DRUG

NATIONAL  AUTHORITY

GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS

National Drug Authority
Secretariat Office
Plot 46-48, Lumumba Avenue
P. O. Box 23096
Kampala, Uganda
Tel: +256 - 0414 - 255665/347391/2
Fax: +256 - 0414 - 255758
E-mail: ndaug@nda.or.ug
Website: http://www.nda.or.ug

Authorization of these guidelines

	Authorized by
Title	Executive Secretary/Registrar
Name	Gordon K. Sematiko
Signature	
Date	24th May 2013

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INTRODUCTION

National Drug Authority (NDA) was established in 1993 by the National Drug Policy and Authority Statute which in 2000 became the National Drug Policy and Authority (NDP/A) Act, Cap. 206 of the Laws of Uganda (2000 Edition). The Act established a National Drug Policy and National Drug Authority to ensure the availability, at all times, of essential, efficacious and cost-effective drugs to the entire population of Uganda, as a means of providing satisfactory healthcare and safeguarding the appropriate use of drugs.

The Vision of NDA: *"A world class drug regulatory agency effectively protecting and promoting public health".*

The Mission of NDA: "*To ensure access to quality, safe and efficacious human and veterinary medicines and other healthcare products through the regulation and control of their production, importation, distribution and use*".

The National Drug Policy and Authority Act, Sections 2(d) and 5(e) mandate NDA to exercise control on manufacture, production and on the quality of drugs. One of the means of achieving this is through compliance with Good Manufacturing Practice (GMP) requirements as laid down in these guidelines. These guidelines shall therefore be used for GMP inspection of local and foreign manufacturers of medicinal products**.**

Local and foreign manufacturers of medicinal products shall be subjected to periodic GMP inspections by NDA and those that are GMP compliant shall be issued with GMP compliance certificates.

Objective of these guidelines

These guidelines are intended to provide guidance to the pharmaceutical manufacturer on how to comply with GMP.

These guidelines shall form the basis of GMP inspection by NDA as one of the requirements for registration of pharmaceutical products in the Uganda.

Policy

These guidelines are developed in accordance with the National Drug Policy and Authority Act Cap 206, Sections 2(d): *"to improve government regulation and control on manufacture, production, importation, exportation, marketing and use of drugs"; and Section 5(e): "control the quality of drugs".*

Scope

These guidelines apply to all manufacturers of medicinal products within and outside Uganda whose products are registered or subjected to registration in Uganda. The guidelines also apply to manufacturers irrespective of their size, type of products, product range or location of the manufacturing facilities including production units in hospitals.

INTERPRETATION

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Active pharmaceutical ingredient: A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

Authorized person: A person responsible for the release of batches of finished product for sale or distribution. The batch documentation of a batch of a finished product must be signed by an authorized person from the production department and the batch test results by an authorized person from the quality control department for batch release.

Batch (or lot): A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number (or lot number): A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

Batch numbering system: standard operating procedure describing the details of the batch numbering.

Batch records: All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bulk product: Any product that has completed all processing stages up to, but not including, final packaging.

Calibration: The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Certification: The final review and formal approval of a validation or revalidation, followed by approval of a process for routine use.

Challenge tests/worst case: A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, that pose the greatest chance of process or product failure when compared with ideal conditions.

Clean area: An area with defined environmental control of particulate and microbial contamination; constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Consignment (or delivery): The quantity of starting material, or of a drug product, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Critical process: A process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination: Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Finished product: A product that has undergone all stages of production, including packaging in its final container and labeling.

In-process control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Installation qualification: The performance of tests to ensure that the installations (such as machines, measuring devices, utilities, manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

Intermediate product: Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Large-volume parenterals: Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

Manufacture: All operations of purchase of materials and products, production, packaging, quality control, release, storage, shipment of finished products, and the related controls.

Manufacturer: A company that carries out at least one step of manufacture.

Manufacturing process: The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

Marketing authorization (product licence, registration certificate): A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.

Master formula: A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master record: A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Operational qualification: Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

Packaging: All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Packaging material: Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical product: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Qualification of equipment: The act of planning, carrying out and recording the results of tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.

Quality assurance: See Chapter 2

Quality control: See Chapter 2

Quarantine: The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Reconciliation: A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

Recovery (or blending): The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.

Reprocessing: The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Returned product: Finished product sent back to the manufacturer.

Revalidation: Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

Specification: A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Standard operating procedure (SOP): An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

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

System: A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation: The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Validation: The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes—including equipment, buildings, personnel and materials—are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

Validation protocol (or plan): A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process—or a part thereof—for routine use.

Validation report: A document in which the records, results and evaluation of a completed validation program are assembled. It may also contain proposals for the improvement of processes and/or equipment.

CHAPTER 1: QUALITY MANAGEMENT

Principle

The manufacturer must assume responsibility of quality of medicinal products manufactured so as to ensure that they are fit for their intended use, comply with the requirements of market authorization and do not place patients at risk due inadequate safety, quality or efficacy. The achievement f this objective is the responsibility of management and requires the participation and commitment by staff in different departments and at all levels within the company, by the company's suppliers and distributors.

To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality assurance incorporating GMP and thus Quality control. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance systems should be adequately resourced with competent personnel and suitable and sufficient premises, equipment and facilities.

1.1 The basic concepts of Quality assurance, GMP, and Quality control are inter-related aspects of Quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

Quality assurance

1.2 "Quality assurance" 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 objective of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

(a) medicinal products are designed and developed in a way that takes account of the requirements of GMP, GLP and GCP;
(b) production and control operations are clearly specified in a written form and GMP requirements are adopted;
(c) managerial responsibilities are clearly specified in job descriptions;
(d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
(e) all necessary controls on starting materials, intermediate products, and bulk products and any other in-process controls, calibrations, and validations are carried out;
(f) the finished product is correctly processed and checked, according to the defined procedures;
(g) medicinal products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in

accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of medicinal products;

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

(i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system.

