assigned to the production of Bacille Calmette-Guerin (BCG) products shall not work with other infectious agents. In particular, they shall not work with virulent strains of Mycobacterium tuberculosis, nor shall they be exposed to a known risk of tuberculosis infection. Additionally, they shall be carefully monitored with regular health checks that screen for tuberculosis infection.

3.7. If personnel working in BCG manufacturing and in animal quarters, need to be reassigned to other manufacturing units, they shall not be allowed into such units until they pass their health check.

4. Starting materials:-

4.1. The source, origin and suitability of active substances, starting materials (for example, cryo-protectants and feeder cells), buffers and media (for example, reagents, growth media, serum, enzymes, cytokines, growth factors and amino acids) and other components of the finished product shall be clearly defined and controlled according to the principles set out in Part I of this Schedule.

4.2. Manufacturers shall retain information describing the source and quality of the biological materials used for at least one year after the expiry date of the finished products and according to regulations concerning biological products. It has been found that documents retained for longer periods may provide useful information related to Adverse Events Following Immunisation (AEFI) and other investigations.

4.3. All starting material suppliers (i.e., manufacturers) shall be initially qualified on the basis of documented criteria and a risk-based approach. Regular assessment of their status shall also be carried out. Particular attention shall be given to the identification and monitoring of any variability that may affect biological processes. When starting materials are sourced from brokers who could increase the risk of contamination by performing repackaging operations under GMP they shall be carefully qualified; an audit may form part of such qualification, as needed.

4.4. An identity test or equivalent, shall be performed on each batch of received starting materials prior to release. The number of containers sampled shall be justified on the basis of QRM principles and in agreement with all applicable guidelines. The identification of all starting materials shall be in compliance with the requirements appropriate to the stage of manufacture. The level of testing shall be commensurate with the qualification level of the supplier and the nature of the materials used. In the case of starting material used to manufacture active substances, the number of samples taken shall be based on statistically recognised criteria and QRM principles. However, for starting materials and intermediates used in the formulation of finished product, each container shall be sampled for identity testing in accordance with the main principles of GMP for pharmaceutical products unless reduced testing has been validated.

4.5. The sampling process shall not adversely affect the quality of the product. Incoming starting materials shall be sampled under appropriate conditions in order to prevent contamination and cross-contamination.

4.6. Where justified (such as the special case of sterile starting materials) it may be acceptable to reduce the risk of contamination by not performing sampling at the time of receipt but to perform the testing later, on the samples taken at the time of use. In such cases, release of the finished product is conditional upon satisfactory results of these tests.

4.7. Where, the necessary tests for approving starting materials take a significantly long time, it may be permissible by exception to process starting materials before the test results are available. The use of these materials shall be clearly justified in a documented manner, and the risks shall be understood and assessed under the principles of QRM. In such cases, release of the finished product is conditional upon satisfactory results from the tests. It must be ensured that this is not standard practice and occurs only with justification of the risk taken.

4.8. The risk of contamination of starting materials during their passage along the supply chain shall be assessed, with particular emphasis on adventitious agents such as those causing Transmissible spongiform encephalopathies (TSEs). Other materials that come into direct contact with manufacturing equipment or with potential product contact surfaces (such as filter media, growth media during aseptic process simulations and lubricants) shall also be controlled. A quality risk assessment shall be performed to evaluate the potential for adventitious agents in biological starting materials.

4.9. Where required, the sterilisation of starting materials shall be carried out by heat, whenever possible. Where necessary, other appropriate validated methods may also be used for this purpose (such as irradiation and filtration).

4.10. The controls required for ensuring the quality of sterile starting materials and of the aseptic manufacturing process shall be based on the principles and guidance contained in Part II of this Schedule.

4.11. The transport of critical materials, reference materials, active substances, human tissues and cells to the manufacturing site shall be controlled as part of a written quality agreement between the responsible parties, if they are different commercial entities. Manufacturing sites shall have documentary evidence of adherence to the specified storage and transport conditions, including cold chain requirements, if

required. The required traceability starting at tissue establishments through the recipients, and including the traceability of materials in contact with the cells or tissues shall be ensured, maintained and documented.

5. Seed lots and cell banks:-

5.1. The recommendations set out in GMP for API shall be followed taking into consideration specific guidance for API manufactured by cell culture or fermentation.

5.2. Where human or animal cells are used as feeder cells in the manufacturing process, appropriate controls over their sourcing, testing, transport and storage shall be in place.

5.3. In order to prevent the unwanted drift of genetic properties which might result from repeated subcultures or multiple generations, the production of biological products obtained by microbial culture, cell culture or propagation in embryos and animals shall be based on a system of master and working seed lots or cell banks or both; which is the beginning of the manufacturing process of certain biological products (for example, vaccines).

5.4. The number of generations (expressed as passages or doublings) between the seed lot or cell bank and the finished product, defined as maximum, shall be consistent with the marketing authorisation dossier and shall not be exceeded.

5.5. Cell-based medicinal products are often generated from a cell stock obtained from a limited number of passages. In contrast with the two-tier system of Master Cell Banks (MCBs) and Working Cell Banks (WCBs), the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life-cycle of the product. Cell stock changes shall be covered by a validation protocol and communicated to the National Regulatory Authority (NRA), as applicable.

5.6. Establishment and handling of the MCBs and WCBs shall be performed under conditions which are demonstrably appropriate. These shall include an appropriately controlled environment to protect the seed lot and the cell bank, and the personnel handling them. During the establishment of the seed lot and cell bank, no other living or infectious material (such as viruses, cell lines or microbial strains) shall be handled simultaneously in the same area or by the same persons.

5.7. Quarantine and release procedures for master and working cell banks or seed lots shall be followed, including adequate characterisation and testing for contaminants. Initially, full characterisation testing of the MCB shall be done, including genetic identification. A new MCB (from a previous initial clone, MCB or WCB) shall be subjected to the same established testing as the original MCB, unless otherwise justified. Thereafter, the viability, purity and other stability indicating attributes of seed lots and cell banks shall be checked regularly according to justified criteria. Evidence of the stability and recovery of the seed lots and banks shall be documented and records shall be kept in a manner that permits trend evaluation.

5.8. Each storage container shall be adequately sealed, clearly labelled and kept at an appropriate temperature. A stock inventory shall be kept. The storage temperature shall be recorded continuously and, where applicable, the liquid nitrogen level shall be monitored. Any deviation from the set limits, and any corrective and preventive action taken, shall be recorded. Temperature deviations shall be detected as early as possible (for example, through the use of an alarm system for temperature and nitrogen levels).

5.9. Seed lots and cell banks shall be stored and used in such a way so as to minimise the risks of contamination or alteration (for example, stored in qualified ultra-low temperature freezers or liquid nitrogen storage containers). Control measures for the storage of different seeds or cells or both in the same area or equipment shall prevent mix-up and shall take into account the infectious nature of the materials in order to prevent cross-contamination.

5.10. Master Seed Lots (MSLs), MCBs, and preferably also Working Seed Lots (WSLs) and WCBs, shall be stored in two or more controlled separate sites in order to minimise the risk of total loss due to natural disaster, equipment malfunction or human error. A contingency plan shall be in place.

5.11. The storage and handling conditions for the cell or seed banks shall be defined. Access shall be controlled and restricted to authorised personnel and appropriate access records maintained. Records of location, identity and inventory of individual containers shall also be kept. Once containers are removed from the seed lot or cell bank management system, they shall not be returned to the stock.

6. Premises and equipment:-

6.1. In general, preparations containing live microorganisms or live viruses shall not be manufactured and containers shall not be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of

the live microorganisms and viruses, then the use of multi-product facilities may be justifiable. In such cases, measures such as campaign production, closed systems or disposable systems or both shall be considered and shall be based on QRM principles

6.2. Documented QRM shall be carried out for every additional product in a biological manufacturing multi-product facility, which may include a potency and toxicological evaluation based on cross-contamination risks. Other factors to be taken into account include facility or equipment design and use, personnel and material flows, microbiological controls, physicochemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from product evaluation. The outcome of the QRM process shall be the basis for determining the necessity for premises and equipment to be dedicated to a particular product or product family, and the extent to which this shall be the case. This may include dedicating specific product contact parts.

6.3. Inactivated vaccines, antisera and other biological products including those made by rDNA techniques, toxoids and bacterial extracts may, following inactivation, be manufactured on the same premises provided that adequate decontamination and cleaning measures are implemented on the basis of QRM.

6.4. Cleaning and sanitisation shall take into account the fact that processes often include the handling of growth media and other growth-promoting agents. Validation studies shall be carried out to ensure the effectiveness of cleaning, sanitisation and disinfection, including elimination of residues of used agents. Environmental and personnel safety precautions shall be taken during the cleaning and sanitisation processes. The use of cleaning and sanitising agents shall not pose any major risk to the performance of equipment. The use of closed systems to improve asepsis and containment shall be considered where practicable. Where open systems are utilised during processing (for example, during addition of growth supplements, media, buffers and gases, and during sampling and aseptic manipulations during the handling of live cells such as in cell-therapy products) control measures shall be put in place to prevent contamination, mix-up and cross-contamination. Logical and unidirectional flows of personnel, materials and processes, and the use of clean-in-place and sterilise-in-place systems, shall be considered wherever possible. Where sterile single-use systems such as bags and connectors are utilised, they shall be qualified with respect to suitability, extractables, leachables and integrity.

6.5. Because of the variability of biological products, and of the corresponding manufacturing processes, approved starting materials that have to be measured or weighed for the production process (such as growth media, solutions and buffers) may be kept in small stocks in the production area for a specified period of time according to defined criteria for the duration of manufacture of the batch or of the campaign. Appropriate storage conditions and controls shall be maintained during such temporary storage. These materials shall not be returned to the general stock. Materials used to formulate buffers, growth media and so on shall be weighed and made into a solution in a contained area using local protection (such as a classified weighing booth) and outside the aseptic processing areas in order to minimise particulate contamination of the later.

6.6. In manufacturing facilities, the mix-up of entry and exit of personnel shall be avoided through the use of separate changing rooms or through procedural controls where Biosafety Risk Group 3 or 4 organisms are handled.

7. Containment:-

7.1. Airborne dissemination of live microorganisms and viruses used for the production process, including those from personnel, shall be avoided.

7.2. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Drainage systems shall be designed in such a way that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Specific and validated decontamination systems shall be considered for effluents when infectious or potentially infectious materials are used for production. Regulations issued by the Central Government in this regard shall be complied with in order to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

7.3. Dedicated production areas shall be used for the handling of live cells capable of persistence in the manufacturing environment, for pathogenic organisms of Biosafety Risk Group 3 or 4 or for spore-forming organisms until the inactivation process is accomplished and verified. For Bacillus anthracis, Clostridium tetani and Clostridium botulinum strictly dedicated facilities shall be utilised for each individual product. Up to date information on these and other high-risk or “special” agents shall be

sought from major information resources. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product shall be processed at any one time.

7.3.1. Use of any pathogenic organism above Biosafety Risk Group 3 may be allowed according to the biohazard classification of the organism, the risk assessment of the biological product and its emergency demand.

7.4. Production of BCG related product shall take place in a dedicated area and by means of dedicated equipment and utilities (such as HVAC systems) in order to minimise the hazard of cross-contamination.

7.5. Specific containment requirements apply to poliomyelitis vaccine to minimise poliovirus facility associated risk and for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses. The measures and procedures necessary for containment (i.e., for protecting the environment and ensuring the safety of the operator) shall not conflict with those for ensuring product quality.

7.6. Air-handling systems shall be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas as required. The need for dedicated air handling units or single pass systems shall be based on QRM principles, taking into account the biohazard classification and containment requirements of the relevant organism, and process and equipment risks. In the case of Biosafety Risk Group 3 organisms, air shall not be recirculated to any other area in the facility and shall be exhausted through HEPA filters that are regularly checked for performance. A dedicated non-recirculating ventilation system and HEPA filtering of exhaust air are required when handling Biosafety Risk Group 4 organisms.

7.7. Primary containment equipment shall be designed and initially qualified for integrity in order to ensure that the escape of biological agents or material into the immediate working area and outside environment is prevented. Thereafter, in line with relevant guidelines and quality risk management principles, periodical tests shall be performed to ensure that the equipment is in proper working condition.

7.8. Activities associated with the handling of live biological agents (such as centrifugation and blending of products which can lead to aerosol formation) shall be contained in such a way so as to prevent contamination of other products or the egress of live agents into the working or outside environment or both. The viability of such organisms and their biohazard classification shall be taken into consideration as part of the management of such risks. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures shall be available for each organism or groups of related organisms. Where different strains of a single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative strain, unless the strains vary significantly in their resistance to the decontaminating agents used.

7.9. Areas where Biosafety Risk Group 3 or 4 organisms are handled shall always have a negative air pressure relative to the environment. This will ensure the containment of the organism in unlikely events such as failure of the door interlock. Air-lock doors shall be interlocked to prevent them from being opened simultaneously. Differential pressure alarms shall be present wherever required and shall be validated and monitored.

7.10. Air vent filters shall be hydrophobic and subject to integrity testing at intervals determined by a QRM approach.

7.11. Where the filtration of exhaust air is necessary, the safe changing of filters shall be ensured or bag-in-bag-out housings shall be employed. Once removed, filters shall be decontaminated and properly destroyed. In addition to HEPA filtration other inactivation technologies such as heat inactivation and steam scavenging may be considered for exhaust air to ensure effective inactivation of pathogenic organisms of Biosafety Risk Group 3 or 4.

8. Clean rooms:-

8.1. In order to address the specific manufacturing processes involved in the production of biological products, and particularly vaccines, the environmental monitoring of clean rooms in vaccine manufacturing facilities; points to consider for manufacturers of human vaccines guidance document may be used to develop the environmental classification requirements for biological manufacturing processes. As part of the control strategy, the degree of environmental control of particulate and microbial contamination of the production premises shall be adapted to the intermediate or finished product and also to the production step, taking into account the potential level of contamination of the starting materials and the risks to the finished product.

8.2. The environmental monitoring programme shall be supplemented with methods to detect the presence of the specific microorganisms used for production (for example, recombinant yeast and toxin or

polysaccharide producing bacteria). The environmental monitoring programme may also include detection of the produced organisms and adventitious agents of production organisms, especially when campaign manufacture is applied on the basis of QRM principles.

9. Production:-

9.1. Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention shall be paid to the control strategy for ensuring that effective steps are in place for preventing or minimising the occurrence of unwanted bioburden, endotoxins, viruses of animal and human origin and associated metabolites.

9.2. The QRM process shall be the basis for implementing the technical and organisational measures required to control the risks of contamination and cross-contamination. These could include, though are not limited to-

(i) carrying out processing and filling in segregated areas;

(ii) containing material transfer by means of an airlock and appropriate type of pass box with validated transfer procedures, clothing change and effective washing and decontamination of equipment;

(iii) recirculation of only treated (HEPA filtered) air;

(iv) acquiring knowledge of the key characteristics (for example, pathogenicity, detectability, persistence and susceptibility to inactivation) of all cells, organisms and any adventitious agents within the same facility;

(v) when considering the acceptability of concurrent work in cases where production is characterised by multiple small batches from different starting materials (for example, cell-based products) taking into account factors such as the health status of donors and the risk of total loss of a product from or for specific patients during development of the cross-contamination control strategy;

(vi) preventing the risk of live organisms and spores entering non-related areas or equipment by addressing all potential routes of cross-contamination (for example, through the HVAC system) through the use of single use components and closed systems;

(vii) conducting environmental monitoring specific to the microorganism being manufactured in adjacent areas while paying attention to cross-contamination risks arising from the use of certain monitoring equipment (used for airborne particle monitoring) in areas handling live or spore-forming organisms or both; and

(viii) using campaign-based production.

9.3. When applicable, the inoculum preparation area shall be designed so as to effectively control the risk of contamination, and shall be equipped with a biosafety hood for primary containment.

9.4. If possible, growth media shall be sterilisedin situ by heat or in-line microbial-retentive filters. Additionally, in-line microbial-retentive filters shall be used for the routine addition of gases, media, acids, alkalis and so on to fermenters or bioreactors.

9.5. Data from continuous monitoring of certain production processes (fermentation) shall form part of the batch record. Where continuous culture is used, special consideration shall be given to parameters such as temperature, pH, pO2, CO2 and the rate of feed or carbon source with respect to growth of cells.

9.6. In cases where a viral inactivation or removal process is performed, measures shall be taken (for example, in relation to facility layout, unidirectional flow and equipment) to avoid the risk of recontamination of treated products by non-treated products.

9.7. A wide variety of equipment and components (for example, resins, matrices and cassettes) are used for purification purposes. QRM principles shall be applied to devise the control strategy regarding such equipment and associated components when used in campaign manufacture and in multi-product facilities. The reuse of components at different stages of processing of one product is discouraged but, if performed, shall be validated. Acceptance criteria, operating conditions, regeneration methods, lifespan and sanitisation or sterilisation methods, cleaning process, and hold time between the use of reused components shall be defined and validated. The reuse of components for different products is not acceptable.

9.8. Where adverse donor (human or animal) health information becomes available after procurement or processing or both, and this information relates to product quality, then appropriate measures shall be taken including product recall, if applicable.

9.9. Antibiotics may be used during the early stages of production to help prevent inadvertent microbial contamination or to reduce the bioburden of living tissues and cells. In this case, the use of antibiotics shall be well justified, and they shall be cleared from the manufacturing process at the stage specified in the marketing authorisation. Acceptable residual levels shall be defined and validated. Penicillin and other beta lactam antibiotics shall not be used at any stage of the process.

9.10. A procedure shall be in place to address equipment or accessories failure or both (air vent filter failure) which shall include a product impact review. If such failures are discovered following batch release, the Licensing Authority shall be notified and the need for a batch recall shall be considered.

10. Campaign production:-

10.1. The decision to use a facility or filling line for campaign manufacture shall be justified in a documented manner and shall be based on a systematic risk approach for each product (or strain) taking into account the containment requirements and the risk of cross-contamination to the next product. Campaign changeover procedures, including sensitive techniques used for the determination of residues, shall be validated and proper cleaning acceptance criteria shall be defined on a toxicology basis of product residues from the last campaign, as applicable. Equipment assigned to continued production or to campaign production of successive batches of the same intermediate product shall be cleaned at appropriate validated intervals to prevent build-up and carryover of contaminants (product degradants or objectionable levels of microorganisms).

10.2. For downstream operations of certain products (for example, pertussis or diphtheria vaccines) campaign production may be acceptable if well justified. For finishing operations (formulation and filling) the need for dedicated facilities or the use of campaigns in the same facility will depend on the specific characteristics of the biological product, on the characteristics of the other products (including any non-biological products), on the filling technologies used (single use closed systems). Labelling and packaging operations can be carried out in a multiproduct facility.

10.3. Campaign changeover involves intensive decontamination or sterilisation (if required) and cleaning of the equipment and manufacturing area. Decontamination or sterilisation (if required) and cleaning shall include all equipment and accessories used during production, as well as the facility itself. The following recommendations shall be considered, namely:-

(i) waste shall be removed from the manufacturing area or sent to the bio-waste system in a safe manner;

(ii) materials shall be transferred by a validated procedure; and

(iii) the Quality Unit shall confirm area clearance by inspection, and review the campaign changeover data (including monitoring results) prior to releasing the area for the next product.

10.4. When required, the corresponding diluent for the product can be filled in the same facility in line with the defined campaign production strategy for finished product.

10.5. When campaign-based manufacturing is considered, the facility layout and the design of the premises and equipment shall permit effective cleaning and decontamination or sterilisation (if required) based on QRM principles and validated procedures following the production campaign. In addition, consideration may need to be given at the design stage of facility layout to the possible need for fumigation.

11. Labelling:-

11.1. The information provided on the inner label (also called the container label) and on the outer label (on the packaging) shall be readable and legible and the content approved by the Licensing Authority.

11.2. Minimal key information shall be printed on the inner label and additional information shall be provided on the outer label (for example, carton) or product leaflet or both.

11.3. The suitability of labels for low and ultra-low storage temperatures shall be verified, if applicable. The label shall remain properly attached to the container under different storage conditions during the shelf-life of the product. The label and its adhesive shall have no adverse effect on the quality of the product caused by leaching, migration or other means.

12. Validation:-

12.1. Biological processes, handling of live materials and using campaign-based production, if applicable, are the major aspects of biological product manufacturing which require process and cleaning validation. The validation of such processes given the typical variability of biological products, the possible use of harmful and toxic materials and the need for inactivation processes plays an important role in

demonstrating production consistency and in proving that the critical process parameters and product attributes are controlled.

12.2. A QRM approach shall be used to determine the scope and extent of validation.

12.3. All critical biological processes (including inoculation, multiplication, fermentation, cell disruption, inactivation, purification, virus removal, removal of toxic and harmful additives, filtration, formulation and aseptic filling) are subject, as applicable, to process validation. Manufacturing control parameters to be validated may include specific addition sequences, mixing speeds, time and temperature controls, limits of light exposure and containment.