(j) deviations are reported, investigated and recorded

(k) there is a system for approving changes that may have an impact on product quality

Good manufacturing practices (GMP)

1.3 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization and product specifications. GMP rules are directed primarily to diminishing the risks, inherent in any pharmaceutical production that cannot be prevented completely through the testing of final products. Such risks are essentially of two types: cross-contamination (in particular by unexpected contaminants) and mix-ups (confusion) caused by false labels being put on containers. The basic requirements of GMP are that:

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing medicinal products of the required quality that comply with their specifications;

(b) critical steps of manufacturing processes and any significant changes made to the processes are validated;

(c) all necessary facilities are provided, including:

(i) appropriately qualified and trained personnel;
(ii) adequate premises and space;
(iii) suitable equipment and services;
(iv) correct materials, containers, and labels;
(v) approved procedures and instructions;
(vi) suitable storage and transport, and;
(vii) adequate personnel, laboratories, and equipment for in-process controls under the responsibility of the production management.

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

(e) operators are trained to carry out procedures correctly;

(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;

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

(h) the proper storage and distribution of the products minimizes any risk to their quality;
(i) a system is available to recall any batch of product from sale or supply;
(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent recurrence.

Quality control

1.4 Quality control is the part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are neither released for use, nor for sale or supply, until their quality has been judged to be satisfactory. Quality control should not be confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

Each manufacturer should have a quality control department. The independence of quality control from production is considered fundamental. The quality control department should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

(a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
(b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.
(c) Test methods must be well documented and validated.
(d) Records must be made (manually and/or by recording instruments) 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 marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labeled.
(f) Records must be made of the results of inspecting and testing starting materials, 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) No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from the production department together with the authorized person from the quality control department.

(h) Sufficient reference samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

1.5 The quality control department as a whole will also have other duties, such as to establish, validate, and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labeling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

1.6 Assessment of finished products should 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.

1.7 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Sanitation and hygiene

A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of drug products. 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 should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *hygiene,* please refer to chapter 2, “Personnel”, and for *sanitation* to chapter 3, “Premises”.)

CHAPTER 2: PERSONNEL

Principle

The establishment and maintenance of a satisfactory system of quality assurance 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 should be clearly understood by the individuals concerned and recorded.

General

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

2.2 The manufacturer must have an organization chart. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP.

2.3 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

2.4 Steps should be taken to prevent unauthorized people from entering production, storage, and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

2.5 Key personnel include the head of production, the head of quality control, the head of sales/distribution, and the authorized person(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

2.6 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by Section 19 of the NDP/A (issue of licence) regulations, 1995 or national legislations. Their education should include the study of an appropriate combination of;

(a) pharmaceutical sciences and technology,
(b) chemistry (analytical or organic) or biochemistry,
(c) chemical engineering,
(d) microbiology,
(e) pharmacology and toxicology,

2.7 They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such 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 quality control of pharmaceutical products.

2.8 The heads of the production and quality control departments generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

(a) the authorization of written procedures and other documents, including amendments;
(b) the 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 quality assurance;
(f) the approval and monitoring of suppliers of materials;
(g) the approval and monitoring of contract manufacturers;
(h) the designation and monitoring of storage conditions for materials and products;
(i) the retention of records;
(j) the monitoring of compliance with GMP requirements;
(k) the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

2.9 The head of the production department generally has the following responsibilities:

(a) to ensure that products are produced and stored according to 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 before they are made available to the quality control department;
(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 made available;
(f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

2.10 The head of the quality control department generally has the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
(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 quality control procedures;

(e) to approve and monitor analyses 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 done;
(h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Training

2.11 The manufacturer should provide training in accordance with a written programme for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.12 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available, approved by the head of either production or quality control, as appropriate. Training records should be kept.

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

2.14 The concept of quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personal hygiene

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

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

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

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

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

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

2.21 Eating, drinking, smoking, chewing, and storage of plants, food, drinks, smoking material, and personal medicines should not be permitted in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.

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

2.23 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the guidelines under annexes.

CHAPTER 3: PREMISES

Principle

Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

General

3.1 Premises should 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.

3.2 Premises used for the manufacture of drug products should be suitably designed and constructed to facilitate good sanitation.

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

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

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

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

Production Area

3.7 In order to minimize 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 sensitizing materials (e.g., penicillins) or biological preparations (e.g., live microorganisms). The production of certain additional products, such as certain antibiotics, hormones, cytotoxic substances, highly active medicinal products, and non-medicinal products, should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products. 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 are made.

3.8 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.9 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

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

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

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

3.13 Production areas should be effectively ventilated, with air-control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled, to the operations undertaken, and to the external environment. These areas should be regularly monitored during production and non-production periods to ensure compliance with their design specifications.

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

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

Storage areas

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

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

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

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

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

3.21 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

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

3.23 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labeling, and special attention should be paid to the safe and secure storage of these materials.

Weighing Areas

3.24 The weighing of starting materials and the estimation of yield by weighing should usually be carried out in separate weighing areas designed for that use, for example with provisions for dust control.

Quality control Areas

3.25 Quality control laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other.

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

3.27 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

3.28 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.

Ancillary areas

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

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

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

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

CHAPTER 4: EQUIPMENT

Principle

The layout, design and location of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

General

4.1 Manufacturing equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

4.2 Repairs and maintenance operations should not present any hazard to the quality of the products.

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

4.4 Washing and cleaning equipment should be chosen and used so as not to be a source of contamination.

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

4.6 Production equipment should 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.

4.7 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated and checked at defined intervals using appropriate methods. Adequate records of such tests should be maintained.

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

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

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

4.11 Water for pharmaceutical use (PW, WFI) and other water pipes should be sanitized, according to written procedures that detail the action limits for microbial contamination and the measures to be taken.

4.12 Control-laboratory equipment and instruments should be suited to the testing procedures undertaken.

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

CHAPTER 5: DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications 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 authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. Documents must be free from errors and available in writing. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General

5.1 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

5.2 Documents should be approved, signed, and dated by appropriate authorized persons. No document should be changed without authorization.

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

5.4 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

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

5.6 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

5.7 Records should 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 and associated standard operating procedures should be retained for at least one year after the expiry date of the finished product.

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

Labels

5.9 Labels applied to containers, equipment, or premises should 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 (for example: quarantined, accepted, rejected, or clean).

5.10 All finished drug products should be identified by labeling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;

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

(c) the batch number assigned by the manufacturer;

(d) the expiry date 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 or the person responsible for placing the product on the market.

5.11 For reference standards, the label or accompanying document should indicate concentration, date of manufacture, expiry date, date the closure is first opened, and storage conditions, where appropriate.

Documents required

Specifications and testing procedures

5.12 There should be appropriately approved and dated specifications and testing procedures for identity, content, purity, and quality for starting and packaging materials, and finished products; where appropriate, they should also be available for intermediate and bulk products. Specifications for water, solvents, and reagents (e.g., acids and bases) used in production should be included.

5.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routing testing.

5.14 Each specification and test procedure should be approved and maintained by the quality control unit.

5.15 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

5.16 Pharmacopoeias, reference standards, reference spectra, and other reference materials should be available in the quality control laboratory.

Specifications for starting and packaging materials

5.17 Specifications for starting and primary or printed packaging materials should provide, if applicable,

(a) description of the materials, including:

(i) the designated name (if applicable, the International Nonproprietary Name) and internal code reference;
(ii) the reference, if any, to a pharmacopoeial monograph;
(iii) qualitative and quantitative requirements with acceptance limits.
(iv) the approved supplier;
(v) a specimen of printed materials;

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

(c) storage conditions and precautions;

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

Packaging material should conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains. The material should be examined for critical and major physical defects as well as for the correctness of identity markings.

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

Specifications for intermediate and bulk products

5.19 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used in the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

5.20 Specifications for finished products should include:

(a) the designated name of the product and the code reference where applicable;
(b) the designated name(s) of the active ingredient(s) (if applicable, the International Nonproprietary Name(s);
(c) the formula or a reference to the formula;
(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.

Master formulae and Processing instructions

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

5.22 The master formula should include:

(a) the name of the product, with a product reference code relating to its specification;
(b) a description of the dosage form, strength of the product, and batch size;
(c) a list of all starting materials to be used (if applicable, with the International Nonproprietary Names), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

5.23 The processing Instructions should include:

(a) a statement of the processing location and the principal equipment to be used;
(b) the methods, or reference to the methods, to be used for preparing the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing;
(c) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
(d) the instructions for any in-process controls with their limits;
(e) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
(f) any special precautions to be observed.

Packaging instructions

5.24 There should be formally approved packaging instructions for each product pack size and type. These should normally include, or make reference to the following:

(a) the name of the product;
(b) a description of its pharmaceutical form, strength, and method of application where applicable;
(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 operations begin;
(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
(h) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

5.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved master formula. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

5.26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

5.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

(a) the name of the product;
(b) the number of the batch being manufactured;
(c) dates and times 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 operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g., weighing);
(f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

(g) any relevant processing operation or event and the major equipment used;
(h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
(i) 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;
(j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

5.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions, and the method of preparing such records should be designed to avoid transcription errors.

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

5.30 The following information should be recorded at the time each action is taken and, after completion, the date and the person responsible should be clearly identified by signature or electronic password:
(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(s) and time(s) of the packaging operations;
(c) the name of the responsible person carrying out the packaging operation;
(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 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 batch number, expiry date, and any additional overprinting;
(h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
(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.

Procedures (SOPs) and records

Receipts

5.31 There should be written standard procedures and records for the receipt of each delivery of each starting material and primary and printed packaging material.

5.32 The records of the receipts should include:
(a) the name of the material on the delivery note and the containers;
(b) the "in-house" name and/or code of material if different from (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;
(h) any relevant comment (e.g., state of the containers).

5.33 There should be written standard operating procedures for the internal labeling, quarantine, and storage of starting materials, packaging materials, and other materials, as appropriate.

Sampling

5.34 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

5.35 The sampling instructions should 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(s) of sample(s) to be taken;
(e) instructions for any required subdivision of the sample;
(f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling;
(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

Testing

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

5.37 Analysis records should include at least the following data:
(a) the name of the material or product and, where applicable, dosage form;
(b) the batch number and, where appropriate, the manufacturer and/or supplier;
(c) references to the relevant specifications and testing procedures;
(d) test results, including observations and calculations, and reference to any specifications (limits);

(e) dates of testing;
(f) the initials of the persons who performed the testing;
(g) the initials of the persons who verified the testing and the calculations, where appropriate;
(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

Others

5.38 There should be a standard operating procedure 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.

5.39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

5.40 The standard operating procedure for batch numbering should assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.

5.41 Batch-number allocation should be immediately recorded, e.g., in a logbook. The record should include date of allocation, product identity, and size of batch.

5.42 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

5.43 Records should be maintained for the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

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

5.45 Logbooks should be kept with major and critical equipment and should record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

5.46 Clear standard operating procedures should be available for major items of manufacturing and test equipment and placed in close proximity to the equipment.

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

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

CHAPTER 6: GOOD PRACTICES IN PRODUCTION

Principle

Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

6.1 Production should be performed and supervised by competent people.

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

6.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

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

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

6.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms used should be labeled 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 should also mention the stage of production.