12.4. After initial process validation studies have been finalised and routine production has begun, critical processes shall be subject to monitoring and trending with the objective of assuring consistency and detecting any unexpected variability. The monitoring strategy shall be defined, taking into consideration factors such as the inherent variability, complexity of quality attributes and heterogeneity of biological products. A system or systems for detecting unplanned departures from the process as designed shall be in place to ensure that the process remains in a state of control. Collection and evaluation of information and data on the performance of the process will allow for detection of undesired process variability and will determine whether action shall be taken to prevent, anticipate or correct problems so that the process remains under control.

12.5. Cleaning validation shall be performed in order to confirm the effectiveness of cleaning procedures designed to remove biological substances, growth media, process reagents, cleaning agents, inactivation agents and so on. Careful consideration shall be given to cleaning validation when campaign-based production is practiced.

12.6. Critical processes for inactivation or elimination of potentially harmful microorganisms of Biosafety Risk Group 2 or above, including genetically modified ones, are subject to validation.

12.7. Process revalidation may be triggered by a process change as part of the change control system. In addition, because of the variability of processes, products and methods, process revalidation may be conducted at pre-determined regular intervals according to risk considerations. A detailed review of all changes, trends and deviations occurring within a defined time period for example, one year, based on the regular Product Quality Review (PQR) may indicate a need for process revalidation.

12.8. The integrity and specified hold times of containers used to store intermediate products shall be validated unless such intermediate products are freshly prepared and used immediately.

13. Quality Control:-

13.1. As part of quality control sampling and testing procedures for biological materials and products, special consideration shall be given to the nature of the materials being sampled (for example, the need to avoid contamination, ensure biocontainment or cold chain requirements) in order to ensure that the testing carried out is representative.

13.2. Samples for post-release use typically fall into one of two categories reference samples or retention samples for the purposes of analytical testing and identification respectively. For finished products the reference and retention samples will in many instances be presented identically as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

13.2.1. Reference samples of biological starting materials shall be retained under the recommended storage conditions for at least one year beyond the expiry date of the corresponding finished product. Reference samples of other starting materials (other than solvents, gases and water) as well as intermediates for which critical parameters cannot be tested in the final product shall be retained for at least two years after the release of the product if their stability allows for this storage period. Certain starting materials such as components of growth media need not necessarily be retained.

13.2.2. Retention samples of a finished product shall be stored in their final packaging at the recommended storage conditions for at least one year after the expiry date.

13.3. For cell-based products, microbiological tests (for example, sterility tests or purity checks) shall be conducted on cultures of cells or cell banks free of antibiotics and other inhibitory substances in order to provide evidence of the absence of bacterial and fungal contamination, and to be able to detect fastidious organisms where appropriate. Where antibiotics are used, they shall be removed by filtration at the time of testing.

13.4. The traceability, proper use and storage of reference standards shall be ensured, defined and recorded. The stability of reference standards shall be monitored, and their performance trended. The

National or World Health Organisation (WHO) Recommendations for the preparation, characterisation and establishment of biological reference standards shall be followed.

13.5. All stability studies including real time or real condition stability, accelerated stability and stress testing shall be carried out. Trend analysis of the test results from the stability monitoring programme shall assure the early detection of any process or assay drift and this information shall be part of the PQR of biological products.

13.6. For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative or validated techniques are available, the frequency of testing may take into account a risk-based approach. The principle of bracketing and matrix designs may be applied if scientifically justified in the stability protocol.

13.7. All analytical methods used in the quality control and in-process control of biological products shall be well characterised, validated and documented to a satisfactory standard in order to yield reliable results. The fundamental parameters of this validation include linearity, accuracy, precision, selectivity, specificity, sensitivity and reproducibility.

13.8. For test methods described in relevant pharmacopoeial monographs, qualification of the laboratory test equipment and personnel shall be performed. In addition, repeat precision and comparability precision shall be shown in the case of animal tests. Repeatability and reproducibility shall also be demonstrated by reviewing retrospective test data. In addition to the common parameters typically used for validating assays (accuracy and precision) additional measurements (for example, of the performance of references, critical reagents or cell lines or both) shall be considered during the validation of bioassays based on the biological nature of the assay and reagents used.

14. Documentation (batch processing records):-

14.1. In general, the processing records of regular production batches shall provide a complete account of the manufacturing activities of each batch of biological product showing that it has been produced, tested and dispensed into containers in accordance with the approved procedures. In the case of vaccines, a batch processing record and a summary protocol shall be prepared for each batch for the purpose of lot release by the Licensing Authority. The information included in the summary protocol for independent lot release of vaccines by regulatory authorities. The summary protocol and all associated records shall be of a type approved by the Licensing Authority.

14.2. Manufacturing batch records shall be retained for at least one year after the expiry date of the batch of the biological product and shall be readily retrievable for inspection by the Licensing Authority. It has been found that documents retained for longer periods may provide useful information related to AEFI and other investigations.

14.3. Starting materials may require additional documentation on source, origin, supply chain, method of manufacture and controls applied in order to ensure an appropriate level of control, including the microbiological quality, if applicable.

14.4. Some product types may require a specific definition of what materials constitute a batch particularly somatic cells in the context of ATMPs. For autologous and donor matched situations, the manufactured product shall be viewed as a batch.

15. Use of animals:-

15.1. A wide range of animals is used for the manufacture or quality control of biological products. Special considerations are required when animal facilities are present at a manufacturing site.

15.2. The presence of live animals in the production area shall be avoided unless otherwise justified. Embryonated eggs are allowed in the production area, if applicable. If the extraction of tissues or organs from animals is required then particular care shall be taken to prevent contamination of the production area (for example, appropriate disinfection procedures shall be undertaken).

15.3. Areas used for performing tests involving animals or microorganisms shall be well separated from premises used for the manufacturing of products and shall have completely separate ventilation systems and separate staff. The separation of different animal species before and during testing shall be considered, as the necessary animal acclimatisation process, as part of the test requirements.

15.4. In addition to monitoring compliance with TSE regulations and other adventitious agents that are of concern (including those causing zoonotic diseases and diseases in source animals) shall also be monitored and recorded in line with specialist advice on establishing such programmes. Instances of ill health occurring in the source or donor animals shall be investigated with respect to their suitability and the suitability of in-contact animals, for continued use (for example, in manufacture, as sources of

starting materials and for quality control and safety testing). Decisions shall be documented.

15.5. A look-back procedure shall be in place in relation to the decision making process used to evaluate the continued suitability of the biological active substance or finished product in which animal sourced starting materials have been used or incorporated. This decision making process may include the retesting of reference samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source or donor animals shall be documented and shall be taken into account when considering the removal of those animals from the programme for defined periods.

15.6. Particular care shall be taken to prevent and monitor infections in source or donor animals. Measures taken shall cover sourcing, facilities, husbandry, biosafety procedures, testing regimes, control of bedding and feed materials, one hundred percent fresh air supply, appropriate design of the HVAC system, water supply and appropriate temperature and humidity conditions for the species being handled. This is of special relevance to Specific Pathogen-Free (SPF) animals where pharmacopoeial monograph requirements shall be met. Housing and health monitoring shall also be defined for other categories of animals (for example, healthy flocks or herds).

15.7. For products manufactured from transgenic animals, traceability shall be maintained in the creation of such animals from the source animals.

15.8. For different animal species and lines, key criteria shall be defined, monitored and recorded. This may include the age, sex, weight and health status of the animals.

15.9. Animals, biological agents and tests carried out shall be appropriately identified to prevent any risk of mix-up and to control all identified hazards.

15.10. The facility layout shall ensure a unidirectional and segregated flow of healthy animals, inoculated animals and waste decontamination areas. Personnel and visitors shall also follow a defined flow in order to avoid cross-contamination.

16. Complaints:-

16.1. The person responsible for handling complaints and deciding on the measures to be taken to deal with them shall have appropriate training or experience in the specific features of the quality control of biological products.

16.2. There are basically two types of complaints, product quality complaints and adverse reactions or events.

16.3. The first type of complaint may be caused by problems such as faulty manufacture, product defects or deterioration as well as, particular to biological products, adulteration of the biological products. These complaints shall be recorded in detail and the causes thoroughly investigated (e.g., by comparison with the reference samples kept from the same batch). There shall also be written procedures to describe the action to be taken.

16.4. To address the second type of complaint, reports of any adverse reaction or event shall be entered in a separate register in accordance with requirements. An investigation shall be conducted to find out whether the adverse reaction or event is due to a quality problem and whether such reactions or events have already been reported in the literature or whether it is a new observation. In either case, complaint records shall be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products. The safety monitoring of biological products shall be carried out through pharmacovigilance systems dealing with specific issues relating to adverse reactions and adverse events following treatment with biological products.

16.5. The licensing authority shall be kept informed of any complaints leading to a recall or restriction on supply and the records shall be available for inspection.

17. Product recalls:- Recall and Rapid Alert System for Drugs (including Biological and Vaccine) shall be in place for the product recall.

PART V

SPECIFIC REQUIREMENTS FOR RADIOPHARMACEUTICAL PRODUCTS

Note.- Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of Radiopharmaceutical Products. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Principles:- Radiopharmaceuticals shall be manufactured in accordance with the basic principles of GMP. The matters covered under this Part shall therefore be considered as supplementary to the general requirements for GMP and relate specifically to the production and control of radiopharmaceuticals. Many radiopharmaceuticals are released and administered to patients shortly after their production because of their short half-lives, so that quality control may sometimes be retrospective. In view of the same, strict adherence to GMP is mandatory.

2. Personnel:-

2.1. The manufacturing establishment, whether a hospital radiopharmacy, centralised radio-pharmacy, nuclear centre or institution, industrial manufacturer or Positron Emission Tomography (PET) Centre and its personnel shall be under the control of a person who has a proven record of academic achievement together with a demonstrated level of practical expertise and experience in radio-pharmacy and radiation hygiene. Supporting academic and technical personnel shall have the necessary post graduate or technical training and experience appropriate to their functions.

2.2. Personnel required to work in radioactive, clean and aseptic areas shall be selected with care, to ensure that they can be relied on to observe the appropriate codes of practice and are not subject to any disease or condition that can compromise the integrity of the product. Health checks on personnel shall be requested before employment and periodically thereafter. Any changes in personal health status (e.g., in haematology) may require the temporary exclusion of the person from further radiation exposure.

2.3. Only the minimum number of personnel required shall be present in clean and aseptic areas when work is in progress. Access to these areas shall be restricted during the preparation of radiopharmaceuticals, kits or sterile set-ups. Inspection and control procedures shall be conducted from outside these areas as far as possible.

2.4. During the working day, personnel may pass between radioactive and non-radioactive areas only if the safety rules of radiation control (health physics control) are followed.

2.5. The release of a batch may be approved only by an authorised person or a person with academic qualifications officially registered as a suitably qualified person, and with appropriate experience in the manufacture of radiopharmaceuticals.

2.6. To ensure the safe manufacture of radiopharmaceuticals, personnel shall be trained in GMP, the safe handling of radioactive materials and radiation safety procedures. They shall also be required to take periodic courses and receive training to keep abreast of the latest developments in their fields.

2.7. Training records shall be maintained and periodic assessments of the effectiveness of training programmes shall be made.

2.8. All personnel engaged in production, maintenance and testing shall follow the relevant guidelines for handling radioactive products and be monitored for possible contamination or irradiation exposure or both.

3. Premises and equipment:-

3.1. As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials must be specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility. Interior surfaces (walls, floors and ceilings) shall be smooth, impervious and free from cracks; they shall not shed matter and shall permit easy cleaning and decontamination. Drains shall be avoided wherever possible and, unless essential, shall be excluded from aseptic areas.

3.2. Specific disposal systems shall be mandatory for radioactive effluents. These systems shall be effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility.

3.3. Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material and be regularly sanitised. Adequate precautions shall be taken to avoid contamination of the drainage system with radioactive effluents.

3.4. Lighting, heating, ventilation and, if necessary, air-conditioning shall be designed to maintain a satisfactory temperature and relative humidity to ensure the comfort of personnel working in protective clothing. Buildings shall be in a good state of repair. The condition of the buildings shall be reviewed regularly and repairs carried out when and where necessary. Special care shall be exercised to ensure that building repair or maintenance operations do not compromise the products. Premises shall provide sufficient space for the operations to be carried out, allowing an efficient flow of work and

effective communication and supervision. All buildings and rooms shall be clean, sanitary and free from radioactive contamination.

3.5. Ventilation of radiopharmaceutical production facilities shall meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Suitable pressure and airflow patterns shall be maintained by appropriate isolation or enveloping methods. Air handling systems for both radioactive and non-radioactive areas shall be fitted with alarms so that the working personnel in the laboratory are warned of any failure of these systems.

3.6. Dedicated facilities and equipment shall be used for the manufacture of any radiopharmaceutical product derived from human blood or plasma. Autoclaves used in production areas for radio-pharmaceuticals may be placed behind a lead shield to minimise the radiation exposure of the operators. Such autoclaves shall be checked for contamination immediately after use to minimise the possibility of cross-contamination by radioactivity of the products in the next autoclave cycles.

3.7. All containers of radiopharmaceutical substances, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross-contamination shall be prevented by the adoption of some or all of the following measures, namely:-

(i) processing and filling in segregated areas;

(ii) avoiding the manufacture of different products at the same time, unless they are effectively segregated;

(iii) containing material transfer by means of airlocks, air extraction, changing clothes and careful washing and decontamination of equipment;

(iv) protecting against the risks of contamination caused by recirculation of untreated air or by accidental re-entry of extracted air;

(v) using "closed systems" of manufacture;

(vi) taking care to prevent aerosol formation; and

(vii) using sterilised containers.

3.8. Positive pressure areas shall be used to process sterile products. In general, any radioactivity shall be handled within specifically designed areas maintained under negative pressures. The production of sterile radioactive products shall therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met.

3.9. Separate air-handling units shall be used for radioactive and non-radioactive areas. Air from operations involving radioactivity shall be exhausted through appropriate filters that are regularly checked for performance.

3.10. Pipework, valves and vent filters shall be properly designed to facilitate validated cleaning and decontamination.

4. Production:-

4.1. SOPs must be available for all operating procedures and shall be regularly reviewed and kept up to date for all manufacturing operations. All entries on batch records shall be initiated by the operator and independently checked by another operator or supervisor.

4.2. Specifications for starting materials shall include details of their source, origin and (where applicable) method of manufacture and of the controls used to ensure their suitability for use. Release of a finished product shall be conditional on satisfactory results being obtained in the tests on starting materials.

4.3. Careful consideration shall be given to the validation of sterilisation methods.

4.4. A wide variety of equipment is used in the preparation of radiopharmaceuticals. Equipment for chromatography shall, in general, be dedicated to the preparation and purification of one or several products labelled with the same radionuclide to avoid radioactive cross-contamination. The life span of columns shall be defined. Great care shall be taken in cleaning, sterilising and operating freeze-drying equipment used for the preparation of kits.

4.5. A list of critical equipment shall be drawn up, including any equipment such as a balance, pyrogen oven, dose calibrator, sterilising filter, etc., where an error in the reading or function could potentially cause harm to the patient being given the final product. These devices shall be calibrated or tested at regular intervals and shall be checked daily or before production is started. The results of these tests shall be included in the daily production records.

4.6. Specific equipment for radioactive measurements may be required as well as radioactive reference standards. For the measurement of very short half-lives, national central laboratories shall be contacted to calibrate the apparatus. Where this is not possible, alternative approaches, such as documented procedures, may be used.

4.7. In the case of labelling kits, freeze drying shall be carried out as an aseptic procedure. If an inert gas such as nitrogen is used to fill vials, it must be filtered to remove possible microbial contamination.

4.8. The dispensing, packaging and transportation of radiopharmaceuticals shall comply with the relevant provisions of the Atomic Energy Act 1962 and the rules made thereunder.

5. Labelling:-

5.1. All products shall be clearly identified by labels, which must remain permanently attached to the containers under all storage conditions. An area of the container shall be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling, the label shall appear on its package.

5.2. The labels of radiopharmaceuticals shall comply with the requirements specified in rule 96.

5.3. The label on the container shall show-

(a) the name of the drug product or the product identification code or both;

(b) the name of the radionuclide;

(c) the name of the manufacturer or the company and the person responsible for placing the drug on the market;

(d) the radioactivity per unit dose-

(i) for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in the container;

(ii) for solid preparations, such as freeze dried preparations, the total radioactivity at a stated date and, if necessary, hour;

(iii) for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour, and the number of capsules in the container; and

(iv) where relevant, the international symbol for radioactivity.

5.4. The label on the package shall state-

(a) the qualitative and quantitative composition;

(b) the radioactive isotopes and the amount of radioactivity at the time of dispatch;

(c) the route of administration;

(d) the expiry date;

(e) any special storage conditions; and

(f) mandatory information related to transport regulations for radioactive materials.

5.5. The leaflet in the package shall contain the specific product information and indications for use. This information is especially important for preparation kits (cold kits), and shall include-

(a) the name of the product and a description of its use;

(b) the contents of the kit;

(c) the identification and quality requirements concerning the radio labelling materials that can be used to prepare the radiopharmaceutical, namely-

(i) the directions for preparing the radiopharmaceutical, including the range of activity and the volume, together with a statement of the storage requirements for the prepared radiopharmaceutical;

(ii) a statement of the shelf-life of the prepared radio pharmaceutical;

(iii) the indications and contraindications (pregnancy, children, drug reactions, etc.) in respect of the prepared radiopharmaceutical;

(iv) warnings and precautions in respect of the components and the prepared radiopharmaceutical, including radiation safety aspects;

(v) where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical, including the route of elimination and the effective half-life;

(vi) the radiation dose that a patient will receive from the prepared radiopharmaceutical;

(vii) the precautions to be taken by users and patients during the preparation and administration of the product and the special precautions for the disposal of the container and any unconsumed portions;

(viii) a statement of the recommended use of the prepared radio- pharmaceutical and the recommended dosage;

(ix) a statement of the route of administration of the prepared radiopharmaceutical; and

(x) if appropriate, for particular kits (i.e., those subject to variability beyond the recommended limits), the methods and specifications needed to check radiochemical purity.

6. Production and distribution records:-

6.1. The processing records of regular production batches must provide a complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the written procedures.

6.2. Separate records for the receipt, storage, use and disposal of radioactive materials shall be maintained in accordance with the relevant provisions of the Atomic Energy Act 1962 and the rules made thereunder.

6.3. Distribution records shall be kept. Since the return of radioactive products is not practical, the purpose of recall procedures for such products is to prevent their use rather than an actual return.

7. Quality assurance and quality control:-

7.1. Radiopharmaceuticals are nearly always used before all quality control testing (e.g., tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential.

7.2. Quality assurance or quality control or both shall have the following principal responsibilities, namely-

(a) the preparation of detailed instructions for each test and analysis;

(b) ensuring the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination;

(c) ensuring that environmental monitoring and equipment and process validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;

(d) the release or rejection of starting materials and intermediate products;

(e) the release or rejection of packaging and labelling materials;

(f) the release or rejection of each batch of finished preparation;

(g) the evaluation of the adequacy of the conditions under which the starting materials, intermediate products and finished radiopharmaceutical preparations are stored;

(h) the evaluation of the quality and stability of the finished products and, when necessary, of the starting materials and intermediate products;

(i) the establishment of expiry dates on the basis of the validity period related to specified storage conditions;

(j) the establishment and revision of the control procedures and specifications;

(k) assuming the responsibility for retaining samples of radiopharmaceutical products; and

(l) assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceutical products.

7.3. Whenever the size of the establishment permits, quality assurance and quality control duties shall be organised in separate groups. Quality assurance shall also include the monitoring and validation of the production process.

7.4. A manufacturer's quality control laboratory shall be separated from the production area. The control laboratory shall be designed, equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, the preparation of records and the performance of the necessary tests.

7.5. The performance of all qualitative and quantitative tests mentioned in the specifications for the starting materials may be replaced by a system of certificates issued by the supplier of these materials, provided that-

(a) there is a history of reliable production;

(b) the producer or supplier is regularly audited; and

(c) at least one specific identity test is conducted by the manufacturer of the finished radiopharmaceutical.

7.6. Samples of the intermediate and final products shall be retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control. These samples shall be kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g., for radiopharmaceuticals with a short half-life.

7.7. Sampling procedures may be adapted for the purposes of sampling, the type of controls being applied, and the nature of the material being sampled (e.g., a small batch size or its radioactive content or both). The procedure shall be described in a written protocol.

PART VI

SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

This Part shall apply to phytopharmaceutical drugs as defined under clause (eb) of rule 2,in addition to other relevant Parts based on the dosage form.

Note.—Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of Phytopharmaceuticals. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General:-

1.1. Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, phytopharmaceuticals are prepared from materials of plant origin, which are often obtained from varied geographical or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of phytopharmaceuticals are often substantially different from those employed for conventional pharmaceutical products.

1.2. Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of Phytopharmaceuticals. For this reason, application of GMPs in the manufacture of Phytopharmaceuticals is an essential tool to assure their quality.

2. Quality assurance in the manufacture of Phytopharmaceuticals:- In addition to the use of modern analytical techniques (especially High Performance Thin-Layer Chromatography (HPTLC), Gas Chromatography (GC), High Performance Liquid Chromatography (HPLC), Capillary Electrophoresis (CE), Mass Spectrometry (MS) and Atomic Absorption (AA) to characterise phytopharmaceuticals, quality assurance also requires the control of starting materials, storage and processing. For this reason, an appropriate quality assurance system shall be applied in the manufacture of phytopharmaceuticals.

3. Good manufacturing practice for Phytopharmaceuticals:- The general principles of GMP are set out in the Part I. Cultivation and collection of medicinal plants, as the starting materials for phytopharmaceuticals are not covered under this Schedule. The first critical step of their production where the application of GMP starts shall be clearly designated. This is of particular importance for those products which consist solely of comminuted or powdered plant materials.

4. Sanitation and hygiene:-

4.1. Because of their origin, plant materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, phytopharmaceuticals that may be especially prone to microbiological contamination are produced. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene during manufacture is necessary.

4.2. Water supply to the manufacturing unit shall be monitored and if necessary treated appropriately to ensure consistency of quality.

4.3. Waste from the manufacturing unit shall be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste bins shall be available, emptied and cleaned as needed, on daily basis.

5. Qualification and validation:-

5.1. Qualification of critical equipment, process validation and change control are particularly important in the production of Phytopharmaceuticals with unknown therapeutically active constituents. In this case, the reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches.

5.2. The written procedure shall specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (e.g., retrospective, prospective or concurrent) and the number of process runs.

5.3. A formal change control system shall be established to evaluate the potential effects of any changes on the quality of the Phytopharmaceuticals, particularly content of the active ingredients. Scientific judgement shall be used to determine which additional testing and validation studies are appropriate to justify a change in a validated process.

6. Complaints:-

6.1. The person responsible for handling complaints and deciding on the measures to be taken to deal with them shall have appropriate training or experience in the specific features of the quality control of Phytopharmaceuticals.

6.2. There are basically two types of complaints, product quality complaints and adverse reactions or events.

6.3. The first type of complaint may be caused by problems such as faulty manufacture, product defects or deterioration, particular to Phytopharmaceuticals, adulteration of the plant material. These complaints shall be recorded in detail and the causes thoroughly investigated (e.g., by comparison with the reference samples kept from the same batch). There shall also be written procedures to describe the action to be taken.

6.4. To address the second type of complaint, reports of any adverse reaction or event shall be entered in a separate register. An investigation shall be conducted to find out whether the adverse reaction or event is due to quality problem and whether such reactions or events have already been reported in the literature or whether it is a new observation. In either case, complaint records shall be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products.

6.5. The licensing authority shall be kept informed of any complaints leading to a recall or restriction on supply and the records shall be made available for inspection.

7. Product recalls:-In case of quality failures or serious adverse events of life threatening situations, the products shall be recalled in prompt and effective manner up to the retailers' level. There shall be a SOP for storage of recalled Phytopharmaceuticals in a secure segregated area.

8. Contract production and analysis:-

8.1. The contract partner shall have adequate premises and equipment for the production of Phytopharmaceuticals according to GMP. Validated methods shall be applied for cleaning the equipment and premises carefully before using them to produce different products. In the case of raw materials used for producing food, it is realistic to require manufacturing departments to be separated from those where the plant raw material will be cut or powdered for use in the preparation of drugs.

8.2. Technical aspects of the contract shall be drawn up by the competent persons suitably knowledgeable on the specific characteristics of Phytopharmaceuticals, including their production and quality control testing.

9. Self-inspection:-At least one member of the self-inspection team shall possess a thorough knowledge of Phytopharmaceuticals.

10. Personnel:-

10.1. The release of phytopharmaceuticals shall be authorised by a person who has been trained in the specific features of the processing and quality control of plant materials, plant preparations and finished phytopharmaceutical products.

10.2. Personnel dealing with the production and quality control of Phytopharmaceuticals shall have adequate qualifications and training in the specific issues relevant to Phytopharmaceuticals.

11. Training:-

11.1. The personnel shall have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of Phytopharmaceuticals).

11.2. Training records shall be maintained and periodic assessments of the effectiveness of training programmes shall be made.

12. Personal hygiene:-

12.1. Personnel entrusted with the handling of plant materials, plant preparations and finished plant products shall be required to have a high degree of personal hygiene and to have received adequate training in maintaining appropriate standards of hygiene. The personnel shall not work, if they have infectious diseases or skin diseases. Written procedures listing the basic hygiene requirements shall be made available.

12.2. Personnel must be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing. They shall wear suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture.

13. Premises:-

13.1. As a general principle, premises shall be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to good manufacturing practices for pharmaceutical products as given in Part I.

13.2. Because of their potential for degradation and infestation with certain pests as well as their sensitivity to microbiological contamination, production and particularly storage of plant materials and plant preparations shall assume special importance.

13.3. **Storage areas-**

13.3.1. Storage areas shall be well organised and tidy. Special attention shall be paid to cleanliness and good maintenance. Any accidental spillage shall be cleaned up immediately using methods that minimise the risk of cross- contamination of other materials and shall be reported.

13.3.2. The set-up of storage areas depends on the type of materials stored. The areas shall be well labelled and materials stored in such a way so as to avoid any risk of cross-contamination. An area shall be identified for the quarantine of all incoming plant materials.

13.3.3. Storage areas shall be laid out to permit effective and orderly segregation of the various categories of materials stored and to allow rotation of stock. Different plant materials shall be stored in separate areas.

13.3.4. To protect the stored material and reduce the risk of pest attacks, the duration of storage of any plant material in unpacked form shall be kept to a minimum.

13.3.5. Incoming fresh plant materials shall be processed, unless specified otherwise, as soon as possible. If appropriate, they shall be stored between 2 °C and 8 °C, whereas frozen materials shall be stored below –18 °C.

13.3.6. Where materials are stored in bulk, to reduce the risk of mould formation or fermentation, it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas shall also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures shall be taken to limit the spread of animals and microorganisms brought in with the plant material and to prevent cross-contamination.

13.3.7. Plant materials, even when stored in fibre drums, bags or boxes, shall be stored off the floor and suitably spaced to permit cleaning and inspection.

13.3.8. The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; appropriate steps shall be taken to ensure that these conditions are provided, maintained, monitored and recorded.

13.3.9. Plant materials, including raw plant materials, shall be kept in a dry area protected from moisture and processed following the principle of "first in, first out" (FIFO).

13.4. **Production areas-**

13.4.1. Production areas shall comply with the general requirements of good manufacturing practices for pharmaceutical products: main principles (see Part I). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. Moreover, the special nature of the production of Phytopharmaceuticals requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism shall be employed to prevent accumulation of fumes and vapours.

13.4.2. To facilitate cleaning and to avoid cross-contamination, adequate precautions shall be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g., by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

14. Equipment:-

14.1. Processing of plant materials may generate dust or material which is susceptible to pest-infestation or microbiological contamination and cross- contamination. Effective cleaning of the equipment is therefore particularly important.

14.2. Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment shall be dried immediately after cleaning to prevent the growth of microorganisms. Cleaning with compressed air and brushes shall be done with care and avoided if possible, as these methods increase the risk of product contamination.

14.3. Non-wooden equipment shall be used unless tradition demands wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.), this shall be dedicated, unless otherwise justified. When such equipment is used, it is advisable that it does not come into direct contact with chemicals or contaminated material. If the use of wooden equipment is unavoidable, special consideration must be given to its cleaning as wooden materials may retain odours, be easily discoloured and are easily contaminated.

15. Materials:-

15.1. All incoming plant materials shall be quarantined and stored under appropriate conditions that take into account the degradability of plant materials and plant preparations.

15.2. Only permitted substances shall be used for fumigation and allowable limits for their residues together with specifications for the apparatus used shall be set.

16. Reference samples and standards:- The reference standard for a phytopharmaceuticals may be a botanical sample of the plant material; a sample of the plant preparation, e.g., Extract; or a chemically defined substance, e.g., a known active constituent, a marker substance or a known impurity. The reference standard shall be of a quality appropriate to its purpose. If the phytopharmaceuticals is not described in a recognised pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the medicinal plant (e.g., if the whole medicinal plant is a tree) shall be available. All reference standards shall be stored under appropriate conditions to prevent degradation. Their expiry or revalidation date or both shall be determined and indicated.

17. Documentation:- The general principles for documentation are set out in Part I.

18. Specifications:-

18.1. The specifications for starting materials, for plant preparations and finished phytopharmaceuticals are primarily intended to define the quality rather than to establish full characterisation, and shall focus on those characteristics found to be useful in ensuring safety and efficacy. Consistent quality for Phytopharmaceuticals (finished products) can only be assured, if the starting plant materials are defined in a rigorous and detailed manner. In some cases more detailed information may be needed on aspects of collection or agricultural production. For instance, the selection of seeds, conditions of cultivation and harvesting are important aspects in producing a reproducible quality of Phytopharmaceuticals. Their characterisation (which also includes a detailed evaluation of the botanical and phytochemical aspects of the medicinal plant, manufacture of the Phytopharmaceutical preparation and the finished Phytopharmaceutical product) is therefore essential to allow the establishment of specifications which are both comprehensive and relevant. The specifications for plant materials shall as far as possible include, as a minimum, the following information-

18.1.1. **Plant materials**:-

18.1.1.1. The family and botanical name of the plant used according to the binomial system (genus, species, variety and the authority, i.e., the reference to the originator of the classification, e.g., Linnaeus).

18.1.1.2. Details of the source of the plant, such as country or region (also collected from the wild and, where applicable, method of cultivation, dates and conditions of harvesting (e.g., whether there was extreme weather), collection procedures, collection area, and brand, quantity and date of pesticide application, as per the WHO Guidelines on good agricultural and collection practices.

18.1.1.3. Whether the whole plant or only a part is used. In the latter case, which part of the plant is used and its state, e.g., whole or reduced. For dried plant material, the drying system shall be specified, if applicable.

18.1.1.4. A description of the plant material based on visual (macroscopic) or microscopic examination or both.

18.1.2. Suitable identity tests including, where appropriate, identification tests (such as Thin Layer Chromatography (TLC) or other chromatographic fingerprint) for known active ingredients or markers. A reference sample shall be available for identification purposes.

18.1.3. Details of the assay, where appropriate, of active constituents or markers.

18.1.4. Limit tests such as dry residue of liquids, ash value (total ash and ash insoluble in hydrochloric acid), water-soluble extractives, moisture or water content and loss on drying (taking into account the presence of essential oils if any).

18.1.5. Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination in plant materials or plant preparations used in the manufacture of Phytopharmaceuticals.

18.1.6. Tests for toxic metals and for likely contaminants, foreign materials and adulterants.

18.1.7. Tests for fungal, microbiological contamination, fumigant residues (if applicable), mycotoxins (aflatoxins), pest-infestations, radioactivity and their acceptable limits.

18.1.8. Other appropriate tests (e.g., particle size, swelling index and residual solvents in Phytopharmaceutical preparations and biological fingerprints such as induced fluorescent markers).

18.1.9. Specifications for starting materials (and also of primary or printed packaging materials) shall include, if applicable, reference to a pharmacopoeial monograph.

18.1.10. If the plant material for processing does not comply with its quality specifications, the norms that apply for its rejection and to storage and disposal of the rejected plant material, shall be included.

18.1.11. Qualitative and quantitative information on the active ingredients or constituents with known therapeutic activity in plant materials and plant preparations shall be given as described in paragraph 23.5 (Packaging materials and labelling) of this Part.

19. Finished phytopharmaceuticals:-

19.1. Tests for microbiological contamination and tests for other toxicants.

19.2. Uniformity of weight (e.g., for tablets, single-dose powders, suppositories, capsules and powder in sachets), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (tablets or capsules), if applicable.

19.3. Physical appearance such as colour, odour, form, shape, size and texture.

19.4. Loss on drying or water content.

19.5. Identity tests, qualitative determination of relevant substances of the plants (e.g., fingerprint chromatograms).

19.6. Quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available.

19.7. Limit tests for residual solvents.

19.8. Other specifications as per the general monograph under the Indian Pharmacopeia for the applicable dosage forms.

19.9. The control tests and specifications for the finished phytopharmaceutical product shall be such as to allow the qualitative and quantitative determination of the main active constituents. If the therapeutic activity of constituents is known, these constituents shall be indicated in the documentation. If such substances are not known (e.g., because they are part of a complex mixture), the constituents useful for assessing the quality shall be identified as markers. In both cases, the assay (i.e., quantitative determination) specifications shall be defined. When the therapeutic activity of the constituents cannot be determined quantitatively, specifications shall be based on the determination of markers.

19.10. If either the final product or the phytopharmaceutical preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the mixture of several active ingredients may be determined. The need for such a procedure shall be justified.

19.11. The concept of different acceptance criteria for release versus shelf-life specifications applies to finished phytopharmaceutical drugs only and not to plant materials and plant preparations. Adequate retest periods shall be established for the latter. Example, where this may be applicable include assay and impurity (degradation product) levels.

20. Plant preparations:-The specifications of plant preparations consist, depending on the preparation in question, of the relevant items of the specifications for plant materials or for finished phytopharmaceutical products as specified in the preceding paragraph.

21. Processing instructions:-

21.1. The processing instructions shall describe the different operations to be performed on the plant material, such as drying, crushing, milling and sifting. They shall also include the time and, if applicable, temperatures required in the drying process and the methods to be used to control fragment or particle size. Instructions on removing foreign matter and other unwanted materials shall also be given.

21.2. The drying conditions chosen shall be appropriate to the type of plant material processed. This depends on both the character of the active ingredients (e.g., essential oils) and the type of plant part collected (e.g., root, leaf or flower). Drying by direct exposure to sunlight, if not specifically contraindicated, is possible, but drying on the ground shall be avoided. If the plant shall be processed fresh, without drying, the reasons and criteria determining the use of fresh material shall be stated.

21.3. For the production of processed extracts, the instructions shall specify details of any vehicle or solvent that may be used, the duration and temperature needed for extraction, and any concentration stages and methods that may be required.

21.4. The permissible environmental conditions e.g., temperature, humidity and standard of cleanliness, shall be stated.

21.5. Any treatment, such as fumigation, used to reduce fungal or microbiological contamination or other infestation, together with methods of determining the extent of such contamination and potential residues, shall be documented. Instructions on the conduct of such procedures shall be available and shall include details of the process, tests and allowable limits for residues together with specifications for apparatus used.

21.6. Steps in the processes of blending and adjustment to reach defined contents of pharmacologically active constituents shall be clearly documented.

21.7. The rules that apply to the disposal of spent plant material after processing shall also be elaborated.

22. Good practices in production:-

22.1. To ensure not only the quality, but also the safety and efficacy of complex products of biological origin such as Phytopharmaceuticals, it is essential that the steps in their production are clearly defined.

22.2. Selection of the first production step covered in this Part,-

22.2.1. For medicinal plants which are either cultivated or collected from the wild, and which may be used in crude form or subjected to simple processing techniques (cutting or comminuting) the first critical step of their production, i.e., where the application of these guidelines starts, shall be clearly designated. The rationale for this designation shall be stated and documented. Guidance is provided below. However, for processes such as extraction, fermentation and purification, this rationale shall be established on a case to case basis-

(a) collection or cultivation or harvesting of medicinal plants shall follow other relevant guidance;

(b) generally, post harvest processing including primary cutting is (or shall be) covered by Good Agricultural Practices guidelines (GAP). If further comminuting is carried out in the manufacturing processing, it shall be covered by GMP. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of plant materials, application of the parameters under this Part may be extended to encompass these steps;

(c) when the active ingredient, consists exclusively of comminuted or powdered herbs, application of parameters under this Part starts at the physical processing following primary cutting and comminuting, and includes packaging;

(d) when phytopharmaceutical extracts are used, the principles of parameters under this Part shall apply to any production step following postharvest processing; and

(e) in the case of finished plant products manufactured by fermentation, application of GMP shall cover any production step following primary cutting and comminuting. Particular attention shall be given to the introduction of cells from a cell bank into the fermentation process.

22.3. **General considerations**-

22.3.1. Materials shall be handled in a fashion that is not detrimental to the product. On arrival at the processing facility, the plant material shall be promptly unloaded and unpacked. During this operation, the plant material shall not come into direct contact with the soil. Moreover, it shall not be exposed directly to the sun (except in cases where this is a specific requirement, e.g., sun-drying) and it shall be protected from rain and microbiological contamination.

22.3.2. Attention shall be paid to "classification" of clean area requirements taking into account the possible high degree of initial microbial contamination of plant materials. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to processing of plant materials. Specific and detailed requirements shall be developed to cover microbial contamination of equipment, air, surfaces and personnel, and also for rest rooms, utilities, ancillary and supporting systems (e.g., water and compressed air).

22.3.3. Care shall be taken to choose cleaning methods appropriate to the characteristics of the plant materials being processed. Washing dried plant materials with water is generally inappropriate. When it is necessary to clean them, an air duster or air shower shall be employed. In cases when immersion of plant materials in water or other appropriate agents (such as disinfectants) for cleaning is unavoidable (e.g., to eliminate suspected coliform bacteria), it shall be kept to a minimum.

22.3.4. The presence of plant materials from different species and varieties, or different plant parts shall be controlled during the entire production process to avoid contamination, unless it is assured that these materials are equivalent.

22.3.5. If time limits are specified in the master production instructions, these limits shall not be exceeded, to ensure the quality of intermediates and finished products. The less is known about the constituents responsible for the therapeutic activity, the more strictly this rule shall be obeyed. Such time limits, however, may be inappropriate when processing to achieve a target value (e.g., drying to a predetermined specification) because completion of processing steps is determined by in-process sampling and testing.

22.4. **Mixing of batches and blending**-

22.4.1. Phytopharmaceutical drugs with constituents of known therapeutic activity are often standardised (i.e., adjusted to a defined content of such constituents). The methods used to achieve such standardisation shall be documented. If another substance is added for these purposes, it is necessary to specify, as a range, the quantity that may be added. Blending different batches of a specific plant material (e.g., before extraction) or by mixing different lots of similar plant preparations may also be acceptable. Records shall be maintained to ensure traceability. The blending process shall be adequately controlled and documented and the blended batch shall be tested for conformity with established specifications where appropriate.

22.4.2. Batches shall be mixed only if it can be guaranteed that the mixture will be homogeneous. Such processes shall be well documented.

22.4.3. Out-of-specification batches of phytopharmaceutical drugs shall not be blended with other batches for the purpose of meeting specifications, except for standardization of the content of constituents with known pharmaceutical therapeutic effect. Every batch incorporated into the blend shall have been manufactured using an established process and shall have been individually tested and found to meet with the appropriate specifications prior to blending.

22.4.4. Where particular physical attributes of the material are critical, blending operations shall be validated to show uniformity of the combined batch. Validation shall include testing of critical attributes (e.g., particle size distribution, bulk density and tap density) that may be affected by the blending process.

22.4.5. The expiry date of the blended batch shall be chosen according to the date of manufacture of the oldest batch in the blend.

23. Good practices in quality control:-

23.1. **General-**

23.1.1. The personnel of quality control units shall have the necessary expertise in Phytopharmaceuticals to enable them to carry out identification tests and recognise adulteration, the presence of fungal growth or infestations and lack of uniformity in a consignment of plant materials.

23.1.2. The quality control of the plant material, plant preparations and finished plant products shall establish their quality, but does not imply the control of every single constituent.

23.2. **Sampling-** Plant materials are an aggregate of individual plants or different parts of the same plant and thus, have an element of heterogeneity, sampling shall be carried out with special care by personnel with the necessary expertise.

23.3. **Testing-**

23.3.1. The identity and quality of plant material, plant preparations and of finished phytopharmaceutical products shall be tested.

23.3.2. Plant material, plant preparations (including extracts) and finished products can be categorised as follows-

(a) the active constituents are identified, and may be quantified as such;

(b) the main group of components which contribute to the activity (i.e., the constituents with known therapeutic activity) are known and can be quantified as a total (e.g., essential oils) or calculated using a representative substance belonging to the group (e.g., flavonoids);

(c) the former is not identified or not quantifiable or both, but marker substances are; and

(d) others, where quantification (i.e., specification for a certain quantity of a constituent) is not applicable or feasible.

23.3.3. Identification methods may be based on-

(i) physical and if applicable, macroscopic (organoleptic) and microscopic tests;

(ii) chromatographic procedures [TLC, HPLC, HPTLC or Gas Liquid Chromatography (GLC)], spectrometric techniques [ultraviolet-visible (UV-VIS), IR, Nuclear Magnetic Resonance (NMR), MS]; and

(iii) chemical reactions.

23.3.4. The identification test methods shall be specific for the plant material, preparation or finished product and ideally shall be capable of discriminating between the required plant material and potential substitutes or adulterants that are likely to occur. The identification methods used for group (a) and group(b) shall be capable of detecting the said active ingredients and at least the main ingredients shall be stated on the label. For group (c), the analytical procedure shall be based on characteristic constituents, if any.

23.3.5. Reference samples of plant materials shall be made available for use in comparative tests e.g., visual and microscopic examination and chromatography.

23.3.6. Quantitative determination of known active components for members of group(a) and group(b) and of markers for members of group (c) is necessary.

23.3.7. The development and execution of quality control methods for plant materials, preparations and the finished products shall be in line with paragraph 18 (Specifications) of this Part. Tests and quality requirements that are characteristic of the given analyte shall be selected.