6.7 Access to production premises should be restricted to authorized personnel.

6.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

6.9 In-process controls are mostly performed within the production area. They should not carry any risk for the quality of the product.

Prevention of cross-contamination and bacterial contamination in production

6.10 When dry materials and products are used in production, special pre-cautions should be taken to prevent the generation and dissemination of dust.

6.11 Contamination of a starting material or of a product by another material or product has to be avoided. This risk of accidental cross-contamination arises from the uncontrolled

release of dust, gases, 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 sensitizing 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 and/or over a long time.

6.12 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

(a) production in segregated areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
(b) providing appropriate airlocks, pressure differentials, and air extraction;
(c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
(d) wearing protective clothing in areas where products with special risk of cross-contamination are processed;
(e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
(f) using a "closed system" of production;
(g) testing for residues;
(h) using cleanliness status labels on equipment.

6.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

6.14 Production areas where susceptible products are processed should undergo periodic microbiological monitoring.

Validation

6.15 Validation studies should reinforce Good Manufacturing Practices and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

6.16 Whenever a new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to consistently yield a product of the required quality.

6.17 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.

6.18 Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

Starting materials

6.19 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

6.20 Starting materials should be purchased only from suppliers named in the relevant specification 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 of benefit that all aspects of the production and control of the starting material in question, including handling, labeling, and packaging requirements as well as complaints and rejection procedures, are discussed between the manufacturer and the supplier.

6.21 For each consignment, the containers should be checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

6.22 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled, if required, with the prescribed data.

6.23 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

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

6.25 Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:

(a) the designated name of the product and the internal code reference where applicable;
(b) the batch number(s) given by the supplier and on receipt by the manufacturer, if any;
(c) where appropriate, the status of the contents (e.g., on quarantine, on test, released, rejected, returned, recalled);
(d) where appropriate, an expiry date or a date beyond which retesting is necessary.
(e) When fully computerized storage systems are used, not all of the above information need be in a legible form on the label.

6.26 There should 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 should be identified.

6.27 Only starting materials released by the quality control department and within their shelf-life should be used.

6.28 Starting materials should 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 labeled containers.

6.29 Each dispensed material and its weight or volume should be independently checked and the check recorded.

6.30 Materials dispensed for each batch of the final product should be kept together and conspicuously labeled as such.

6.31 All incoming materials should be quarantined immediately after receipt or processing, until they are released for use.

6.32 All materials and products should 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-in, first-out rule.

Processing operations: intermediate and bulk products

6.33 Before any processing operation is started, steps should 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.

6.34 Intermediate and bulk products should be kept under appropriate conditions.

6.35 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

6.36 Any necessary in-process controls and environmental controls should be carried out and recorded.

6.37 Means should be instituted of indicating failures of equipment or of services (e.g., water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. Production equipment should be cleaned according to detailed written procedures and stored only under clean and dry conditions.

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

6.39 Any significant deviation from the expected yield should be recorded and investigated.

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

Packaging materials

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

6.42 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

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

6.44 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

Packaging operations

6.45 When the program for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.

6.46 Before packaging operations are begun, steps should 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 previously used and not required for the current operation. The line clearance should be performed according to an appropriate checklist and recorded.

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

6.48 All products and packaging materials to be used should be checked on delivery to the packaging department for quality, identity and conformity with the packaging instructions.

6.49 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

6.50 Normally, filling and sealing should be followed as quickly as possible by labeling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

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

6.52 Special care should 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.

6.53 Checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly.

6.54 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

6.55 On-line control of the product during packaging should include at least 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;
(e) the correct functioning of line monitors.
(f) Samples taken away from the packaging line should not be returned.

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

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

6.58 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

Finished products

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

6.60 The evaluation of finished products and the documentation necessary for release of a product for sale are described in Chapter 7, “Good practices in quality control”.

Rejected, Recovered and Returned materials

6.61 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved by authorized personnel and recorded.

6.62 The reprocessing of rejected products should 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 authorized procedure after evaluation of the risks

involved. A record should be kept of the reprocessing. A reprocessed batch should be given a new batch number.

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

6.64 The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be considered by the quality control department.

6.65 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; they may be considered for resale, re-labelling, or bulking with a subsequent batch only after they have been critically assessed by the quality control department 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 should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover the active ingredient may be possible. Any action taken should be appropriately recorded.

Waste materials

6.66 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

6.67 Waste material should not be allowed to accumulate. It should 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.

Miscellaneous

6.68 Rodenticides, insecticides, fumigating agents, and sanitizing materials should not be permitted to contaminate equipment, staring materials, packaging materials, in-process materials, or finished products.

CHAPTER 7: GOOD PRACTICES IN QUALITY CONTROL

Principle

Quality control is concerned with sampling, specifications, and testing as well as with the organization, documentation, and release procedures that ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality control is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of quality control from production is considered fundamental to the satisfactory operation of Quality control. (see also Chapter 1)

General

7.1 Each holder of manufacturing authorization should have a Quality Control Department. This department should be independent from other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

7.2 The principle duties of the head of Quality Control and the Quality Control department as a whole are summarized in Chapter 1. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

Documentation

7.3 Laboratory documentation should follow the principles given in chapter 5. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department.

(a) Specifications;
(b) Sampling procedures;
(c) Testing procedures and records (including analytical worksheets and/or laboratory notebooks)
(d) Analytical reports and/or certificates;
(e) Data from environmental monitoring, where required;
(f) Validation records of test methods, where applicable;
(g) Procedures for and record for calibration of instruments and maintenance of equipment.

7.4 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.

7.5 For some kinds of data (e.g. analytical test results, yields, environmental controls,..) it is recommended that records be kept in a manner permitting trend evaluation.

7.6 In addition to the information which is part of the batch record, other original data such

as laboratory notebooks and/or records should be retained and readily available.

Sampling

7.7 The sample taking should be done in accordance with approved written procedures that describe:

(a) the method of sampling;
(b) the equipment to be used;
(c) the quantity of sample to be taken;
(d) instructions for any required sub-division of the sample;
(e) the type and condition of the sample container to be used;
(f) the identification of containers sampled;
(g) any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials
(h) the storage conditions
(i) instructions for the cleaning and storage of sampling equipment.

7.8 Reference samples should be representative of the batch of materials or products from which they are taken.

7.9 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.

7.10 Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit at least a full examination.

Control of starting materials and intermediate, bulk products

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

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

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

7.14 Care should 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 should be clean. Some particularly hazardous or potent materials may

require special precautions.

7.15 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

7.16 Each sample container should 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 signature of the person who has taken the sample; and
(e) the date of sampling.

Test requirements

Starting and packaging materials

7.17 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameters.

7.18 An identity test should be conducted on a sample from each container of starting material.

7.19 In lieu of 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 (see sections 10.7 and 10.8) and through on-site audits of the supplier's capabilities. (This does not affect section 7.18). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain the following information:

(a) identification of the issuing supplier, signature of the competent official, and statement of his or her qualifications;
(b) the name and batch number of the material tested;
(c) a statement of specifications and methods used; and
(d) a statement of test results obtained and the date of testing.

In-process control

7.20 In-process control records should be maintained and form a part of the batch records (see section 6.24).

Finished products

7.21 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

7.22 Products failing to meet the established specifications or any other relevant quality

criteria should be rejected. Reprocessing may be performed, if feasible, but the reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

Production record review

7.23 Production and control records should be reviewed and any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, 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 should be made and should include the conclusion and follow-up action.

Stability studies

7.24 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities, or dissolution profile) associated with the formulation in the marketed package.

7.25 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labeled storage conditions.

7.26 This mainly applies to the medicinal product in the package, in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

7.27 The on-going stability programme should be described in a written protocol following the general rules of Chapter 5 and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 4 and annex 5.

7.28 The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

(a) number of batch(es) per strength and different batch sizes, if applicable
(b) relevant physical, chemical, microbiological and biological test methods
(c) acceptance criteria
(d) reference to test methods
(e) description of the container closure system(s)
(f) testing intervals (time points)
(g) description of the conditions of storage (NDA recognised conditions for long term testing, consistent with the product labelling, should be used)

(h) other applicable parameters specific to the medicinal product.

7.29 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

7.30 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

7.31 Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.

7.32 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to them relevant competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 9 of the GMP Guide and in consultation with the National Drug Authority.

7.33 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

7.34 The quality control department should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

7.35 The quality control department should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

7.36 A written programme for ongoing stability determination should be developed and implemented to include elements such as:

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

(b) the complete 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 conclusions of the study.

7.37 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

Reagents and culture media

7.38 All reagents and culture media should be recorded upon receipt or preparation.

7.39 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labeled. The label should indicate the concentration, standardization factor, shelf-life, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

7.40 Both positive and negative controls should be applied to verify the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

7.41 Reference standards may be available in the form of official reference standards. Reference standards prepared by the producer should be tested, released, and then stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

7.42 Official reference standards should be used only for the purpose described in the appropriate monograph.

7.43 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization. All in-house reference standards should be based on official reference standards, when available.

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

CHAPTER 8: CONTRACT PRODUCTION AND ANALYSIS

Principle

Contract production and analysis 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. There must be a written contract between the contract giver and the contract accepter which clearly establishes
the duties of each party. The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility.

General

8.1 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

8.2 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

8.3 The contract should permit the contract giver to audit the facilities of the contract accepter.

8.4 In the case of contract analysis, the final approval for release must be given by the authorized person(s).

The contract giver

8.5 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work or tests required and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

8.6 The contract giver should provide the contract accepter with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract accepter is fully aware of any problems associated with the product, work, or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products.

8.7 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person(s).

The contract accepter

8.8 The contract accepter must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the

contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

8.9 The contract accepter should 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. Arrangements made between the contract accepter and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract accepter.

8.10 The contract accepter should refrain from any activity that may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

The contract

8.11 A contract should be drawn up between the contract giver and the contract accepter that specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and GMP. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

8.12 The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

8.13 The contract should describe clearly who is responsible for purchasing, testing, and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract accepter should take samples at the premises of the manufacturer.

8.14 Manufacturing, analytical, and distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

8.15 The contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the processing of information if the contract analysis shows that the tested product must be rejected.

CHAPTER 9: COMPLAINTS AND PRODUCT RECALL

Principle

All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.

Complaints

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

9.2 There should 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.

9.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the study of such problems.

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

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

9.6 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

9.7 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

9.8 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

Recalls

9.9 A person responsible for the execution and coordination of recalls should be designated, as well as sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency. This person should normally be independent of the sales and marketing organization. If this person is different from the authorized person, the latter should be made aware of any recall operation.

9.10 There should be established written procedures, regularly checked and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly at least down to the level of the hospital or pharmacy.

9.11 All competent authorities of all countries to which a given product may have been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

9.12 The distribution records should be readily available to the person(s) responsible for recalls, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

9.13 The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

9.14 The effectiveness of the arrangements for recalls should be evaluated from time to time.

9.15 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

CHAPTER 10: SELF-INSPECTION AND QUALITY AUDITS

Principle

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

Items for self-inspection

10.1 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items: personnel, premises, equipment, sanitation and hygiene, documentation, production and in-process controls, quality control, recall procedures & complaints management, maintenance of buildings and equipment, storage of starting materials and finished products, validation and revalidation programs, calibration of instruments or measurement systems, labels control, results of previous self-inspections and any corrective steps taken.