23.3.8. Particularly for plant materials in group (d) and for finished products containing such materials, characteristic chromatograms (fingerprint chromatograms) may be applicable. Using these methods may ensure that the main constituents can be easily followed throughout the production process. Caution is necessary, however, for every delivery of plant materials and every batch of plant preparations (including extracts) will have slightly different chromatograms or fingerprints resulting from differences in chemical compositions caused by intrinsic or extrinsic factors.

23.4. **Stability studies-**

23.4.1. If the expiry date for a plant material or phytopharmaceutical preparation is given, some stability data to support the proposed shelf-life under the specified storage conditions shall be available. Stability data are always required to support the shelf-life proposed for the finished products (guidance document reference)

23.4.2. Finished phytopharmaceutical products may contain several plant materials or plant preparations, and it is often not feasible to determine the stability of each active ingredient. Moreover, because the plant material, in its entirety, is regarded as the active ingredient, a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Chromatography allows tracing of changes which may occur during storage of a complex mixture of biologically active substances contained in plant materials. It shall be shown, as far as possible, e.g., by comparisons of appropriate characteristics or fingerprint chromatograms that the identified active ingredient (if any) and other substances present in the plant material or finished product are likewise stable and that their content as a proportion of the whole remains within the defined limits.

23.4.3. The fingerprint methods used for the stability studies shall be as similar as possible to those used for quality control purposes.

23.4.4. For identified active ingredients, constituents with known therapeutic activity and markers, widely used general methods of assay and physical and sensory or other appropriate tests may be applied.

23.4.5. To determine the shelf-life of finished products, strong emphasis shall also be placed on other tests in paragraph 18 (Specifications), i.e., moisture content, microbial contamination and general dosage form control tests.

23.4.6. The stability of preservatives and stabilisers shall be monitored. When these are not used, alternative tests shall be done to ensure that the product is self-preserving over its shelf-life.

23.4.7. Samples used for stability studies shall be stored in the containers intended for marketing.

23.4.8. Normally the first three commercial production batches shall be included in the stability monitoring programme to confirm the expiry date. However, where data from previous studies, including pilot batches, show that the product is expected to remain stable for at least two years, fewer than three batches can be used. The testing frequency depends on the characteristics of the phytopharmaceutical medicinal products and shall be determined on a case-to-case basis.

23.4.9. 23.4.9 The protocol for on-going stability studies shall be documented. This would normally involve one batch per year being included in a stability monitoring programme.

23.5. **Packaging materials and labeling-**

23.5.1. All packaging materials, such as bottles and other materials shall be stored properly. Controls on the issue and use of these packaging materials shall be adequate to ensure that incorrect labels and cartons are not used.

23.5.2. All containers and closures shall be thoroughly cleaned and dried before being used to pack the products.

23.5.3. 23.5.3 There shall be adequate information on the label (or the package insert) to

inform the users of the composition of the product (in addition to the brand name, if any), indications or actions, directions for use, cautions and adverse reactions if any, and the expiry date.

23.5.4. Finished plant products may contain several plant materials or plant preparations. Unless otherwise fully justified, the full quantitative composition of the phytopharmaceutical ingredients shall be stated on the product label. If this is not possible, at least the main ingredients shall be stated on the label while the full qualitative composition could appear on the package insert.

23.5.5. The qualitative and quantitative particulars of the active ingredients in plant materials and plant preparations shall be expressed in the following manner, namely-

23.5.5.1. For plant materials and plant preparations consisting of comminuted or powdered plant materials-

(a) the quantity of the plant material must be stated or, if constituents with known therapeutic activity are unidentified, the quantity of the plant material or phytopharmaceutical preparation shall be stated; or

(b) the quantity of the plant material or phytopharmaceutical preparation shall be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity.

23.5.5.2. For plant preparations produced by steps, which exceed commination, the nature and concentration of the solvent and the physical state of the extract shall be given. Furthermore, the following shall be indicated-

(a) the equivalent quantity or the ratio of a phytopharmaceutical material to phytopharmaceutical preparation must be stated, if therapeutic activity of the constituents is unknown (this does not apply to fatty or essential oils); or

(b) if the therapeutic activity of the constituents is known, the quantity of the phytopharmaceutical preparation may be given as a range, corresponding to a defined quantity of the constituents with known therapeutic activity.

23.5.6. The composition of any solvent or solvent mixture used and the physical state of the extract shall be identified.

23.5.7. If any other substance is added during the manufacture of the phytopharmaceutical preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substances shall be described as such or as "other ingredients" and the genuine extract as the "active ingredient". However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content or for any other purpose, the final mixture shall be regarded as the genuine extract and listed as the "active ingredient" in the unit formula.

PART VII

SPECIFIC REQUIREMENTS FOR THE MANUFACTURE OF INVESTIGATIONAL PHARMACEUTICAL PRODUCTS FOR CLINICAL TRIALS IN HUMANS

Note.—Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of Investigational Pharmaceutical Products for Clinical Trials in Humans. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General considerations:-

1.1. This Part supplements the general principle of GMP as specified in Part I and the guidelines on Good Clinical Practices (GCP) for clinical trials on pharmaceutical products in India. The application of the principles of GMP to the preparation of investigational products to be used in Phase I or Phase II or Phase III of the clinical studies is necessary.

1.1.1. To assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials.

1.1.2. To assure consistency between the investigational product and the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product.

1.1.3. To protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilisation, contamination and cross-contamination, mix-ups, wrong labelling, etc.) or from starting materials and components of inadequate quality.

1.1.4. To document all changes in the manufacturing process.

1.2. In this context, the selection of an appropriate dosage for clinical trials is important. While it is accepted that in early trials (Phase I or Phase II), the dosage form may be very different from the anticipated final formulation (e.g., a capsule instead of a tablet), in the pivotal Phase III studies, it shall be similar to the projected commercial presentation; otherwise these trials will not necessarily prove that the marketed product is both efficacious and safe.

1.3. If there are significant differences between the clinical and commercial dosage forms, data shall be submitted to the Licensing Authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials. Final manufacturing methods must be revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.

1.4. This document specifically addresses those practices that may be different for investigational products, which are usually not manufactured in accordance with a set routine and which may possibly be incompletely characterised during the initial stages of clinical development.

2. Quality assurance:-

2.1. Quality assurance of pharmaceutical products has been defined and discussed in detail in Part I.

2.2. The quality of dosage forms in Phase III clinical studies shall be characterised and assured at the same level as for routinely manufactured products. The quality assurance system, designed, established and verified by the manufacturer, shall be described in writing, taking into account the GMP principles to the extent that they are applicable to the operations in question. This system shall also cover the interface between the manufacture and the trial site (e.g., shipment, storage, occasional additional labelling).

3. Validation:-

3.1. Some of the production processes for investigational products that have not received marketing authorisation may not be validated to the extent necessary for a routine production operation. The product specifications and manufacturing instructions may vary during development. The increased complexity in the manufacturing operations requires a highly effective quality assurance system.

3.2. For sterile products, there shall be no reduction in the degree of validation of sterilising equipment required. Validation of aseptic processes presents special problems when the batch size is small, since the number of units filled may not be adequate for a validation exercise. Filling and sealing, which is often done by hand, can compromise the maintenance of sterility. Greater attention shall therefore be given to environmental monitoring.

4. Complaints:- The conclusions of any investigation carried out in response to a complaint shall be discussed between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, to determine the cause and to take any necessary corrective action.

5. Recalls:- Recall procedures shall be understood by the sponsor, investigator and monitor in addition to the persons responsible for recalls as described in the guide on GMP.

6. Personnel:- Although it is likely that the number of staff involved will be small, people shall be separately designated as responsible for production and quality control. All production operations shall be carried out under the control of a clearly identified responsible person. Personnel concerned with development, involved in production and quality control, need to be instructed in the principles of GMP.

7. Premises and equipment:-

7.1. During the manufacture of investigational products, different products may be handled in the same premises and at the same time and this reinforces the need to eliminate all risks of contamination, including cross-contamination. Special attention shall be paid to line clearance in order to avoid mix-ups. Validated cleaning procedures shall be followed to prevent cross-contamination.

7.2. For the production of particular products, campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account shall be taken of the solubility of the product and excipients in various cleaning agents.

8. Materials:-

8.1. **Starting materials-**

8.1.1. The consistency of production may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties shall therefore be defined, documented in their specifications, and controlled. Existing compendial Standards, shall be taken into consideration. Specifications for active ingredients shall be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active ingredients shall be periodically reassessed.

8.1.2. Detailed information on the quality of active and non-active ingredients, as well as of packaging materials, shall be available so as to make it possible to recognise and as necessary, allow for any variation in production.

8.1.3. Chemical and biological reference standards for analytical purposes.

8.1.4. Reference standards from reputable sources shall be used, if available; otherwise the reference substances for the active ingredients shall be prepared, tested and released as reference materials by the producer of the investigational pharmaceutical product or by the producer of the active ingredient used in the manufacture of that product.

8.1.5. Detailed information on reference products for clinical trials shall be in accordance with the New Drugs and Clinical Trial Rules, 2019.

8.1.6. In studies in which an investigational product is compared with a marketed product, steps shall be taken to ensure the integrity and quality of the reference products (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made in the product, data shall be available (e.g., on stability, comparative dissolution) that demonstrate that these changes do not influence the original quality characteristics of the product.

9. Documentation:-

9.1. Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), master formulae and processing and packaging instructions may be changed frequently as a result of new experience in the development of an investigational product. Each new version shall take into account the latest data and include a reference to the previous version so that traceability is ensured. Rationale for changes shall be stated and recorded.

9.2. Batch processing and packaging records shall be retained for at least two years after the termination or discontinuance of the clinical trial, or after the approval of the investigational product.

9.3. The sponsor may request the processing or packaging of a certain number of units or their shipping. It may only be given by the sponsor to the manufacturer of an investigational product. It shall be in writing (though it may be transmitted by electronic means), precise enough to avoid any ambiguity and formally authorised, and refer to the approved product specification file.

9.4. **Product specification files-**

9.4.1. A product specification file or files shall contain the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and shipping. It shall indicate who has been designated or trained as the authorised person responsible for the release of batches. It shall be continuously updated while at the same time ensuring appropriate traceability to the previous versions.

9.5. **Specifications-**

9.5.1. In developing specifications, special attention shall be paid to characteristics which affect the efficacy and safety of pharmaceutical products, namely-

(a) the accuracy of the therapeutic or unitary dose, homogeneity, content uniformity;

(b) the release of active ingredients from the dosage form: dissolution time, etc.; and

(c) the estimated stability, if necessary, under accelerated conditions, the preliminary storage conditions and the shelf-life of the product.

9.5.2. In addition, the package size shall be suitable for the requirements of the trial.

9.5.3. Specifications may be subject to change as the development of the product progresses. Changes shall, however, be made in accordance with a written procedure and clearly recorded. Specifications

shall be based on all available scientific data, current state-of-the-art technology and the regulatory and pharmacopoeial requirements.

9.6. **Master formulae and processing instructions-**

9.6.1. These may be changed in the light of experience, but allowance must be made for any possible repercussions on stability and above all on bioequivalence between batches of finished products. Changes shall be made in accordance with a written procedure and clearly recorded.

9.6.2. It may sometimes not be necessary to produce master formulae and processing instructions, but for every manufacturing operation or supply there shall be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

9.7. **Packaging instructions**- The number of units to be packaged shall be specified before the start of the packaging operations. Account shall be taken of the number of units necessary for carrying out quality controls and of the number of samples from each batch used in the clinical trial to be kept as a reference for further rechecking and control. Reconciliation shall be carried out at the end of the packaging and labelling process.

9.8. **Labelling instructions-**

9.8.1. The information presented on labels shall include-

(a) the name of the sponsor;

(b) a statement "for clinical research use only";

(c) a trial reference number;

(d) a batch number;

(e) the patient identification number;

(f) the storage conditions; and

(g) the expiry date (month or year) or a retest date.

9.8.2. Additional information may be displayed in accordance with the order (e.g., dosing instructions, treatment period and standard warnings). When necessary for blinding purposes, the batch number may be provided separately. A copy of each type of label shall be kept in the batch packaging record.

9.9. **Processing and packaging batch records-** Processing and packaging batch records shall be kept in sufficient detail for the sequence of operations to be accurately traced. They shall contain any relevant remarks which increase existing knowledge of the product, allow improvements in the manufacturing operations and justify the procedures used.

9.10. **Coding (or randomisation) systems-**

9.10.1. Procedures shall be established for the generation, distribution, handling and retention of any randomisation code used in packaging' investigational products.

9.10.2. A coding system shall be introduced to permit the proper identification of "blinded" products. The code, together with the randomisation list, must permit proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation. The coding system must permit determination without delay in an emergency situation of the identity of the actual treatment product received by individual subjects.

10. Production:-

10.1. Products intended for use in clinical trials (late Phase II and Phase III studies) shall as far as possible be manufactured at a licensed facility, namely-

(a) a pilot plant, primarily designed and used for process development;

(b) a small-scale facility (sometimes called a "pharmacy") separate both from the company's pilot plant and from routine production;

(c) a larger-scale production line assembled to manufacture materials in larger batches, e.g., for late Phase III trials and first commercial batches; and

(d) the normal production line used for licensed commercial batches, and sometimes for the production of investigational pharmaceutical products if the number, e.g., of ordered ampoules, tablets or other dosage forms, is large enough;

10.1.1. The relation between the batch size for investigational pharmaceutical products manufactured in a pilot plant or small-scale facility to the planned full-size batches may vary widely depending on the pilot plant or "pharmacy" batch size demanded and the capacity available in full-size production.

10.1.2. The present guidelines are applicable to licensed facilities of the first and second types. It is easier to assure compliance with GMP in facilities of the second type, since processes are kept constant in the course of production and are not normally changed for the purpose of process development. Facilities of the remaining types shall be subject to all GMP rules for pharmaceutical products.

10.1.3. Administratively, the manufacturer has yet another possibility, namely to contract out the preparation of investigational products. Technically, however, the licensed facility will be of one of the above-mentioned types. The contract must then clearly state, *inter alia*, the use of the pharmaceutical products in clinical trials. Close cooperation between the contracting parties is essential.

10.2. **Manufacturing operations-**

10.2.1. Validated procedures may not always be available during the development phase, which makes it difficult to know in advance what critical parameters and in-process controls would help to control these parameters. Provisional production parameters and in-process controls may then usually be deduced from experience with analogous products. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continuously to the experience gained in production.

10.2.2. For sterile investigational products, assurance of sterility shall be not less than for licensed products. Cleaning procedures shall be appropriately validated and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

10.3. **Packaging and labeling-**

10.3.1. The packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) when "blinded" labels are used than for licensed products. Supervisory procedures such as label reconciliation, line clearance, etc., and the independent checks by quality control staff shall accordingly be intensified.

10.3.2. The packaging must ensure that the investigational product remains in good condition during transport and storage at intermediate destinations. Any opening of or tampering with the outer packaging during transport shall be readily discernible.

10.4. **Blinding operations-** In the preparation of "blinded" products, in-process control shall include a check on the similarity in appearance and any other required characteristics of the different products being compared.

11. Quality control:-

11.1. As processes may not be standardised or fully validated, end-product testing is more important in ensuring that each batch meets its specification. The test or analysis of materials and investigational products shall be in compliance to Schedule L1.

11.2. Product release is often carried out in two stages, before and after final packaging-

11.2.1. Bulk product assessment- This shall cover all relevant factors, including production conditions, the results of in-process testing, a review of manufacturing documentation and compliance with the product specification file and the order.

11.2.2. Finished product assessment- This shall cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the product specification file and the order.

11.3. When necessary, quality control shall also be used to verify the similarity in appearance and other physical characteristics, odour and taste of "blinded" investigational products.

11.4. Samples of each batch of product shall be retained in the primary container used for the study or in a suitable bulk container for at least two years after the termination or completion of the relevant clinical trial. If the sample is not stored in the pack used for the study, stability data shall be available to justify the shelf-life in the pack used. Properly stored reatained sample e.g., API or drug substance, in-process material, phase-I investigational drug) that can be subsequently analysed for comparison can provide important links in reproducing comparable products.

12. Shipping, returns, and destruction:-

12.1. The shipping, return and destruction of unused products shall be carried out in accordance with the written procedures laid down in the protocol. All unused products sent outside the manufacturing plant shall, as far as possible, either be returned to the manufacturer or destroyed in accordance with clearly defined instructions.

12.2. **Shipping-**

12.2.1. Investigational products shall be shipped in accordance with the shipping orders given by the sponsor.

12.2.2. A shipment is sent to an investigator only after the following two-step release procedure:- (i) the release of the product after quality control ("technical green light"); and (ii) the authorisation to use the product, given by the sponsor ("regulatory green light"). Both releases shall be recorded.

12.2.3. The sponsor shall ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol.

12.2.4. A detailed inventory of the shipments made by the manufacturer shall be maintained and shall make particular mention of the addressee's identification.

12.3. **Returns-**

12.3.1. Investigational products shall be returned under agreed conditions defined by the sponsor, specified in written procedures and approved by authorised staff members.

12.3.2. Returned investigational products shall be clearly identified and stored in a dedicated area. Inventory records of returned medicinal products shall be kept. The responsibilities of the investigator and the sponsor are dealt with in greater detail in the guidelines on GCP.

12.4. **Destruction-**

12.4.1. The sponsor is responsible for the destruction of unused investigational products, which shall therefore not be destroyed by the manufacturer without prior authorisation by the sponsor. Destruction operations shall be carried out in accordance with the environmental safety requirements.

12.4.2. Destruction operations shall be recorded in such a manner that all operations are documented. The records shall be kept by the sponsor.

12.4.3. If requested to destroy products, the manufacturer shall deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents shall permit the batches involved to be clearly identified.

PART VIII

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ORAL SOLID DOSAGE FORMS (TABLETS AND CAPSULES)

Note.—Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of oral Solid Dosage Forms (Tablets and capsules). In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. General:-

1.1. The processing of dry materials and products creates problems of dust control and cross-contamination. Special attention is, therefore, needed in the design, maintenance and use of premises and equipment in order to overcome these problems. Wherever required, enclosed dust control manufacturing systems shall be employed**.**

1.2. Suitable environmental conditions for the products handled shall be maintained by installation of air conditioning, wherever necessary. Effective air extraction systems, with discharge points situated to avoid contamination of other products and processes shall be provided. Filters shall be installed to retain dust and to protect the factory and local environment.

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

1.4. All ingredients for a dry product shall be sifted before use unless the quality of the input material can be assured. Such sifting shall normally be carried out at dedicated areas.

1.5. Where the facilities are designed to provide special environmental conditions of pressure differentials between rooms, these conditions shall be regularly monitored and any deviation shall be brought to the immediate attention of the Production and Quality assurance departments.

1.6. Care shall be taken to guard against any material lodging and remaining undetected in any processing or packaging equipment. Particular care shall be taken to ensure that any vacuum, compressed air or air-extraction nozzles are kept clean and that there is no evidence of lubricants leaking into the product from any part of the equipment.

1.7. Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct Oral Solid Dosage (OSD) manufacturing site, measures shall be taken to ensure that dust cannot move from one cubicle to another.

1.8. Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade shall be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.

1.9. The corridor shall be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

1.10. Highly potent products shall be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.

1.11. The pressure cascade for each facility shall be individually assessed according to the product handled and level of protection required.

1.12. Building structure shall be given special attention to accommodate the pressure cascade design.

1.13. Ceilings and walls, close fitting doors and sealed light fittings shall be in place, to limit ingress or egress of air.

1.14. The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas shall be such that there is no risk of overlap in the acceptable operating range, e.g., 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in the failure of the pressure cascade, where the first room is at the maximum pressure limit and the second room is at its minimum pressure limit.

1.15. Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used to segregate areas.

1.16. The effect of room pressure tolerances shall be calculated and taken into consideration.

1.17. The pressure control and monitoring devices used shall be calibrated and qualified. Compliance with specifications shall be regularly verified and the results recorded. Pressure control devices shall be linked to an alarm system set according to the levels determined by a risk analysis.

1.18. Manual control systems, where used, shall be set up during commissioning, with set point marked, and shall not change unless other system conditions change.

1.19. Airlocks can be important components in setting up and maintaining pressure cascade systems and also to limit cross-contamination.

1.20. Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:-

(a) Cascade airlock: higher pressure on one side of the airlock and lower pressure on the other;

(b) Sink airlock: lower pressure inside the airlock and higher pressure on both outer sides; and

(c) Bubble airlock: higher pressure inside the airlock and lower pressure on both outer sides.

1.21. Doors shall open to the high pressure side, so that room pressure assists in holding the door closed and in addition self-closers shall be provided. If the doors open to the low pressure side, the door closer springs shall be sufficient to hold the door closed and prevent the pressure differential from pushing the door open. There shall be a method to indicate if both doors to airlocks are open at the same time, or alternatively these shall be interlocked. The determination of which doors shall be interlocked shall be the subject of a risk assessment study.

1.22. Central dust extraction systems shall be interlocked with the appropriate air-handling systems, to ensure that they operate simultaneously.

1.23. Room pressure differential between adjacent cubicles, which are linked by common dust extraction ducting, shall be avoided.

1.24. Air shall not flow through the dust extraction ducting or return air ducting from the room with the higher pressure to the room with the lower pressure (this would normally occur only if extract or return systems were inoperative). Systems shall be designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure.

1.25. Adequate room pressure differential indication shall be provided so that each critical room pressure can be traced back to ambient pressure (by summation of the room pressure differentials), in order to determine the room actual absolute pressure. Room pressure indication gauges shall have a range and graduation scale which enables the reading to accuracy, as appropriate; normal operating range, alert and action limits shall be defined and displayed at the point of indication. A colour coding gauge may be helpful. Room pressure indication may be either analogue or digital, and may be represented as either pressure differentials or absolute pressures. Whichever system is used any out-of-specification condition shall be easily identifiable.

1.26. Material Pass-Through-Hatches (PTH) or Pass Boxes (PB) can also be used for separating two different zones. PTHs fall into two categories, namely a dynamic PTH or a passive PTH. Dynamic PTHs have an air supply to or extraction from them, and can then be used as bubble, sink or cascade PTHs.

1.27. Where appropriate, temperature and relative humidity shall be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator where necessary.

1.28. Maximum and minimum room temperatures and relative humidity shall be appropriate. Alert and action limits on temperatures and humidity shall be set, as appropriate.

1.29. The operating band or tolerance between the acceptable minimum and maximum temperatures shall not be made too close. Tight control tolerances may be difficult to achieve and can also add unnecessary installation and running costs.

1.30. Cubicles or suites, in which products requiring low relative humidity are processed, shall have well sealed walls and ceilings and shall also be separated from adjacent areas with higher relative humidity by means of suitable airlocks.

1.31. Precautions shall be taken to prevent moisture migration that increases the load on the HVAC system.

1.32. Humidity control shall be achieved by removing moisture from the air, or adding moisture to the air, as relevant.

1.33. Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.

1.34. Duct material in the vicinity of the humidifier shall not add contaminants to air that will not be removed by filtration further downstream.

1.35. Air filters shall not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth.

1.36. Cold surfaces shall be insulated to prevent condensation within the clean area or on air-handling components.

1.37. When specifying relative humidity, the associated temperature shall also be specified.

1.38. Chemical driers using silica gel or lithium chloride are acceptable, provided that they do not become sources of contamination.

1.39. Wherever possible, dust or vapour contamination shall be removed at source. Point-of-use extraction, i.e., as close as possible to the point where the dust is generated, shall be employed. Spot ventilation or capture hoods may be used as appropriate.

1.40. Point-of-use extraction shall be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.

1.41. Dust extraction ducting shall be designed with sufficient transfer velocity to ensure that dust is carried away and does not settle in the ducting. Periodic checks shall be performed to ensure that there is no build-up of the dust in the ducting.

1.42. The required transfer velocity shall be determined on the density of the dust (the denser the dust, the higher the transfer velocity shall be, e.g., 15–20 m/s).

1.43. Airflow direction shall be carefully chosen to ensure that the operator does not contaminate the product and also so that the operator is not put at risk by the product.

1.44. Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow shall be used to assist in removing dust and vapours from the room.

1.45. Typically, in a room operating with turbulent airflow, the air shall be introduced from ceiling diffusers, located at the door entry side of the room and extracted from the rear of the room at low level to help give a flushing effect in the room. Correct flushing of the rooms may be verified by airflow visualisation smoke tests.

1.46. When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, shall be used.

1.47. Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and shall be provided with adequate filtration to prevent contamination of the ambient air.

1.48. Where the powders are not highly potent, final filters on a dust exhaust system shall be fine dust filters with a filter classification of 5µ.

1.49. Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they shall usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow.

1.50. Mechanical-shaker dust collectors shall not be used for applications where continuous airflow is required, in order to avoid unacceptable fluctuations in room pressures, except in the case where room pressures are automatically controlled.

1.51. When wet scrubbers are used, the dust-slurry shall be removed by a suitable means, e.g., a drainage system or waste removal contractor.

1.52. The quality of the exhaust air shall be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

1.53. Where necessary, additional filtration may be provided downstream of the dust collector.

1.54. The systems for fume, dust and effluent control shall be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross-contamination, e.g., an exhaust-air discharge point located close to the HVAC system fresh air inlet.

1.55. Fumes shall be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).

1.56. Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.

1.57. Deep-bed scrubbers shall be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers shall be specific to the effluent being treated.

1.58. The type and quantity of the vapours to be removed shall be known to enable the appropriate filter media, as well as the volume of media required to be determined.

1.59. There shall be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

1.60. Depending on the airborne contaminants in the return air system it may be acceptable to use re-circulated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus, prevent cross-contamination.

1.61. HEPA filters may not be required where the air handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.

1.62. Re-circulation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.

1.63. HEPA filters may be located in the air handling unit or placed terminally. Where HEPA filters are terminally mounted they shall preferably not be connected to the ducting by means of flexible ducting. Due to the high air pressure required for the terminal filter; this connection shall preferably be a rigid duct connection. Where flexible ducting is used, it shall be as short as possible and properly fixed to withstand duct pressure.

1.64. Air containing dust from highly toxic processes or solvents or flammable vapours shall never be re-circulated to the HVAC system.

1.65. Adequate airlocks, such as personnel airlocks (PAL), material airlocks (MAL), change rooms and passages shall be provided to protect passage between different cleanliness conditions. These shall have supply and extract air systems as appropriate.

1.66. Areas such as airlocks, change rooms and passages, shall be designed so that the required pressure cascades can be achieved.

1.67. Detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials shall be prepared and maintained.

1.68. Where possible, personnel and materials shall not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone; (if moving from a lower cleanliness zone to a higher cleanliness zone, changing or decontamination procedures shall be followed).

1.69. The final stage of the changing room shall, in the "at rest" state, be the same good manufacturing practices classification grade as the area into which it leads.

2. Sifting, mixing and granulation:-

2.1. Unless operated as a closed system, mixing, sifting and blending equipment shall be fitted with dust extractors or in a dedicated area for each operation.

2.2. Residues from sieving operations shall be examined periodically for evidence of the presence of unwanted materials.

2.3. Critical operating parameters like time and temperature for each mixing, blending and drying operation shall be specified in a Master Formula, monitored during processing, and recorded in the batch records.

2.4. Filter bags fitted to fluid-bed-drier shall not be used for different products, without being washed in between use. With certain highly potent or sensitising products, bags specific to one product only shall be used. Air entering the drier shall be filtered. Steps shall be taken to prevent contamination of the site and local environment by dust in the air leaving the drier due to close positioning of the air-inlets and exhaust.

2.5. Granulation and coating solutions shall be made, stored and used in a manner which minimises the risk of contamination or microbial growth.

3. Compression (Tablets):-

3.1. Each tablet compressing machine shall be provided with effective dust control facilities to avoid cross contamination. Unless the same product is being made on each machine or unless the compression machine itself provides its own enclosed air controlled environment, the machine shall be installed in separate cubicles.

3.2. Suitable physical, procedural and labelling arrangements shall be made to prevent mix up of materials, granules and tablets on compression machinery.

3.3. Accurate and calibrated weighing equipment shall be readily available and used for in-process monitoring of tablet weight variation. Procedures used shall be capable of detecting out of limits tablets.

3.4. At the commencement of each compression run and in case of multiple compression points in a compression machine, sufficient individual tablets shall be examined at fixed intervals to ensure that a tablet from each compression station or from each compression point has been inspected for suitable Pharmacopoeial parameters like "appearance", "weight variation", "disintegration", "hardness", "friability" and "thickness". The results shall be recorded as part of the batch documentation.

3.5. Tablets shall be de-dusted, preferably by automatic device and shall be monitored for the presence of foreign materials besides any other defects.

3.6. Tablets shall be collected into clean, labelled containers.

3.7. Rejected or discarded tablets shall be isolated in identified containers and their quantity recorded in the Batch Manufacturing Record.

3.8. In-process control shall be employed to ensure that the products remain within specification. During compression, samples of tablets shall be taken at regular intervals of not greater than thirty minutes to ensure that they are being produced in compliance with specified in-process specification. The tablets shall also be periodically checked for additional parameters such as "appearance", "weight variation", "disintegration", "hardness", "friability" and "thickness" and contamination by lubricating oil.

4. Coating (Tablets):-

4.1. Air supplied to coating pans for drying purposes shall be filtered air and of suitable quality. The area shall be provided with suitable exhaust system and environmental control (temperature and humidity) measures.

4.2. Coating solutions and suspensions shall be made afresh and used in a manner which shall minimise the risk of microbial growth. Their preparation and use shall be documented and recorded.

5. Filling of Hard Gelatin Capsule:- Empty capsules shells shall be regarded as "drug component" and treated accordingly. They shall be stored under conditions which shall ensure their safety from the effects of excessive heat and moisture

6. Printing (Tablets and Capsules):-

6.1. Special care shall be taken to avoid product mix-up during any printing of tablets and capsules. Where different products or different batches of the same product, are printed simultaneously, the operations shall adequately be segregated. Edible grade colours and suitable printing ink shall be used for such printing.

6.2. After printing, tablets and capsules shall be approved by Quality Control before release for packaging or sale.

7. Packaging (Strip and Blister):-

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

7.2. Uncoated tablets shall be packed on equipment designed to minimise the risk of cross-contamination. Such packaging shall be carried out in an isolated area when potent tablets or Beta lactum containing tablets are being packed.

7.3. The strips coming out of the machine shall be inspected for defects such as misprint, cuts on the foil, missing tablets and improper sealing.

7.4. Integrity of individual packaging strips and blisters shall be subjected to vacuum test periodically to ensure leak proofness of each pocket strip and blister and records maintained.

PART IX

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ORAL LIQUIDS (SYRUPS, ELIXIRS, EMULSIONS AND SUSPENSIONS)

Note.- Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Syrups, Elixirs, Emulsions and Suspensions. In addition to these requirements, the following specific requirements shall also be followed, namely:-

1. Principle:- Syrups, Elixirs, Emulsions and Suspensions may be susceptible to microbial and other contamination during manufacture. Therefore, special measures must be taken to prevent any contamination.

2. Building and Equipment:-

2.1. The premises and equipment shall be designed, constructed and maintained to suit the manufacturing of Oral Liquids. The layout and design of the manufacturing area shall strive to minimise the risk of cross-contamination and mix-ups.

2.2. The use of closed systems of processing and transfer is recommended in order to protect the product from contamination. Production areas where the products or open clean containers are exposed shall normally be effectively ventilated with filtered air.

2.3. Manufacturing area shall have entry through double door air-lock facility. It shall be made fly proof by use of 'fly catcher' or 'air curtain'.

2.4. Drainage shall be of adequate size and have adequate traps, without open channels and the design shall be such as to prevent back flow. Drains shall be shallow to facilitate cleaning and disinfecting.

2.5. The production area shall be cleaned and sanitised at the end of every production process.

2.6. Tanks, containers, pipe work and pumps shall be designed and installed so that they can be easily cleaned and sanitised. Equipment design shall be to prevent accumulation of residual microbial growth or cross-contamination.

2.7. Stainless Steel or any other appropriate material shall be used for parts of equipments coming in direct contact with the products. The use of glass apparatus shall be minimum.

2.8. Arrangements for cleaning of containers, closures and droppers shall be made with the help of suitable machines or devices equipped with high pressure air, water and steam jets.

2.9. The quality of materials received in bulk tankers shall be checked before they are transferred to bulk storage tanks.

2.10. Care shall be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.

2.11. The furniture used shall be smooth, washable and made of stainless steel or any other appropriate material which is scratch proof, washable and smooth.

3. Purified Water:-

3.1. The chemical and microbiological quality of purified water used shall be specified and monitored routinely. The microbiological evaluation shall include testing for absence of pathogens and shall not exceed 100 cfu per ml.

3.2. There shall be a written procedure for operation and maintenance of the purified water system. Care shall be taken to avoid the risk of microbial proliferation with appropriate methods like recirculation, use of Ultra Violet (UV) treatment, treatment with heat and sanitising agent. After any chemical sanitisation of the water system, a flushing shall be done to ensure that the sanitising agent has been effectively removed.

4. Manufacturing:-

4.1. Manufacturing personnel shall wear wherever required non fibre shedding clothing to prevent contamination of the product.

4.2. Materials likely to shed fibre like gunny bags, or wooden pallets shall not be carried into the area where products or cleaned containers are exposed.

4.3. Care shall be taken to maintain the homogeneity of emulsion by use of appropriate emulsifier and suspensions by use of appropriate stirrer during filling. Mixing and filling processes shall be specified and monitored. Special care shall be taken at the beginning of the filling process after stoppage due to any interruption and at the end of the process to ensure that the product is uniformly homogenous during the filling process.

4.4. The primary packaging area shall have an air supply which is filtered through level-3 filters [Production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable]. The temperature of the area shall not exceed 30 degrees centigrade.

4.5. When the bulk product is not immediately packed, the maximum period of storage and storage conditions shall be specified in the Master Formula. The maximum period of storage time of a product in the bulk stage shall be validated.**PART X**

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF TOPICAL PRODUCTS i.e., EXTERNAL PREPARATIONS (CREAMS, OINTMENTS, PASTES, MULSIONS, LOTIONS, SOLUTIONS, DUSTING POWDERS AND IDENTICAL PRODUCTS)

Note.- Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Topical Products i.e., External Preparations (Creams, Ointments, Pastes, Emulsions, Lotions, Solutions, Dusting powders and identical products used for external applications). In addition to these requirements, the following specific requirements shall also be followed, namely:—

(1) The entrance to the area where topical products are manufactured shall be through a suitable airlock. Outside the airlock, insectocutors shall be installed.

(2) The air to this manufacturing area shall be filtered through suitable filters and shall be air-conditioned. The HVAC system shall be in place.

(3) The area shall be fitted with an exhaust system of suitable capacity to effectively remove vapours, fumes, smoke or floating dust particles.

(4) The equipment used shall be designed and maintained to prevent the product from being accidentally contaminated with any foreign matter or lubricant.

(5) Suitable cleaning equipment and material shall be used in the process of cleaning or drying the process equipment or accessories used.

(6) Water used in compounding shall be Purified Water IP.

(7) Powders, whenever used, shall be suitably sieved before use.

(8) Heating vehicles and a base like petroleum jelly shall be done in a separate mixing area in suitable stainless steel vessels, using steam, gas, electricity, solar energy, etc.

(9) A separate packing section may be provided for primary packaging of the products.

For production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable).

PART XI

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF METERED–DOSE– INHALERS (MDI)

Note.– The Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied with, *mutatis mutandis*, for the manufacture of Metered-Dose-Inhalers (MDI). In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. **Principle:**- Manufacture of pressurised aerosol products for inhalation with metering valves requires some special provisions arising from the particular nature of this pharmaceutical form. It shall occur under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and in the case of suspensions, of uniformity is also of particular importance. There are presently two common manufacturing and filling methods as follows:–

   (a) Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is filled into the container, the valve is crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.

   (b) One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure or at a low temperature or both. The suspension is then filled directly into the container in one shot.

2. **General:**- Manufacture of Metered-Dose-Inhalers shall be done under conditions which shall ensure minimum microbial and particulate contamination. Assurance of the quality of components and the bulk product is very important. Where medicaments are in suspended state, uniformity of suspension shall be established. Manufacture and filling shall be carried out as far as possible in a closed system.

3. **Building and civil works:**-

   3.1. The building shall be located on a solid foundation to reduce risk of cracking walls and floor due to the movement of equipment and machinery.

   3.2. All building surfaces shall be impervious, smooth and non-shedding. Flooring shall be continuous and provided with a cover between the floor and the wall as well as between the wall and the ceiling. Ceiling shall be solid, continuous and proceeded a cone with the walls. Light fittings and air-grills shall be flush with the ceiling. All service lines requiring maintenance shall be erected in such a manner that these are accessible from outside the production area.

   3.3. The manufacturing area shall be segregated into change rooms for personnel, container preparation area, bulk preparation and filling area, quarantine area and spray testing and packing areas.

   3.4. Secondary change rooms shall be provided for operators to change from factory clothing to special departmental clothing before entering the manufacturing and filling area.

3.5. Separate area shall be provided for de-cartooning of components before they are air washed.

3.6. The propellants used for manufacture shall be delivered to the manufacturing area distribution system by filtering them through 2µ filters. The bulk containers of propellants shall be stored, suitably identified, away from the manufacturing facilities.

4. Environmental conditions:-

4.1. Where products or clean components are exposed, the area shall be supplied with filtered air of Grade C and personnel shall be entered through airlocks.

4.2. The requirements of temperature and humidity in the manufacturing area shall be decided depending on the type of product and propellants handled in the facility. Other support areas shall have comfort levels of temperature and humidity.

4.3. There shall be a difference in room pressure between the manufacturing area and the support areas and the differential pressure shall be not less than 15 Pascals, (0.06 inches or 1.5 mm water gauge).

4.4. There shall be a written schedule for the monitoring of environmental conditions. Temperature and humidity shall be monitored daily.

4.5. The HVAC system shall be in place.

5. Garments:-

5.1. Personnel in the manufacturing and filling section shall wear suitable single piece garment made out of non-shedding, tight weave material. Personnel in support areas shall wear clean factory uniforms.

5.2. Gloves made of suitable material having no interaction with the propellants shall be used by the operators in the manufacturing and filling areas. Preferably, disposable gloves shall be used.

5.3. Suitable department specific PPE like footwear and safety glasses shall be used, wherever hazard exists.

6. Sanitation:-

6.1. There shall be written procedures for the sanitation of the MDI manufacturing facility. Special care shall be taken to handle residues and rinses of propellants.

6.2. Use of water for cleaning shall be restricted and controlled. Routinely used disinfectants are suitable for sanitising the different areas. Records of sanitation shall be maintained.

7. Equipment:-

7.1. Manufacturing equipment shall be of closed system. The vessels and supply lines shall be of stainless steel.

7.2. Suitable check weights, spray testing machines and labelling machines shall be provided in the department.

7.3. All the equipment shall be suitably calibrated and their performance validated on receipt and thereafter periodically.

8. Manufacture:-

8.1. Metering valves for aerosols are a more complex engineering article than most pharmaceutical components. Specifications, sampling and testing shall be appropriate for this situation. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

8.2. All propellants (e.g., liquid or gaseous propellants) shall be filtered to remove particles greater than 0.2µ. An additional filtration where possible immediately before filling is desirable.

8.3. There shall be an approved Master Formula Records for the manufacture of metered dose inhalers.

8.4. The primary packing material shall be appropriately cleaned by compressed air suitably filtered through 0.2µ filter. The humidity of the compressed air shall be controlled as applicable.

8.5. The valves shall be carefully handled and after de-cartooning, these shall be kept in clean, closed containers in the filling room.

8.6. Containers and valves shall be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g., lubricants) or undue microbiological contaminants. After cleaning valves shall be kept in clean, closed containers and precautions taken not to introduce contamination during subsequent handling, e.g., taking samples. Containers shall be provided to the filling line in a clean condition or cleaned on line immediately before filling.

8.7. For suspensions, the bulk shall be kept stirred continuously. Precautions shall be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

8.8. In-process controls shall include periodical checking of weight of bulk formulation filled in the containers. In a two-shot-filling process (liquid filling followed by gaseous filling), it shall be ensured that one hundred per cent check on weight is carried out.

8.9. Controls after filling shall ensure the absence of undue leakage. Any leakage test shall be performed in a way which avoids microbial contamination or residual moisture.

8.10. Filled containers shall be quarantined for a suitable period established by the manufacturer to detect leaking containers prior to testing, labelling and packing.

9. Documentation:- In addition to the routine good manufacturing practices documentation, manufacturing records shall show the following additional information:–

(1) temperature and humidity in the manufacturing area;

(2) periodic filled weights of the formulation;

(3) records of rejections during on line check weighing; and

(4) records of rejection during spray testing.

PART XII

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENTS

Note.— Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I shall be complied for the manufacture of API. In addition to these requirements, the following specific requirements shall also be followed, namely:—

1. Introduction:-

1.1. **General-** This document is intended to provide guidance regarding GMP for the manufacturing of APIs under an appropriate system for managing quality. It is also intended to help and ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess. In this Part "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls.

1.2. **Scope-**

1.2.1. This Part applies to the manufacture of APIs for use in Finished Pharmaceutical Products (FPPs). It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilisation and aseptic processing of sterile APIs are not covered by this Part, but shall be performed in accordance with GMP guidelines for sterile products.

1.2.2. This Part covers APIs that are manufactured by chemical synthesis, extraction, cell culture or fermentation by recovery from natural sources or by any combination of these processes.

1.2.3. Specific guidance for APIs manufactured by cell culture or fermentation is described in paragraph 17 of this Part.

1.2.4. This Part excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it includes APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this Part. In addition, this Part does not apply to medical gases, bulk-packaged FPPs, and manufacturing and control aspects specific to radiopharmaceuticals.

1.2.5. Paragraph 18 contains guidance that only applies to the manufacture of APIs used in the production of FPPs specifically for clinical trials (investigational medicinal products).

1.2.6. An "API starting material" is a raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in house.

1.2.7. API starting materials normally have defined chemical properties and structure. The company shall designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API starting materials" are entered into the

process. For other processes (e.g. fermentation, extraction or purification) this rationale shall be established on a case-to-case basis.