10.2 All self inspections should be conducted in an independent and detailed way by designated competent person (s) from the company who familiar with GMP.

10.3 The frequency at which self-inspections are conducted may depend on company requirements.

10.4 All self-inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

10.5 The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

10.6 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 (see chapter 8, "Contract production and analysis").

Suppliers' audits

10.7 The quality control department should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

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

CHAPTER 11: AUTHORIZED PERSON

11.1 The authorized person is defined as a person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale.

The role and position of the authorized person in the company

11.2 The authorized person as the overall quality controller will be a member of a team whose function includes the following major areas:

(a) implementation (and, when needed, establishment) of the quality system;
(b) participation in the development of the company's quality manual;
(c) supervision of the regular internal audits or self-inspections;
(d) oversight of the quality control department;
(e) participation in external audit (vendor audit);
(f) participation in validation programs.

11.3 Although authorized persons may not have line management responsibility for many activities within this function (although they should be involved in these activities as much as possible), they must be aware of any changes that may affect compliance with technical or regulatory requirements related to the quality of finished products. When any aspect of the company's operations is not in accordance with GMP guidelines or relevant legislation in force, the authorized person must bring this to the attention of senior management. This duty should be reflected in the authorized person's job description.

11.4 The availability of an authorized person should be a prerequisite for issue of a manufacturing licence (authorization). The authorized person (as well as persons responsible for production and quality control) must be approved by the drug regulatory authority. The license holder is obliged to inform the drug regulatory authority, or other responsible authority depending on national (regional) regulations, immediately if the authorized person is replaced unexpectedly. Such provisions will assure to a considerable degree the independence of the authorized person from the management of the company in the fulfillment of his or her duties even when under pressure to depart from professional and technical standards.

11.5 Two authorized persons may be designated: one for production and another for quality control. A company may have a complex structure, or operate at several locations, or both, and sometimes a separate authorized person may be designated who is responsible for the manufacture of clinical trial materials. Consequently it may be necessary to nominate several authorized persons, one of them having the responsibilities of the overall quality controller and the others responsible for site or branch operations. The person authorizing batch release should be independent from production activities.

11.6 The drug regulatory authority should approve the authorized person on the basis of his or her professional curriculum vitae. Authorized persons have duties not only to their employer but also to the competent authorities such as the drug regulatory authority. They should establish good working relations with inspectors and as far as possible provide information on request during site inspections.

11.7 The authorized person depends upon many working colleagues for the achievement of quality objectives, and may delegate some duties to appropriately trained staff while remaining the overall quality controller. It is therefore of paramount importance that he or she establish and maintain a good working relationship with other persons in positions of responsibility, especially those responsible for production and quality control.

Implementation of the quality system

11.8 Authorized persons have a personal and professional responsibility for ensuring that each batch of finished products has been manufactured in accordance with the marketing authorization, GMP rules and all related legal and administrative provisions. This does not necessarily mean that they must have directly supervised all manufacturing and quality control operations. They must be satisfied either directly or, more usually, by proper operation of quality systems that manufacturing and testing have complied with all relevant requirements. Therefore it is recommended that the manufacturer establishes and maintains a comprehensive quality system, covering all aspects of GMP.

11.9 The Authorized person must ensure that there is a quality manual describing the quality policy and objectives (commitment to quality) of the company, the organizational structure, responsibilities and authorities, together with a description of or references to documented quality system procedures.

11.10 The Authorized person must ensure that Research and development activities and the transfer of results of the developmental work to routine manufacture, including original product design, formulation, processes development and validation, should observe GMP principles as guidance. Batches produced for clinical trials must follow applicable GMP. It is of vital importance that the quality of routine production batches corresponds to a specification derived from the composition of development batches. The quality and safety of a pharmaceutical product depend on the application of appropriate procedures, based on GMP, leading to a product within the recognized specification. Standard procedures and recognized specifications cannot be separated.

Routine duties of an authorized person

11.11 Before approving a batch for release the authorized person doing so should always ensure that the following requirements have been met:

(a) The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned.

(b) The principles and guidelines of GMP have been followed.

(c) The principal manufacturing and testing processes have been validated, if different.
(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 quality control have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to and approval by the drug regulatory 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 quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines.
(h) Appropriate audits, self-inspections and spot-checks are being carried out by experienced and trained staff.
(i) Approval has been given by the head of the quality control department.
(j) All relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g., subdivision of output batches from a common input, factors associated with continuous production runs).

11.12 In certain circumstances the authorized person may be responsible for the release of intermediates manufactured on contract.

Education and training

11.13 The pool of expertise drawn upon for candidates for the position of authorized person may differ from country to country. The basic qualifications of a scientific education and practical experience for key personnel, including authorized persons, are outlined in chapter 3 (Personnel).

11.14 Additional requirements may include subjects such as principles of quality assurance and GMP, principles of good laboratory practice as applicable to research and development as well as to quality control, detailed knowledge of the authorized/qualified person's duties and responsibilities, of International Standards ISO 9000–9004 and relationships with suppliers, principles and problems of formulation of pharmaceutical preparations, pharmaceutical microbiology, and principles and practice of sampling and testing of starting materials, packaging components and finished dosage forms.

References

(a) Quality Assurance of Pharmaceuticals. A Compendium of Guidelines and Related Materials. Volume 2, Second updated edition. Good Manufacturing Practices and Inspection. Geneva, World Health Organization, 2007.
(b) GMP Guide – PE 009-7, Pharmaceutical Inspection Cooperation Scheme

Annex 1 Manufacture of sterile medicinal products

Section 1.01 Principle

The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.
Note: This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc.

Section 1.02 General

(a) The manufacture of sterile products should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

(b) The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.

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

In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. The “at rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.
The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms.