1.2.8. Table specified in paragraph 1.2.9. provides guidance on the point at which the API starting material is normally introduced into the process. From this point on, appropriate GMP as defined in this Part shall be applied to these intermediate or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it shall be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

1.2.9. The guidance in this Part would normally be applied to the steps shown in grey in Table below. It does not imply that all steps shown shall be completed. The stringency of GMP in API manufacturing shall increase as the process proceeds from early API steps to final steps, purification and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g., milling and micronising), shall be conducted at least to the standards of this Part.

TABLE

APPLICATION OF THIS GUIDE TO API MANUFACTURING

Type of manufacturing	**Application of this guide to steps (shown in grey) used in this type of manufacturing**				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediates	Isolation and purification	Physical processing and packaging
API derived from animal sources	Collection of organ, fluid or tissue	Cutting, mixing or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
phytopharmaceutical extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants or cultivation and harvesting	Cutting or comminuting			Physical processing and packaging
Biotechnology: fermentation or cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture or fermentation	Isolation and purification	Physical processing and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging

1.2.10. This Part shall not apply to steps prior to the introduction of the defined "API starting material".

2. Quality management:-

2.1. **Principles-**

2.1.1. Quality shall be the responsibility of all persons involved in the manufacturing.

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

2.1.3. The system for managing quality shall encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet

its intended specifications for quality and purity. All quality related activities shall be defined and documented.

2.1.4. There shall be a quality units that is independent of production and that fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organisation.

2.1.5. The persons authorised to release intermediates and APIs shall be specified.

2.1.6. All quality related activities shall be recorded at the time they are performed.

2.1.7. Any deviation from established procedures shall be documented and explained. Critical deviations shall be investigated and the investigation and its conclusions shall be documented.

2.1.8. No materials shall be released or used before the satisfactory completion of evaluation by the quality units unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in paragraph 10.2 of this Part or the use of raw materials or intermediates pending completion of evaluation).

2.1.9. Procedures shall exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality related complaints, recalls and regulatory actions).

2.2. **Responsibilities of the quality units-**

2.2.1. The quality units shall be involved in all quality-related matters.

2.2.2. The quality units shall review and approve all appropriate quality related documents.

2.2.3. The main responsibilities of the independent quality units shall not be delegated. These responsibilities shall be described in writing and shall include but not necessarily be limited to:—

(i) releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;

(ii) establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;

(iii) reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;

(iv) making sure that critical deviations are investigated and resolved;

(v) approving all specifications and master production instructions;

(vi) approving all procedures impacting the quality of intermediates or APIs;

(vii) making sure that internal audits (self-inspections) are performed;

(viii) approving intermediate and API contract manufacturers;

(ix) approving changes that potentially impact quality of intermediates or APIs;

(x) reviewing and approving validation protocols and reports;

(xi) making sure that quality related complaints are investigated and resolved;

(xii) making sure that effective systems are used for maintaining and calibrating critical equipment;

(xiii) making sure that materials are appropriately tested and the results are reported;

(xiv) making sure that there are stability data to support retest or expiry dates and storage conditions on APIs or intermediates where appropriate; and

(xv) performing product quality reviews as defined in paragraph 2.5.

2.3. **Responsibility for production activities-** The responsibility for production activities shall be described in writing and shall include but not necessarily be limited to:-

(i) preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;

(ii) producing APIs and, when appropriate, intermediates according to pre-approved instructions;

(iii) reviewing all production batch records and ensuring that these are completed and signed;

(iv) making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;

(v) making sure that production facilities are clean and when appropriate disinfected;

(vi) making sure that the necessary calibrations are performed and records are kept;

(vii) making sure that the premises and equipment are maintained and records are kept;

(viii) making sure that validation protocols and reports are reviewed and approved;

(ix) evaluating proposed changes in product, process or equipment; and

(x) making sure that new and when appropriate, modified facilities and equipment are qualified.

2.4. **Internal audits (self-inspection)-**

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

2.4.2. Audit findings and corrective actions shall be documented and brought to the attention of the responsible management of the firm. Agreed corrective actions shall be completed in a timely and effective manner.

2.5. **Product quality review-**

2.5.1. Regular quality reviews of APIs shall be conducted with the objective of verifying the consistency of the process. Such reviews shall normally be conducted and documented annually and shall include at least a review of:—

(i) critical in-process control and critical API test results;

(ii) all batches that failed to meet established specifications;

(iii) all critical deviations or non-conformances and related investigations;

(iv) any changes carried out to the processes or analytical methods;

(v) results of the stability monitoring programme;

(vi) quality-related returns, complaints and recalls; and

(vii) adequacy of corrective actions.

2.5.2. The results of this review shall be evaluated and an assessment made of whether corrective action or any revalidation shall be undertaken. Reasons for such corrective action shall be documented. Agreed corrective actions shall be completed in a timely and effective manner.

3. Personnel-

3.1. **Personnel qualifications-**

3.1.1. There shall be an adequate number of personnel qualified by appropriate education, training or experience to perform and supervise the manufacture of intermediates and APIs.

3.1.2. The responsibilities of all personnel engaged in the manufacture of intermediates and APIs shall be specified in writing.

3.1.3. Training shall be regularly conducted by qualified individuals and shall cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employees' functions. Records of training shall be maintained. Training shall be periodically assessed.

3.2. **Personnel hygiene-**

3.2.1. Personnel shall practice good sanitation and health habits.

3.2.2. Personnel shall wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing shall be changed when appropriate. Additional protective apparel, such as head, face, hand and arm coverings shall be worn when necessary to protect intermediates and APIs from contamination.

3.2.3. Personnel shall avoid direct contact with intermediates or APIs.

3.2.4. 3.2.4 Smoking, eating, drinking, chewing and the storage of food shall be restricted to certain designated areas separate from the manufacturing areas.

3.2.5. Personnel with an infectious disease or who have open lesions on the exposed surface of the body shall not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions shall be excluded from activities where their health condition could adversely affect the quality of the APIs, until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardise the safety or quality of the APIs.

3.3. **Consultants-**

3.3.1. Consultants advising on the manufacture and control of intermediates or APIs shall have sufficient education, training and experience or any combination thereof to advise on the subject for which they are retained.

3.3.2. Records shall be maintained stating the name, address, qualifications and type of service provided by these consultants.

4. Buildings and facilities-

4.1. **Design and construction-**

4.1.1. Buildings and facilities used in the manufacture of intermediates and APIs shall be located, designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities shall also be designed to minimise potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities shall also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.1.2. Buildings and facilities shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.1.3. Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.1.4. The flow of materials and personnel through the building or facilities shall be designed to prevent mix-ups or contamination.

4.1.5. There shall be defined areas or other control systems for the following activities:-

(i) receipt, identification, sampling and quarantine of incoming materials, pending release or rejection;

(ii) quarantine before release or rejection of intermediates and APIs;

(iii) sampling of intermediates and APIs;

(iv) holding rejected materials before further disposition (e.g., return, reprocessing or destruction);

(v) storage of released materials;

(vi) production operations;

(vii) packaging and labelling operations; and

(viii) laboratory operations.

4.1.6. Adequate, clean washing and toilet facilities shall be provided for personnel. These washing facilities shall be equipped with hot and cold water as appropriate, soap or detergent, air driers or single use towels. The washing and toilet facilities shall be separate from, but easily accessible to the manufacturing areas. Adequate facilities for showering or changing clothes shall be provided, when appropriate.

4.1.7. Laboratory areas and operations shall normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements and the laboratory and its operations do not adversely affect the production process or intermediates or APIs.

4.2. **Utilities-**

4.2.1. All utilities that could impact on product quality (e.g., steam, gases, compressed air and heating, ventilation and air conditioning) shall be qualified and appropriately monitored and action shall be taken when limits are exceeded. Drawings for these utility systems shall be available.

4.2.2. Adequate ventilation, air filtration and exhaust systems shall be provided, where appropriate. These systems shall be designed and constructed to minimise risks of contamination and cross-contamination and shall include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity and temperature as appropriate to the stage of manufacture. Particular attention shall be given to the areas where APIs are exposed to the environment.

4.2.3. If air is recirculated to production areas, appropriate measures shall be taken to control risks of contamination and cross-contamination.

4.2.4. Permanently installed pipework shall be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems or alternative means. Pipework shall be located to avoid risks of contamination of the intermediates or APIs.

4.2.5. Drains shall be of adequate size and shall be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3. **Water-**

4.3.1. Water used in the manufacture of APIs shall be demonstrated to be suitable for its intended use.

4.3.2. Unless otherwise justified, process water shall, at a minimum, meet World Health Organisation guidelines for drinking (potable) water quality.

4.3.3. If drinking (potable) water is insufficient to assure API quality, and tighter chemical or microbiological water quality specifications are called for, appropriate specifications for physical and chemical attributes, total microbial counts, objectionable organisms or endotoxins shall be established.

4.3.4. Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process shall be validated and monitored with appropriate action limits.

4.3.5. Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile FPP, water used in the final isolation and purification steps shall be monitored and controlled for total microbial counts, objectionable organisms and endotoxins.

4.4. **Containment-**

4.4.1. Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, shall be employed in the production of highly sensitising materials, such as penicillins or cytotoxic drugs or sex hormones or anabolic or androgenic steroids.

4.4.2. Appropriate measures shall be established and implemented to prevent cross-contamination, e.g., from personnel or materials, moving from one dedicated area to another.

4.4.3. Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials shall not be conducted using the buildings and equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials shall be separate from APIs.

4.5. **Lighting-** Adequate lighting shall be provided in all areas to facilitate cleaning, maintenance and proper operations.

4.6. **Sewage and refuse-** Sewage, refuse and other wastes (e.g., solids, liquids, or gaseous by- products from manufacturing) in and from buildings and the immediate surrounding area shall be disposed of in a safe, timely and sanitary manner. Containers and pipes for waste material shall be clearly identified.

4.7. **Sanitation and maintenance:—**

4.7.1. Buildings used in the manufacture of intermediates and APIs shall be properly maintained and repaired and kept in a clean condition.

4.7.2. Written procedures shall be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities.

4.7.3. When necessary, written procedures shall also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitising agents to prevent the contamination of equipment, raw materials, packaging or labelling materials, intermediates and APIs.

5. Process equipment:-

5.1. **Design and construction-**

5.1.1. Equipment used in the manufacture of intermediates and APIs shall be of appropriate design and adequate size and suitably located for its intended use, cleaning, sanitisation (where appropriate) and maintenance.

5.1.2. Equipment shall be constructed so that surfaces that contact raw materials, intermediates or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.1.3. Production equipment shall only be used within its qualified operating range.

5.1.4. Major equipment (e.g., reactors and storage containers) and permanently installed processing lines used during the production of an intermediate or API shall be appropriately identified.

5.1.5. Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants shall not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this shall be evaluated to ensure that there are no detrimental effects upon the fitness for the purpose of the material. Wherever possible, food-grade lubricants and oils shall be used.

5.1.6. Closed or contained equipment shall be used whenever appropriate. Where open equipment is used or equipment is opened, appropriate precautions shall be taken to minimise the risk of contamination.

5.1.7. A set of current drawings shall be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2. **Equipment maintenance and cleaning-**

5.2.1. Schedules and procedures (including assignment of responsibility) shall be established for the preventive maintenance of equipment.

5.2.2. Written procedures shall be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures shall contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures shall include:-

(i) assignment of responsibility for cleaning of equipment;

(ii) cleaning schedules including where appropriate, sanitising schedules;

(iii) a complete description of the methods and materials including dilution of cleaning agents used to clean equipment;

(iv) when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;

(v) instructions for the removal or obliteration of previous batch identification;

(vi) instructions for the protection of clean equipment from contamination prior to use;

(vii) inspection of equipment for cleanliness immediately before use, if practical; and

(viii) establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.2.3. Equipment and utensils shall be cleaned, stored and, where appropriate, sanitised or sterilised to prevent contamination or carryover of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.2.4. Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, this equipment shall be cleaned at

appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of microorganisms).

5.2.5. Non-dedicated equipment shall be cleaned between production of different materials to prevent cross-contamination.

5.2.6. Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents shall be defined and justified.

5.2.7. Equipment shall be identified as to its contents and its cleanliness status by appropriate means.

5.3. **Calibration-**

5.3.1. Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs shall be calibrated according to written procedures and an established schedule.

5.3.2. Equipment calibrations shall be performed using standards traceable to certified standards, if these exist.

5.3.3. Records of these calibrations shall be maintained.

5.3.4. The current calibration status of critical equipment shall be known and verifiable.

5.3.5. Instruments that do not meet calibration criteria shall not be used.

5.3.6. Deviations from approved standards of calibration on critical instruments shall be investigated to determine if these could have had an impact on the quality of the intermediates or APIs manufactured using this equipment since the last successful calibration.

5.4. **Computerised systems-**

5.4.1. GMP-related computerised systems shall be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.

5.4.2. Appropriate installation qualification and operational qualification shall demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.4.3. Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at the time of installation, a retrospective validation could be conducted, if appropriate documentation is available.

5.4.4. Computerised systems shall have sufficient controls to prevent unauthorised access or changes to data. There shall be controls to prevent omissions in data (e.g., the system being turned off and data not captured). There shall be a record of any data change made, the previous entry, the person who made the change and when the change was made.

5.4.5. Written procedures shall be available for the operation and maintenance of computerised systems.

5.4.6. Where critical data are being entered manually, there shall be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.

5.4.7. Incidents related to computerised systems that could affect the quality of intermediates or APIs or the reliability of records or test results shall be recorded and investigated.

5.4.8. Changes to the computerised system shall be made according to a change procedure and shall be formally authorised, documented and tested. Records shall be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records shall demonstrate that the system is maintained in a validated state.

5.4.9. A back-up system shall be provided so that there is no permanent loss of records due to system breakdown or failure. Means of ensuring data protection shall be established for all computerised systems.

5.4.10. Data may be recorded by a second means in addition to the computer system.

6. Documentation and records:-

6.1. **Documentation system and specifications-**

6.1.1. All documents related to the manufacture of intermediates or APIs shall be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in

paper or electronic form.

6.1.2. The issuance, revision, superseding and withdrawal of all documents shall be controlled with maintenance of revision histories.

6.1.3. A procedure shall be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records and distribution records). The retention periods for these documents shall be specified.

6.1.4. All production, control and distribution records shall be retained for at least one year after the expiry date of the batch. For APIs with retest dates, records shall be retained for at least three years after the batch is completely distributed.

6.1.5. Entries in records shall be made indelibly in spaces provided for such entries, directly after performing the activities and shall identify the person making the entry. Corrections to entries shall be dated and signed ensuring that the original entry remains readable.

6.1.6. During the retention period, originals or copies of records shall be readily available at the establishment where the activities described in these records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.1.7. Specifications, instructions, procedures and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy shall be readily available.

6.1.8. Specifications shall be established and documented for raw materials, intermediates where necessary, APIs and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria shall be established and documented for in-process controls.

6.1.9. If electronic signatures are used on documents they shall be authenticated and secure.

6.2. **Equipment cleaning and use record-**

6.2.1. Records of major equipment use, cleaning, sanitisation and sterilisation and maintenance shall show the date, time (if appropriate), product and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

6.2.2. If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance and use can be part of the batch record or maintained separately.

6.3. **Records of raw materials, intermediates, API labelling and packaging materials-**

6.3.1. Records of raw materials, intermediates, API labelling and packaging materials shall be maintained including:-

(i) the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control numbers, if known, or other identification number; the number allocated on receipt; and the date of receipt;

(ii) the results of any test or examination performed and the conclusions derived from this;

(iii) records tracing the use of materials;

(iv) documentation of the examination and review of API labelling and packaging material for conformity with established specifications; and

(v) the final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

6.3.2. Master (approved) labels shall be maintained for comparison to issued labels.

6.4. **Master production instructions (master production and control records):-**

6.4.1. To ensure uniformity from batch to batch, master production instructions for each intermediate and API shall be prepared, dated and signed by one person and independently checked, dated and signed by a person in the quality units.

6.4.2. Master production instructions shall include:-

(i) the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;

(ii) a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;

(iii) an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production shall be included. Variations to quantities shall be included where they are justified;

(iv) the production location and major production equipment to be used;

(v) detailed production instructions, including the-

(a) sequences to be followed;

(b) ranges of process parameters to be used;

(c) sampling instructions and in-process controls with their acceptance criteria, where appropriate;

(d) time limits for completion of individual processing steps and the total process, where appropriate; and

(e) expected yield ranges at appropriate phases of processing or time;

(vi) where appropriate, special notations and precautions to be followed, or cross-references; and

(vii) the instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5. **Batch production records (batch production and control records)-**

6.5.1. Batch production records shall be prepared for each intermediate and API and shall include complete information relating to the production and control of each batch. The batch production record shall be checked before issuance to assure that it is the correct version and is a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document shall include a reference to the current master production instruction being used.

6.5.2. These records shall be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code, together with the date and time can serve as the unique identifier until the final number is allocated.

6.5.3. Documentation of completion of each significant step in the batch production records (batch production and control records) shall include-

(i) dates and, when appropriate, times;

(ii) identity of major equipment (e.g., reactors, driers and mills) used;

(iii) specific identification of each batch, including weights, measures and batch numbers of raw materials, intermediates or any reprocessed materials used during manufacturing;

(iv) actual results recorded for critical process parameters;

(v) any sampling performed;

(vi) signatures of the persons performing and directly supervising or checking each critical step in the operation;

(vii) in-process and laboratory test results;

(viii) actual yield at appropriate phases or times;

(ix) description of packaging and label for intermediate or API;

(x)representative label of API or intermediate, if made commercially available;

(xi) any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation, if stored separately; and

(xii) results of release testing.

6.5.4. Written procedures shall be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation shall extend to other batches that may have been associated with the specific failure or deviation.

6.6. **Laboratory control records-**

6.6.1. Laboratory control records shall include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows-

(i) a description of samples received for testing, including the name of the material or its source, batch number or other distinctive code, the date on which the sample was taken and where appropriate, the quantity and date the sample was received for testing;

(ii) a statement of reference to each test method used;

(iii) a statement of the weight or measure of sample used for each test as described by the method;

(iv) data on or cross reference to the preparation and testing of reference standards, reagents and standard solutions;

(v) a complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;

(vi) a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors and equivalency factors;

(vii) a statement of the test results and how they compare with established acceptance criteria;

(viii) the signature of the person who performed each test and the dates the tests were performed; and

(ix) the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.

6.6.2. Complete records shall also be maintained for-

(i) any modifications to an established analytical method;

(ii) periodic calibration of laboratory instruments, apparatus, gauges and recording devices;

(iii) all stability testing performed on APIs; and

(iv) out of specification (OOS) investigations.

6.7. **Batch production record review-**

6.7.1. Written procedures shall be established and followed for the review and approval of batch production and laboratory control records including packaging and labelling to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.7.2. Batch production and laboratory control records of critical process steps shall be reviewed and approved by the quality units before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality units.

6.7.3. All deviation, investigation and OOS reports shall be reviewed as part of the batch record review before the batch is released.

6.7.4. The quality units can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. Materials management:-

7.1. **General controls-**

7.1.1. There shall be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials.

7.1.2. Manufacturers of intermediates or APIs or both shall have a system for evaluating the suppliers of critical materials.

7.1.3. Materials shall be purchased against an agreed specification, from a supplier or suppliers approved by the quality units.

7.1.4. If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer shall be known to the intermediate or API manufacturer or both.

7.1.5. Changing the source of supply of critical raw materials shall be done according to paragraph 13 of this Part.

7.2. **Receipt and quarantine-**

7.2.1. Upon receipt and before acceptance, each container or grouping of containers of materials shall be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), damage to containers, broken seals and evidence of tampering or contamination. Materials shall be held under quarantine until they have been sampled, examined or tested as appropriate, and then released for use.

7.2.2. Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they shall be identified as correct, tested, if appropriate and released. Procedures shall be available to prevent discharging incoming materials wrongly into the existing stock.

7.2.3. If bulk deliveries are made in non-dedicated tankers, there shall be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following-

(i) certificate of cleaning;

(ii) testing for trace impurities; and

(iii) audit of the supplier.

7.2.4. Large storage containers and their attendant manifolds, filling and discharge lines shall be appropriately identified.

7.2.5. Each container or grouping of containers (batches) of materials shall be assigned and identified with a distinctive code, batch or receipt number. This number shall be used in recording the disposition of each batch. A system shall be in place to identify the status of each batch.

7.3. **Sampling and testing of incoming production materials-**

7.3.1. At least one test to verify the identity of each batch of material shall be conducted, with the exception of the materials described below in paragraph 7.3.2. A supplier's certificate of analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.3.2. Supplier approval shall include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analysis shall be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis shall be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis shall be checked at regular intervals.

7.3.3. Processing aids, hazardous or highly toxic raw materials, other special materials or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels and recording of batch

numbers shall help in establishing the identity of these materials. The lack of on-site testing for these materials shall be justified and documented.

7.3.4. Samples shall be representative of the batch of material from which they are taken. Sampling methods shall specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The decision on the number of containers to sample and the sample size shall be based upon a sampling plan that takes into consideration the criticality of the material, variability of the material, past quality history of the supplier and the quantity needed for analysis.

7.3.5. Sampling shall be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.3.6. Containers from which samples are withdrawn shall be opened carefully and subsequently reclosed. They shall be marked to indicate that a sample has been taken.