For the manufacture of sterile medicinal products 4 grades can be distinguished.

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.

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

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for these grades is given in the following table.

Grade	At rest [b] Maximum permitted number of particles/m³ equal to or above[a]		In operation [b] Maximum permitted number of particles/m³ equal to or above[a]	
	0.5µm[d]	5µm	0.5µm[d]	5µm
A	3,500	1[e]	3,500	1[e]
B[c]	3,500	1[e]	350,000	2,000
C[c]	350,000	2,000	3,500,000	20,000
D[c]	3,500,000	20,000	not defined[f]	not defined [f]

Notes:

(a) Particle measurement based on the use of a discrete airborne particle counter to measure the concentration of particles at designated sizes equal to or greater than the threshold stated. A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone, and is recommended for the surrounding grade B areas. For routine testing the total sample volume should not be less than 1 m³ for grade A and B areas and preferably also in grade C areas.

(b) The particulate conditions given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations. The particulate conditions for grade A “in operation” given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

(c) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate terminal filters such as HEPA for grades A, B and C.

(d) The guidance given for the maximum permitted number of particles in the “at rest” and “in operation” conditions correspond approximately to the cleanliness classes in the EN/ISO 14644-1 at a particle size of 0.5 µm.

(e) These areas are expected to be completely free from particles of size greater than 5 Lm. As it is impossible to demonstrate the absence of particles with any statistical significance, the limits are set to 1 particle /m3. During the clean room qualification it should be shown that the areas can be maintained within the defined limits.

(f) The requirements and limits will depend on the nature of the operations carried out.

Examples of operations to be carried out in the various grades are given in the table below (see also para. 11 and 12):

Grade	Examples of operations for terminally sterilised products (see para. 11)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for terminally sterilized products (see para. 12)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

(a) The areas should be monitored during operation in order to control the particulate cleanliness of the various grades.

(b) Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.

Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization.

Recommended limits for microbiological monitoring of clean areas during operation:

	Recommended limits for microbial contamination [a]			
Grade	Air sample cfu/m³	Settle plates (diam. 90 mm), cfu/4 hours[b]	Contact plates (diam. 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	-

Notes:

(i) These are average values.

(ii) Individual settle plates may be exposed for less than 4 hours.

(a) Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.

Section 1.03 Isolator Technology

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

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 laminar air flow may not exist in the working zone of all such devices. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least grade D.

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

(c) Monitoring should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system.

Section 1.04 Blow/Fill/Seal Technology

(a) 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 environment, provided that grade A/B clothing is used. The environment should 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 for terminal sterilisation should be installed in at least a grade D environment.

Because of this special technology particular attention should be paid to at least the following: equipment design and qualification, validation and reproducibility of cleaning-in-place and sterilisation-in-place, background clean room environment in which the equipment is located, operator training and clothing, and interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

Section 1.05 Terminally Sterilized Products

(a) Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where there is unusual risk to the product because of microbial contamination, for example, because the product actively supports microbial

growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels, preparation should be done in a grade C environment.

Filling of products for terminal sterilisation should be done in at least a grade C environment.
Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilisation.

Section 1.06 Aseptic Preparation

(a) Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.

(i) Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.
(ii) Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.
(iii) Transfer of partially closed containers, as used in freeze drying, should, prior to the completion of stoppering, be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.
(iv) Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

Section 1.07 Personnel

(a) Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.

(b) All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to 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 should be taken over their instruction and supervision.

(c) Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.

(d) High standards of personnel hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person

(e) Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.

(f) Wristwatches, make-up and jewellery should not be worn in clean areas.

(g) The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

The description of clothing required for each grade is given below:

(a) **Grade D:** Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

(b) **Grade C:** Hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

(c) **Grade A/B:** Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

(d) Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session.

(e) Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

Section 1.08 Premises

(a) In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

(b) To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.

(c) False ceilings should be sealed to prevent contamination from the space above them.

(d) Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

(e) Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.

(f) Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimise microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the “at rest” state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.

(g) Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

(h) A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.

(i) It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.

(j) A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

Section 1.09 Equipment

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

(b) As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out after complete reassembly wherever possible.

(c) When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.

(d) Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.

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

Section 1.10 Sanitation

(a) The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

(b) Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

(c) Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

Section 1.11 Processing

(a) Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.

(b) Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

(c) Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst case situations. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth but a contamination rate of less than 0.1% with 95% confidence limit is acceptable. The manufacturer should establish alert and action limits. Any contamination should be investigated.

(d) Care should be taken that any validation does not compromise the processes.

(e) Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.

(f) Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

(g) Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

(h) Containers and materials liable to generate fibres should be minimised in clean areas.

(i) Where appropriate, measures should be taken to minimise the particulate

contamination of the end product.

(j) Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.

(k) The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilization and use should be minimised and subject to a time-limit appropriate to the storage conditions.

(l) The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

(m) The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation which are related to the efficiency of the method to be used. Where appropriate the absence of pyrogens should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

(n) Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Noncombustible gases should be passed through micro-organism retentive filters.

(o) The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

Section 1.12 Sterilisation

(a) All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.

(b) 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 should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

(c) For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.

(d) Validated loading patterns should be established for all sterilisation processes.

(e) Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls.

(f) If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

(g) There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, 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 lot is, in fact, sterile.

(h) Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.

Section 1.13 Sterilisation by Heat

(a) Each heat sterilisation cycle should be recorded on a time/temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation and, where applicable, also checked against a second independent temperature probe located at the same position.

(b) Chemical or biological indicators may also be used, but should not take the place of physical measurements.

(c) Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.

(d) After the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised, unless it can be shown that any leaking container would not be approved for use.

Section 1.14 Moist Heat

(a) Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against 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 should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

(b) The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.

(c) Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

Section 1.15 Dry Heat

(a) The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

Section 1.16 Sterilisation by Radiation

(a) Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal 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 normally an acceptable method of sterilisation.