7.4. **Storage-**

7.4.1. Materials shall be handled and stored in such a manner as to prevent degradation, contamination and cross-contamination.

7.4.2. Materials stored in fibre drums, bags or boxes shall be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.4.3. Materials shall be stored under conditions and for a period that will have no adverse effect on their quality and shall normally be controlled so that the oldest stock is used first.

7.4.4. Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.4.5. Rejected materials shall be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

7.5. **Re-evaluation-** Materials shall be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. Production and in-process controls:-

8.1. **Production operations-**

8.1.1. Raw materials for manufacturing of intermediates and APIs shall be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices shall be of suitable accuracy for the intended use.

8.1.2. If a material is sub-divided for later use in production operations, the container receiving the material shall be suitable and shall be identified that the following information is available-

(i) material name or item code;

(ii) receiving or control number;

(iii) weight or measure of material in the new container; and

(iv) re-evaluation or retest date, if appropriate.

8.1.3. Critical weighing, measuring or sub-dividing operations shall be witnessed or subjected to an equivalent control. Prior to use, production personnel shall verify that the materials are those specified in the batch record for the intended intermediate or API.

8.1.4. Other critical activities shall be witnessed or subjected to an equivalent control.

8.1.5. Actual yields shall be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges shall be established based on previous laboratory, pilot scale or manufacturing data. Deviations in yield associated with critical process steps shall be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.1.6. Any deviation shall be documented and explained. Any critical deviation shall be investigated.

8.1.7. The processing status of major units of equipment shall be indicated either on the individual units of equipment or by appropriate documentation, computer control systems or alternative means.

8.1.8. Materials to be reprocessed or reworked shall be appropriately controlled to prevent unauthorised use.

8.2. **Time limits-**

8.2.1. If time limits are specified in the master production instructions (see paragraph 6.4.2), these time limits shall be met to ensure the quality of intermediates and APIs. Deviations shall be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation or drying to a predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.2.2. Intermediates held for further processing shall be stored under appropriate conditions to ensure their suitability for use.

8.3. **In-process sampling and control-**

8.3.1. Written procedures shall be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria shall be defined based on the information gained during the development stage or historical data.

8.3.2. The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

8.3.3. Critical in-process controls (and critical process monitoring), including the control points and methods, shall be stated in writing and approved by the quality units.

8.3.4. In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality units' approval if the adjustments are made within pre-established limits approved by the quality units. All tests and results shall be fully documented as part of the batch record.

8.3.5. Written procedures shall describe the sampling methods for in-process materials, intermediates and APIs. Sampling plans and procedures shall be based on scientifically sound sampling practices.

8.3.6. In-process sampling shall be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures shall be established to ensure the integrity of samples after collection.

8.3.7. OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring or adjusting the process.

8.4. **Blending batches of intermediates or APIs-**

8.4.1. For the purpose of this Schedule, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g. collecting several centrifuge loads from a single crystallisation batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.4.2. OOS batches shall not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend shall have been manufactured using an established process and shall have been individually tested and found to meet appropriate specifications prior to blending.

8.4.3. Acceptable blending operations include but are not limited to-

(i) blending of small batches to increase batch size;

(I) blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.4.4. Blending processes shall be adequately controlled and documented and the blended batch shall be tested for conformance to established specifications, where appropriate.

8.4.5. The batch record of the blending process shall allow traceability back to the individual batches that make up the blend.

8.4.6. Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations shall be validated to show homogeneity of the combined batch. Validation shall include testing of critical attributes (e.g., particle size distribution, bulk density and tap density) that may be affected by the blending process.

8.4.7. If the blending could adversely affect stability, stability testing of the final blended batches shall be performed.

8.4.8. The expiry or retest date of the blended batch shall be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5. **Contamination control-**

8.5.1. Residual materials can be carried over into successive batches of the same intermediate or API, if there is adequate control. Examples include residue adhering to the wall of a microniser, residual layer of damp crystals remaining in a centrifuge bowl after discharge and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover shall not result in the carry-over of degradants or microbial contamination that may adversely alter the established impurity profile of the API.

8.5.2. Production operations shall be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.5.3. Precautions to avoid contamination shall be taken when APIs are handled after purification.

9. Packaging and identification labelling of APIs and intermediates:-

9.1. **General-**

9.1.1. There shall be written procedures describing the receipt, identification, quarantine, sampling, examination, testing and release and handling of packaging and labelling materials.

9.1.2. Packaging and labelling materials shall conform to the established specifications. Those that do not comply with the specifications shall be rejected to prevent their use in operations for which they are unsuitable.

9.1.3. Records shall be maintained for each shipment of labels and packaging materials showing receipt, examination or testing and whether they are accepted or rejected.

9.2. **Packaging materials-**

9.2.1. Containers shall provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.2.2. Containers shall be clean and where indicated by the nature of the intermediate or API, sanitised to ensure that they are suitable for their intended use. These containers shall not be reactive, additive or absorptive to ensure that they do not alter the quality of the intermediate or API beyond the specified limits.

9.2.3. If containers are reused, they shall be cleaned in accordance with documented procedures and all previous labels shall be removed or defaced.

9.3. **Label issuance and control-**

9.3.1. Access to the label storage areas shall be limited to authorised personnel.

9.3.2. Procedures shall be used to reconcile the quantities of labels issued, used and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies shall be investigated and the investigation shall be approved by the quality units.

9.3.3. All excess labels bearing batch numbers or other batch-related printing shall be destroyed. Returned labels shall be retained and stored in a manner that prevents mix-ups and provides proper identification.

9.3.4. Obsolete and out dated labels shall be destroyed.

9.3.5. Printing devices used to print labels for packaging operations shall be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.3.6. Printed labels issued for a batch shall be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination shall be documented.

9.3.7. A printed label representative of those used shall be included in the batch production record.

9.4. **Packaging and labelling operations-**

9.4.1. There shall be documented procedures designed to ensure that the correct packaging materials and labels are used.

9.4.2. Labelling operations shall be designed to prevent mix-ups. They shall be physically or spatially separated from operations involving other intermediates or APIs.

9.4.3. Labels used on containers of intermediates or APIs shall indicate the name or identifying code, the batch number of the product and the storage conditions, when such information is critical to assure the quality of the intermediate or API.

9.4.4. If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents and special transport conditions and any special legal requirements shall also be included on the label. For intermediates or APIs with an expiry date, this date shall be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date shall be indicated on the label and certificate of analysis.

9.4.5. Packaging and labelling facilities shall be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination shall be documented in the batch production records, the facility log or other documentation system.

9.4.6. Packaged and labelled intermediates or APIs shall be examined to ensure that containers and packages in the batch have the correct label. This examination shall be part of the packaging operation. Results of these examinations shall be recorded in the batch production or control records.

9.4.7. Intermediate or API containers that are transported outside the manufacturer's control shall be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. Storage and distribution:-

10.1. **Warehousing procedures-**

10.1.1. Facilities shall be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records shall be maintained of these conditions, if they are critical for the maintenance of material characteristics.

10.1.2. Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned or recalled materials, separate storage areas shall be assigned for their temporary storage until the decision as to their future use has been taken.

10.2. **Distribution procedures-**

10.2.1. APIs and intermediates shall only be released for distribution to third parties after they have been released by the quality units. APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorised by the quality units and if appropriate controls and documentation are in place.

10.2.2. APIs and intermediates shall be transported in a manner that does not adversely affect their quality.

10.2.3. Special transport or storage conditions for an API or intermediate shall be stated on the label.

10.2.4. The manufacturer shall ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.2.5. A system shall be in place by which the distribution of each batch of intermediate or API or both can be readily determined to permit its recall.

11. Laboratory controls:-

11.1. **General controls-**

11.1.1. The independent quality units shall have at its disposal adequate laboratory facilities.

11.1.2. There shall be documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Laboratory records shall be maintained in accordance with paragraph 6.6.

11.1.3. All specifications, sampling plans and test procedures shall be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, labels and packaging materials conform to established standards of quality and purity. Specifications and test procedures shall be consistent with those included in the registration or filing. There can be specifications in addition to those in the registration or filing. Specifications, sampling plans and test procedures, including changes to them, shall be drafted by the appropriate organisational unit and reviewed and approved by the quality units.

11.1.4. Appropriate specifications shall be established for APIs in accordance with accepted standards and be consistent with the manufacturing process. The specifications shall include a control of the impurities (e.g., organic impurities, inorganic impurities and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms shall be established and met. If the API has a specification for endotoxins, appropriate action limits shall be established and met.

11.1.5. Laboratory controls shall be followed and documented at the time of performance. Any departure from the procedures described in paragraph 11.1.4 shall be documented and explained.

11.1.6. Any OOS result obtained shall be investigated and documented according to the procedure. This procedure shall require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions and conclusions. Any resampling or retesting after OOS results shall be performed according to the documented procedure.

11.1.7. Reagents and standard solutions shall be prepared and labelled following written procedures. “Use by” dates shall be applied as appropriate for analytical reagents or standard solutions.

11.1.8. Primary reference standards shall be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard shall be documented. Records shall be maintained of each primary reference standard’s storage and use in accordance with the supplier’s recommendations. Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier’s recommendations.

11.1.9. Where a primary reference standard is not available from an officially recognised source, an “in-house primary standard” shall be established. Appropriate testing shall be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing shall be maintained.

11.1.10. Secondary reference standards shall be appropriately prepared, identified, tested, approved and stored. The suitability of each batch of secondary reference standard shall be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard shall be periodically requalified in accordance with a written protocol.

11.2. **Testing of intermediates and APIs-**

11.2.1. For each batch of intermediate and API, appropriate laboratory tests shall be conducted to determine conformance to the specifications.

11.2.2. An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process shall normally be established for each API. The impurity profile shall include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed and classification of each identified impurity (e.g., inorganic, organic or solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs of phytopharmaceutical or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B (1).

11.2.3. The impurity profile shall be compared at appropriate intervals with the impurity profile in the regulatory submission or compared with historical data in order to detect changes to the API resulting from modifications to raw materials, equipment operating parameters or the production process.

11.2.4. Appropriate microbiological tests shall be conducted on each batch of intermediate and API where microbial quality is specified.

11.3. **Certificates of analysis-**

11.3.1. Authentic certificates of analysis shall be issued for each batch of intermediate or API on request.

11.3.2. Information on the name of the intermediate or API, including where appropriate its grade, the batch number and the date of release, shall be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date shall be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date shall be indicated on the label and certificate of analysis.

11.3.3. The certificate shall list each test performed in accordance with compendial or customer requirements, including the acceptance limits and the numerical results obtained (if test results are numerical).

11.3.4. Certificates shall be dated and signed by authorised personnel from the quality units and shall show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the certificate of analysis shall show the name, address and telephone number of the repacker or reprocessor and a reference to the name of the original manufacturer.

11.3.5. If new certificates are issued by or on behalf of repackers or reprocessors, agents or brokers, these certificates shall show the name, address and telephone number of the laboratory that performed the analysis. They shall also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which shall be attached.

11.4. **Stability monitoring of APIs-**

11.4.1. A documented, on-going testing programme shall be designed to monitor the stability characteristics of APIs and the results shall be used to confirm appropriate storage conditions and retest or expiry dates.

11.4.2. The test procedures used in stability testing shall be validated and be stability-indicating.

11.4.3. Stability samples shall be stored in containers that simulate the market container. For example, if the API is marketed in bags within fibre drums, stability samples can be packaged in bags of the same material and in smaller drums of similar or identical material composition to the drums in which the API is marketed.

11.4.4. Normally the first three commercial production batches shall be placed on the stability monitoring programme to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

11.4.5. Thereafter at least one batch per year of API manufactured (unless none is produced that year) shall be added to the stability monitoring programme and tested at least annually to confirm the stability.

11.4.6. For APIs with short shelf-lives, testing shall be done more frequently. For example, for those biotechnological or biological and other APIs with shelf-lives of one year or less, stability samples shall be obtained and shall be tested monthly for the first three months,

and at three-monthly intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., nine-month testing) can be considered.

11.5. **Expiry and retest dating-**

11.5.1. When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information shall be available (e.g., published data and test results).

11.5.2. An API expiry or retest date shall be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.5.3. Preliminary API expiry or retest dates can be based on pilot-scale batches if-

(i) the pilot batches employ a method of manufacture and a procedure that simulates the final process to be used on a commercial manufacturing scale; and

(ii) the quality of the API represents the material to be made on a commercial scale.

11.5.4. A representative sample shall be taken for the purpose of performing a retest.

11.6. **Reserve or retention samples-**

11.6.1. The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing.

11.6.2. Appropriately identified reserve samples of each batch of API shall be retained for one year after the expiry date assigned by the manufacturer to the batch, or for three years after distribution of the batch, whichever is longer. For APIs with retest dates, similar reserve samples shall be retained for three years after the batch has been completely distributed by the manufacturer.

11.6.3. The reserve sample shall be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities shall be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. Validation:-

12.1. **Validation policy-**

12.1.1. The company's overall policy, intentions and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems and personnel responsible for design, review, approval and documentation of each validation phase, shall be documented.

12.1.2. The critical parameters and attributes shall normally be identified during the development stage or from historical data and the ranges necessary for the reproducible operation shall be defined. This shall include-

(i) defining the API in terms of its critical product attributes;

(ii) identifying process parameters that could affect the critical quality attributes of the API; and

(iii) determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.1.3. Validation shall extend to those operations determined to be critical to the quality and purity of the API.

12.2. **Validation documentation-**

12.2.1. A written validation protocol shall be established that specifies how validation of a particular process will be conducted. The protocol shall be reviewed and approved by the quality units and other designated units.

12.2.2. The validation protocol shall specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

12.2.3. A validation report that cross-references the validation protocol shall be prepared, summarising the results obtained, commenting on any deviations observed and drawing the

appropriate conclusions, including recommending changes to correct deficiencies.

12.2.4. Any variations from the validation protocol shall be documented with appropriate justification.

12.3. **Qualification-**

12.3.1. Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems shall be completed. Qualification is usually carried out by conducting the following activities, individually or combined:-

(i) Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment or systems is suitable for the intended purpose;

(ii) Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and user requirements;

(iii) Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges;

(iv) Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4. **Approaches to process validation-**

12.4.1. Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.4.2. There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These three approaches and their applicability are outlined in the following paragraph.

12.4.3. Prospective validation shall normally be performed for all API processes referred to in paragraph 12.1.3. Prospective validation performed on an API process shall be completed before the commercial distribution of the FPP manufactured from that API.

12.4.4. Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in FPPs for commercial distribution based on thorough monitoring and testing of the API batches.

12.4.5. An exception can be made for retrospective validation for well- established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities or the production process. This validation approach may be used where-

(a) critical quality attributes and critical process parameters have been identified;

(b) appropriate in-process acceptance criteria and controls have been established;

(c) there have not been significant process or product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and

(d) impurity profiles have been established for the existing API.

12.4.6. Batches selected for retrospective validation shall be representative of all batches made during the review period, including any batches that failed to meet specifications, and shall be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5. **Process validation programme-**

12.5.1. The number of process runs for validation shall depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches shall be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). Generally, for retrospective validation, data from ten to thirty consecutive batches shall be examined to assess process consistency, but fewer batches can be examined, if justified.

12.5.2. Critical process parameters shall be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimise energy consumption or equipment use, need not be included in the process validation.

12.5.3. Process validation shall confirm that the impurity profile for each API is within the limits specified. The impurity profile shall be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6. **Periodic review of validated systems-** Systems and processes shall be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7. **Cleaning validation-**

12.7.1. Cleaning procedures shall normally be validated. In general, cleaning validation shall be directed to those situations or process steps where contamination or carry-over of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.7.2. Validation of cleaning procedures shall reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection shall be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity and stability.

12.7.3. The cleaning validation protocol shall describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled and analytical methods. The protocol shall also indicate the type of samples to be obtained and how they are collected and labelled.

12.7.4. Sampling shall include swabbing, rinsing or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used shall be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports for handling toxic materials and small intricate equipment such as micronisers and microfluidisers).

12.7.5. Validated analytical methods with the sensitivity to detect residues or contaminants shall be used. The detection limit for each analytical method shall be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level shall be established. Residue limits shall be practical, achievable and verifiable and be based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological or physiological activity of the API or its most deleterious component.

12.7.6. Equipment cleaning or sanitisation studies shall address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

12.7.7. Cleaning procedures shall be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise remain undetected by sampling or analysis or both.

12.8. **Validation of analytical methods-**

12.8.1. Analytical methods shall be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference. The suitability of all testing methods used shall nonetheless be verified under actual conditions of use and documented.

12.8.2. Methods shall be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical

validation performed shall reflect the purpose of the analysis and the stage of the API production process.

12.8.3. Appropriate qualification of analytical equipment shall be considered before starting validation of analytical methods.

12.8.4. Complete records shall be maintained of any modification of a validated analytical method. Such records shall include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. Change control:

13.1. A formal change control system shall be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.2. Written procedures shall cover the identification, documentation, appropriate review and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

13.3. Any proposals for relevant changes to GMP shall be drafted, reviewed and approved by the appropriate organisational units and reviewed and approved by the quality units.

13.4. The potential impact of the proposed change on the quality of the intermediate or API shall be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on their nature and extent and the effects these changes may have on the process. Scientific judgement shall be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.5. When implementing approved changes, measures shall be taken to ensure that all documents affected by the changes are revised.

13.6. After the change has been implemented there shall be an evaluation of the first batch produced or tested under the change.

13.7. The potential for critical changes to affect established retest or expiry dates shall be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability programme or can be added to the stability monitoring programme.

13.8. Manufacturers of the current dosage form shall be notified of changes from established production and process control procedures that can impact the quality of the API.

14. Rejection and reuse of materials:-

14.1. **Rejection-** Intermediates and APIs failing to meet established specifications shall be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials shall be recorded.

14.2. **Reprocessing-**

14.2.1. Introducing an intermediate or API, including the one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallisation step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography or milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches it shall be included as part of the standard manufacturing process.

14.2.2. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

14.2.3. Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing shall be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and overreacted materials.

14.3. **Reworking-**

14.3.1. Before a decision is taken to rework batches that do not conform to the established standards or specifications, an investigation into the reason for non-conformance shall be performed.

14.3.2. Batches that have been reworked shall be subjected to appropriate evaluation, testing, stability testing if warranted and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.3.3. Procedures shall provide for comparing the impurity profile of each reworked batch with batches manufactured by the established process. Where routine analytical methods are inadequate to characterise the reworked batch, additional methods shall be used.

14.4. **Recovery of materials and solvents-**

14.4.1. Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.4.2. Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.

14.4.3. Fresh and recovered solvents and reagents can be combined, if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.4.4. The use of recovered solvents, mother liquors and other recovered materials shall be adequately documented.

14.5. **Returns-**

14.5.1. Returned intermediates or APIs shall be identified as such and quarantined.

14.5.2. If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs shall be reprocessed, reworked or destroyed, as appropriate.

14.5.3. Records of returned intermediates or APIs shall be maintained. For each return, documentation shall include-

(i) name and address of the consignee;

(ii) intermediate or API, batch number and quantity returned;

(iii) reasons for return; and

(iv) use or disposal of the returned intermediate or API.

15. Complaints and recalls-

15.1. All quality-related complaints, whether received orally or in writing, shall be recorded and investigated according to the written procedure.

15.2. Complaint records shall include-

(i) name and address of complainant;

(ii) name (where appropriate title) and telephone number of person submitting the complaint;

(iii) nature of the complaint (including name and batch number of the API);

(iv) date on which the complaint was received;

(v) action initially taken (including dates and identity of person taking the action);

(vi) any follow-up action taken;

(vii) response provided to the originator of the complaint (including date on which the response was sent); and

(viii) final decision on intermediate or API batch or lot.

15.3. Records of complaints shall be retained in order to evaluate trends, product-related frequencies and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.4. There shall be a written procedure that defines the circumstances under which a recall of an intermediate or API shall be considered.

15.5. The recall procedure shall designate who shall be involved in evaluating the information, how a recall shall be initiated, who shall be informed about the recall and how the recalled material shall be treated.

15.6. The recalls shall be informed to the Licencing Authorities.

16. Contract manufacturers (including laboratories):-

16.1. All contract manufacturers (including laboratories) shall comply with GMP defined in this Schedule. Special consideration shall be given to the prevention of cross-contamination and to maintaining traceability.

16.2. Contract manufacturers (including laboratories) shall be evaluated by the contract giver to ensure GMP compliance of the specific operations taking place at the contract sites.

16.3. There shall be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.4. The contract shall permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.5. Where sub-contracting is allowed, the contract acceptor shall not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.6. Manufacturing and laboratory records shall be kept at the site where the activity takes place and be readily available.

16.7. Changes in the process, equipment, test methods, specifications or other contractual requirements shall not be made unless the contract giver is informed and approves the changes.

17. Specific guidance for APIs manufactured by cell culture or fermentation:-

17.1. **General-**

17.1.1. The principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins or polypeptides or both are the same, although the degree of control will differ. Where practical, this Part shall address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

17.1.2. The term "bio-technological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by bio-technological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Part. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

17.1.3. The term "classical fermentation" refers to the processes that use microorganisms existing in nature or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

17.1.4. Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. There may be additional process steps, such as physicochemical modification,

that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation and the intended use of the API or intermediate, control of bioburden, viral contamination and endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

17.1.5. Appropriate controls shall be established at all stages of manufacturing to assure intermediate or API quality. This starts at the cell culture or fermentation step, prior steps (e.g., cell banking) shall be performed under appropriate process controls. This covers cell culture or fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

17.1.6. Appropriate equipment and environmental controls shall be used to minimise the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring shall depend on the step in production and the production conditions (open, closed or contained systems).

17.1.7. In general, process controls shall take into account-

(i) maintenance of the working cell bank (where appropriate);

(ii) proper inoculation and expansion of the culture;

(iii) control of the critical operating parameters during fermentation or cell culture;

(iv) monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;

(v) harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;

(vi) monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and

(vii) viral safety concerns as described in ICH Guideline Q5A (2) [Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin].

17.1.8. Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants shall be demonstrated.

17.2. **Cell bank maintenance and record keeping-**

17.2.1. Access to cell banks shall be limited to authorised personnel.

17.2.2. Cell banks shall be maintained under storage conditions designed to maintain viability and prevent contamination.

17.2.3. Records of the use of the vials from the cell banks and storage conditions shall be maintained.

17.2.4. Where appropriate, cell banks shall be periodically monitored to determine suitability for use.

17.3. **Cell culture or fermentation-**

17.3.1. Where aseptic addition of cell substrates, media, buffers and gases is needed, closed or contained systems shall be used where possible. If the inoculations of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there shall be controls and procedures in place to minimise the risk of contamination.

17.3.2. Where the quality of the API can be affected by microbial contamination, manipulations using open vessels shall be performed in a biosafety cabinet or similarly controlled environment.

17.3.3. Personnel shall be appropriately gowned and take special precautions handling the cultures.

17.3.4. Critical operating parameters (for example temperature, pH, agitation rates, addition of gases and pressure) shall be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity shall also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability) may not need to be monitored.

17.3.5. Cell culture equipment shall be cleaned and sterilised after use. As appropriate, fermentation equipment shall be cleaned, and sanitized or sterilised.

17.3.6. Culture media shall be sterilised before use when appropriate to protect the quality of the API.

17.3.7. There shall be appropriate procedures in place to detect contamination and determine the course of action to be taken. This shall include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes shall be identified as appropriate and the effect of their presence on product quality shall be assessed, if necessary. The results of such assessments shall be taken into consideration in the disposition of the material produced.

17.3.8. Records of contamination events shall be maintained.

17.3.9. Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimise the risk of cross-contamination.

17.4. **Harvesting, isolation and purification-**

17.4.1. Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, shall be performed in equipment and areas designed to minimise the risk of contamination.

17.4.2. Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimising degradation, contamination and loss of quality) shall be adequate to ensure that the intermediate or API is recovered with consistent quality.

17.4.3. All equipment shall be properly cleaned and as appropriate, sanitised after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

17.4.4. If open systems are used, purification shall be performed under environmental conditions appropriate for the preservation of product quality.

17.4.5. Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate, if equipment is to be used for multiple products.

17.5. **Viral removal or inactivation steps:**

17.5.1. Viral removal and viral inactivation steps are critical processing steps for some processes and shall be performed within their validated parameters.

17.5.2. Appropriate precautions shall be taken to prevent potential viral contamination from pre-viral to post-viral removal or inactivation steps. Therefore, open processing shall be performed in areas that are separate from other processing activities and have separate air handling units.

17.5.3. The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment shall be appropriately cleaned and sanitised before reuse. Appropriate precautions shall be taken to prevent potential virus carry-over (e.g., through equipment or environment) from previous steps.

18. APIs for use in clinical trials:-

18.1. **General-**

18.1.1. Not all the controls in the previous sections of this guide are appropriate for the manufacture of a new API for investigational use during its development.

18.1.2. The controls used in the manufacture of APIs for use in clinical trials shall be consistent with the stage of development of the pharmaceutical product incorporating the API. Process and test procedures shall be flexible to allow for changes to be made as knowledge of the process increases and clinical testing of a pharmaceutical product progresses from the preclinical stages through the clinical stages. Once pharmaceutical development reaches the stage where the API is produced for use in pharmaceutical products intended for clinical trials, manufacturers shall ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

18.2. **Quality-**

18.2.1. Appropriate GMP concepts shall be applied in the production of APIs for use in clinical trials with a suitable mechanism for the approval of each batch.

18.2.2. A quality unit independent from production shall be established for the approval or rejection of each batch of API for use in clinical trials.

18.2.3. Some of the testing functions commonly performed by the quality units can be performed within other organisational units.

18.2.4. Quality measures shall include a system for testing of raw materials, packaging materials, intermediates and APIs.

18.2.5. Process and quality problems shall be evaluated.

18.2.6. Labelling for APIs intended for use in clinical trials shall be appropriately controlled and shall identify the material as being for investigational use.

18.3. **Equipment and facilities-**

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

18.3.2. Procedures for the use of facilities shall ensure that materials are handled in a manner that minimises the risk of contamination and cross- contamination.

18.4. **Control of raw materials-**

18.4.1. Raw materials used in production of APIs for use in clinical trials shall be evaluated by testing or be received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous a supplier's analysis shall be suffice.

18.4.2. In some instances the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

18.5. **Production-**

18.5.1. The production of APIs for use in clinical trials shall be documented in laboratory notebooks, batch records or by other appropriate means. These documents shall include information on the use of production materials, equipment, processing and scientific observations.

18.5.2. Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

18.6. **Validation-**

18.6.1. Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during development of an API make batch replication difficult or inexact. The combination of controls, calibration and where appropriate, equipment qualification assures quality of the API during this development phase.

18.6.2. Process validation shall be conducted in accordance with paragraph 12 when batches are produced for commercial use, even when such batches are produced on a pilot scale or small scale.

18.7. **Changes-** Changes are expected during development as knowledge is gained and the production is scaled up. Every change in the production, specifications or test procedures shall be adequately recorded.

18.8. **Laboratory controls-**

18.8.1. While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated they shall be scientifically sound.

18.8.2. A system for retaining reserve samples of all batches shall be in place. This system shall ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.

18.8.3. Expiry and retest dating as referred to in paragraph 11.5 applies to existing APIs

used in clinical trials. For new APIs paragraph 11.5 does not normally apply in early stages of clinical trials.

18.9. **Documentation-**

18.9.1. A system shall be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

18.9.2. The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials shall be appropriately documented.

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

PART XIII

REQUIREMENTS OF PLANT AND EQUIPMENT

1. External preparations:- The following equipment is recommended for the manufacture of 'External preparations', i.e., Ointments, Emulsions, Lotions, Solutions, Pastes, Creams, Dusting Powders and such identical products used for external applications whichever is applicable, namely:-

(1) Mixing and storage tanks preferably of stainless steel or any other appropriate material;

(2) Jacketed Kettle stainless steel container (steam, gas or electrically heated);

(3) Mixer (Electrically operated);

(4) Planetary mixer;

(5) A colloid mill or a suitable emulsifier;

(6) A triple roller mill or an ointment mill;

(7) Liquid filling equipment (Electrically operated); and

(8) Jar or tube filling equipment.

Area- A minimum area of thirty square meters for basic installation and ten square meters for ancillary area is recommended.

2. Oral Liquid Preparations:- The following equipment is recommended for the manufacture of oral or internal use preparations, i.e., Syrups, Elixirs, Emulsions and Suspensions, whichever is applicable, namely-

(1) Mixing and storage tanks preferably of Stainless steel or any other appropriate material;

(2) Jacketed Kettle or Stainless steel tank (steam, gas or electrically heated);

(3) Portable stirrer (Electrically operated);

(4) A colloid mill or suitable emulsifier (Electrically operated);

(5) Suitable filtration equipment (Electrically operated);

(6) Semi-automatic or automatic bottle filling machine;

(7) Pilfer proof cap sealing machine;

(8) Water distillation unit or deionizer; and

(9) Clarity testing inspection units.

Area- A minimum area of thirty square meters for basic installation and ten square meters for ancillary area is recommended.

3. Tablets- The Tablet section shall be free from dust and floating particles and may be air-conditioned. For this purpose, each tablet compression machine shall be isolated into cubicles and connected to a vacuum dust collector or an exhaust system. For effective operations, the tablet production department shall be divided into four distinct and separate sections as follows:-

(a) Mixing, Granulation and Drying section;

(b) Tablet compression section;

(c) Packaging section (strip or blister machine wherever required); and

(d) Coating section (wherever required).

3.1. The following electrically operated equipment are recommended for the manufacture of compressed tablets and hypodermic tablets, namely:-

(a) **Granulation-cum-Drying section-**

(1) Disintegrator and sifter;

(2) Powder mixer;

(3) Mass mixer or Planetary mixer or Rapid mixer granulator;

(4) Granulator wherever required;

(5) Thermostatically controlled hot air oven with trays (preferably mounted on a trolley) or Fluid bed dryer; and

(6) Weighing machines;

(b) **Compression section-**

(1) Tablet compression machine, single or multi punch or rotatory;

(2) Punch and dies storage cabinets;

(3) Tablet de-duster;

(4) Tablet Inspection unit or belt;

(5) Dissolution test apparatus wherever required;

(6) In-process testing equipment like single pan electronic balance, hardness tester, friability and disintegration test apparatus; and

(7) Air-conditioning and dehumidification arrangement (wherever necessary).

(c) **Packaging section-**

(1) Strip or blister packaging machine;

(2) Leak test apparatus (vacuum system);

(3) Tablet counters (wherever applicable); and

(4) Air-conditioning and dehumidification arrangement (wherever applicable).

Area- A minimum area of sixty square meters for basic installation and twenty square meters for ancillary area is recommended for un-coated tablets.

(d) **Coating section-**

(1) Jacketed kettle stainless steel container or any other appropriate material (steam, gas or electrically heated for preparing coating suspension);

(2) Coating pan (Stainless steel);

(3) Polishing pan (where applicable);

(4) Exhaust system (including vacuum dust collector);

(5) Air conditioning and Dehumidification Arrangement; and

(6) Weighing machine.

3.2. The coating section shall be made dust free with suitable exhaust system to remove excess powder and fumes resulting from solvent evaporation. It shall be air-conditioned and dehumidified, wherever considered necessary.

Area- A minimum additional area of thirty square meters for coating section for basic installation and ten square meters for ancillary area is recommended. Separate area and equipment for mixing, granulation, drying, tablet compression, coating and packing shall be provided for Penicillin group of drugs on the lines indicated above. In case of operations involving dust and floating particles, care shall be exercised to avoid cross-contamination.

3.3. The manufacture of Hypodermic tablets shall be conducted under aseptic conditions in a separate air-conditioned room, the walls of which shall be smooth and washable. The granulation, compression and packing shall be done in this room.

3.4. The manufacture of effervescent and soluble tablets shall be carried out in air-conditioned and dehumidified areas.

4. Powders:- The following equipment is recommended for the manufacture of powders, namely:-

(1) Disintegrator;

(2) Mixer (electrically operated);

(3) Sifter;

(4) Stainless steel vessels and scoops of suitable sizes;

(5) Filling equipment; and

(6) Weighing machine.

In the case of operation involving floating particles of fine powder, a suitable exhaust system shall be provided. Workers shall be provided with suitable masks during operation.

Area- A minimum area of thirty square meters is recommended to allow for the basic installations. Where the actual blending is to be done on the premises, an additional room shall be provided for the purpose.

5. Capsules:- For the manufacture of capsules, separate enclosed area suitably air-conditioned and dehumidified with an airlock arrangement shall be provided. The following equipment is recommended for filling Hard Gelatin Capsules, namely:-

(1) Mixing and blending equipment (electrically or power driven);

(2) Capsule filling units;

(3) Capsules counters (wherever applicable);

(4) Weighing machine;

(5) Disintegration test apparatus; and

(6) Capsule polishing equipment.

Separate equipment and filling and packaging areas shall be provided in penicillin and non-penicillin sections. In case of operations involving floating particles of fine powder, a suitable exhaust system shall be provided. Manufacture and filling shall be carried out in air-conditioned areas. The room shall be dehumidified.

Area- A minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area each for penicillin and non-penicillin sections is recommended.

6. Surgical dressing- The following equipment is recommended for the manufacture of surgical dressings other than Absorbent Cotton Wool, namely-

(1) Rolling machine;

(2) Trimming machine;

(3) Cutting equipment;

(4) Folding and pressing machine for gauze;

(5) Mixing tanks for processing medicated dressing;

(6) Hot air dry oven;

(7) Steam steriliser or dry heat steriliser or other suitable equipment; and

(8) Work tables and benches for different operations.

Area- A minimum area of thirty square meters is recommended to allow for the basic installations. In case medicated dressings are to be manufactured, another room with a minimum area of thirty square meters shall be provided.

7. Ophthalmic preparations:- For the manufacture of ophthalmic preparations, separate enclosed areas with air lock arrangement shall be provided. The following equipment is recommended for manufacture under aseptic conditions of Eye Ointment, Eye lotions and other preparations for external use, namely-

(1) Thermostatically controlled hot air ovens (preferably double ended);

(2) Jacketed kettle or Stainless steel tanks (steam, gas or electrically heated);

(3) Mixing and storage tanks of stainless steel or Planetary mixer;

(4) Colloid mill or ointment mill;

(5) Tube filling and crimping equipment (semi-automatic or automatic filling machines);

(6) Tube cleaning equipment (air jet type);

(7) Tube washing and drying equipment, if required;

(8) Automatic vial washing machine;

(9) Vial drying oven;

(10) Rubber bung washing machine;

(11) Sintered glass funnel, Seitz filter or filter candle (preferably cartridge and membrane filters);

(12) Liquid filling equipment (semi-automatic or automatic filling machines);

(13) Autoclave (preferably ventilator autoclave);

(14) Air-conditioning and dehumidification arrangement (preferably centrally air-conditioned and dehumidification system); and

(15) Laminar air flow units.

Area: (1) A minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area is recommended. Manufacture and filling shall be carried out in air-conditioned areas under aseptic conditions. The rooms shall be further dehumidified as considered necessary, if preparations containing antibiotics are manufactured.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix up.

8. Pessaries and Suppositories:-

(1) The following equipment is recommended for manufacture of Pessaries and Suppositories, namely-

(i) Mixing and pouring equipment;

(ii) Moulding equipment; and

(iii) Weighing machine.

Area- A minimum area of twenty square meters is recommended to allow for the basic installation.

(2) In the case of pessaries manufactured by granulation and compression, the requirements as indicated under "item 3 of Tablet" shall be provided.

9. Inhalers and Vitrallae:- The following equipment is recommended for manufacture of Inhalers and Vitrallae, namely-

(1) Mixing equipment;

(2) Graduated delivery equipment for measurement of the medicament during filling; and

(3) Sealing equipment.

Area: An area of minimum twenty square metres is recommended for the basic installations.

10. Repacking of drugs and pharmaceutical chemicals:- The following equipment is recommended for repacking of drugs and pharmaceuticals, chemicals, namely:—

(1) Powder disintegrator;

(2) Powder sifter (Electrically operated);

(3) Stainless steel scoops and vessels of suitable sizes;

(4) Weighing and measuring equipment;

(5) Filling equipment (semi-automatic or automatic machine); and

(6) Electric sealing machine.

Area- An area of minimum thirty square metres is recommended for the basic installation. In case of operations involving floating particles of fine powder, a suitable exhaust system shall be provided.

11. Parenteral Preparations:- The whole operation of manufacture of parenteral preparations (small volume injectables and large volume parenterals) in glass and plastic containers may be divided into the following separate areas or rooms, namely-

11.1. **Parenteral preparations in glass containers-**

(1) Water management area: This includes water treatment and storage;

(2) Containers and closures preparation area: This includes washing and drying of ampoules, vials, bottles and closures;

(3) Solution preparation area: This includes preparation and filtration of solution;

(4) Filling capping and sealing area: This includes filling and sealing of ampoules or filling, capping and sealing of vials and bottles;

(5) Sterilisation area;

(6) Quarantine area;

(7) Visual inspection area; and

(8) Packaging area.

The following equipment is recommended for different above mentioned areas, namely-

1. **Water management area-**

(1) Reverse Osmosis (RO) or Electro-deionisation (EDI) water treatment unit;

(2) Distillation (multi column with heat exchangers) unit;

(3) Thermostatically controlled water storage tank;

(4) Transfer pumps; and

(5) Service lines for carrying water into user areas through continuously circulating pipe work loop. The Material of Construction (MOC) for the storage tank and circulating pipe line shall be of SS-316 L Grade.

2. **Containers and closures preparation area-**

(1) Automatic rotary ampoule or vial or bottle washing machine having separate air, water, distilled water jets;

(2) Automatic closures washing machine;

(3) Storage equipment for ampoules, vials, bottles and closure;

(4) Dryer or steriliser (double ended);

(5) Dust proof storage cabinets; and

(6) Stainless steel benches or stools.

3. **Solution preparation area-**

(1) Solution preparation and mixing stainless steel tanks and other containers;

(2) Portable stirrer;

(3) Filtration equipment with cartridge and membrane filters or bacteriological filters;

(4) Transfer pumps; and

(5) Stainless steel benches or stools.

4. **Filling, capping and sealing area-**

(1) Automatic ampoule or vial or bottle filling, sealing and capping machine under laminar air flow work station;

(2) Gas lines (Nitrogen, Oxygen and Carbon di-oxide), wherever required; and

(3) Stainless steel benches or stools.

5. **Sterilisation area-**

(1) Steam steriliser (preferably with computer control for sterilisation cycle along with trolley sets for loading or unloading containers before and after sterilisation);

(2) Hot Air steriliser (preferably double ended); and

(3) Pressure leak test apparatus.

6. **Quarantine area-**

(1) Storage cabinets; and

(2) Raised platforms or steel racks.

7. **Visual inspection area-**

(1) Visual inspection units (preferably conveyor belt type and composite white and black assembly supported with illumination); and

(2) Stainless steel benches or stools.

8. **Packaging area-**

(1) Batch coding machine (preferably automatic);

(2) Labeling unit (preferably conveyor belt type); and

(3) benches or stools.

Area: (1) A minimum area of one hundred and fifty square meters for the basic installation and an ancillary area of one hundred square meters for Small Volume Injectable are recommended. For Large Volume Parenterals, an area of one hundred and fifty square meters each for the basic installation and for ancillary area is recommended. These areas shall be partitioned into suitable enclosures with airlock arrangements.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix-up.

(3) Packaging materials for large volume Parenteral shall have a minimum area of one hundred square meters.

11.2. **Parenteral preparations in plastic containers by Form-Fill-Seal or Blow, Fill-Seal technology**- The whole operation of manufacture of large volume parenteral preparations in plastic containers including plastic pouches by automatic (all operations in one station) Form-Fill-Seal machine or by semi-automatic blow moulding, filling-cum-sealing machine may be divided into following separate areas or rooms, namely-

(1) Water management area;
(2) Solution preparation area;
(3) Container moulding-cum-filling and sealing area;
(4) Sterilisation area;
(5) Quarantine area;
(6) Visual inspection area; and
(7) Packaging area.

The following equipment is recommended for different above mentioned areas namely-

1. **Water management area-**

(1) RO or Electro-deionisation (EDI) water treatment unit;

(2) Distillation unit (multi column with heat exchangers);

(3) Thermostatically controlled water storage tank;

(4) Transfer pumps; and

(5) Service lines for carrying water into user areas through continuously circulating pipe work loop. The Material of Construction (MOC) for the storage tank and circulating pipe line shall be of SS-316 L Grade.

2. **Solution preparation area-**

(1) Solution preparation and storage tanks;

(2) Transfer pumps; and

(3) Cartridge and membrane filters.

3. **Container moulding-cum-filling and sealing area-**

(1) Sterile Form-Fill-Seal machine (all operations in one station with built-in laminar air flow work station having integrated container output conveyor belt through pass box); and

(2) Arrangement for feeding plastic granules through feeding-cum-filling tank into the machine.

4. **Sterilisation area-** Super heated steam steriliser (with computer control for sterilisation cycle along with trolley sets for loading or unloading containers for sterilisation).

5. **Quarantine area-** Adequate number of platforms or racks with storage system.

6. **Visual inspection area-** Visual inspection unit (with conveyor belt and composite white and black assembly supported with illumination).

7. **Packaging area-**

(1) Pressure leak test apparatus (pressure belt or rotating disc type);

(2) Batch coding machine (preferably automatic); and

(3) Labeling unit (preferably conveyor belt type).

Area: (1) A minimum area of two hundred and fifty square meters for the basic installation and an ancillary area of one hundred and fifty square meters for large volume parenteral preparations in plastic containers by Form-Fill-Seal technology is recommended. These areas shall be partitioned into suitable enclosures with air-lock arrangements.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix up.

(3) Packaging materials for large volume Parenteral shall have a minimum area of one-hundred square meters.

6. These rules shall come into force for implementation as under:—

Category of manufacturers **[Based on turnover (INR)]**	**Time line for implementation**
Large manufacturers (Turnover>250 crores)	Six months from the date of publication of these rules.
Small and Medium manufacturers (Turnover ≤ 250 crores)	Twelve months from the date of publication of these rules.

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ARADHANA PATNAIK, Jt. Secy.

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