(b) During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.

(c) Biological indicators may be used as an additional control.

(d) Validation procedures should ensure that the effects of variations in density of the packages are considered.

(e) Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to a irradiation and those which have not.

(f) The total radiation dose should be administered within a predetermined time span.

Section 1.17 Sterilisation with Ethylene Oxide

(a) This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as reducing any residual gas and reaction products to defined acceptable limits for the type of product or material.

(b) Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

(c) Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimise the time before sterilisation.

(d) Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

(e) For each sterilisation cycle, records should 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 and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.

(f) After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.

Section 1.18 Filtration of Medicinal Products which cannot be sterilised in their final container

(a) Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasma's. Consideration should be given to complementing the filtration process with some degree of heat treatment.

(b) Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised microorganism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

(c) Fibre shedding characteristics of filters should be minimal.

(d) The integrity of the sterilised filter should be verified before use and should 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 should be determined during validation and any significant differences during routine manufacturing from this should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

(e) The same filter should not be used for more than one working day unless such use has been validated.

(f) The filter should not affect the product by removal of ingredients from it or by release of substances into it.

Section 1.19 Finishing of Sterile Products

(a) Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

(b) Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

(c) Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

Section 1.20 Quality Control

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

(b) In those cases where parametric release has been authorised, special attention should be paid to the validation and the monitoring of the entire manufacturing process.

(c) Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.:

(i) for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;

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

Annex 2 Manufacture of biological medicinal products for human use

Section 1.21 Scope

The regulatory procedures necessary to control biological products are in large part determined by the sources of products and methods of manufacture. Manufacturing procedures with the scope of these guidelines include:

(a) growth of strains of microorganisms and eukaryotic cells,
(b) extraction of substances from biological tissues, including human, animal and plant tissues (allergens),
(c) recombinant DNA (rDNA) techniques,
(d) hybridoma techniques,
(e) propagation of microorganisms in embryos or animals.

Biological products manufactured by these methods include allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole blood and plasma derivatives, immune sera, immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA) and diagnostic agents for *in vitro* use.

This guidance does not lay down detailed requirements for specific classes of biological products.

Section 1.22 Principle

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The way in which biological medicinal products are produced, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

Control of biological medicinal products usually involves biological analytical techniques which have a greater variability than physico-chemical determinations. In-process controls therefore take on a great importance in the manufacture of biological medicinal products.
The special properties of biological medicinal products require carefull consideration in any code of Good Manufacturing Practice and the development of this annex takes these points into account.

Section 1.23 Personnel

(a) The manufacturing establishment and its personnel shall be under the authority of a person who has been trained in the techniques used in manufacturing biological substances and who possesses the scientific knowledge upon which the manufacture of these products is based. The personnel shall include specialists with training

appropriate to the products made in the establishment.

(b) Personnel required to work in clean and aseptic areas should be selected with care, to ensure that they may be relied upon to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product microbiologically or otherwise. High standards of personal hygiene and cleanliness are essential. Staff should be instructed to report any conditions (e.g. diarrhea, coughs, infected shin or hair, wounds, fever of unknown origin) that may cause the shedding of abnormal numbers or types of organisms into the working environment. Health checks on personnel for such condition should be required before employment and periodically thereafter. Any changes in health status that could adversely affect the quality of the product shall preclude the person concerned form working in the production area.

(c) Only the minimum number of personnel required should be presenting clean and aseptic areas when work is in progress. Inspection and control procedures should be conducted from outside theses areas as for as possible.

(d) During the working day, personnel shall not pass from areas where live microorganisms or animals are handled to premises where other products or organisms are handled unless clearly defined decontamination measures, including a change of clothing and shoes, are followed. Persons not concerned with the production process should not enter the production area except for essential purposes, and in that case they shall be supplied with sterile protective clothing.

(e) The staff engaged in the manufacturing process should be separate from the staff responsible for animal care.

(f) The names and qualifications of those responsible for approving lot processing records (protocols) should be registered with the national control authority.

(g) To ensure the manufacturing of high-quality products, personnel should be trained in good manufacturing and laboratory practices I appropriate fields such as bacteriology, virology, biometry, chemistry, medicine, immunology and veterinary medicine.

(h) Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

(i) All personnel engaged I production, maintenance, testing and animal care (all inspectors) should be vaccinated with appropriate vaccines and where appropriate, be submitted to regular testing for evidence of active tuberculosis. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with these agents.

(j) Where BCG vaccines are being manufactured, access to production areas shall be restricted to staff who are carefully monitored by regular health checks. In the case of manufacture of products derived from human blood or plasma, vaccination of workers

against hepatitis is recommended.

Section 1.24 Premises and Equipment

(a) As a general principle, buildings must be located, designed constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories, operating rooms and all other rooms and buildings (including those for animals) that are used for the manufacture of biological products shall be designed and constructed of materials of the highest standard so that cleanliness, especially freedom form dust, insects and vermin, can be maintained.

(b) Interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks; they shall not shed matter and shall permit easy cleaning and disinfection. Drains shall be avoided whenever possible and, unless essential, should be excluded from aseptic areas. Where installed they should be fitted with effective, easily cleanable traps and with breaks to prevent back-flow. The traps may contain electrically operated heating devices or other means for disinfection. Any floor channels should be open, shallow and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

(c) Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material such as stainless steel, without an overflow, and be supplied with water of potable quality. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Airborne dissemination of pathogenic microorganisms and viruses used for production and the possibility of contamination by other types of viruses or substances during the production process, including those from personnel, shall be avoided.

(d) Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity, to minimize contamination and to take account of the comfort of personnel working in protective clothing. Buildings shall be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space to suit the operations carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms shall be clean and sanitary at all times. If rooms intended for the manufacture of biological substances are used for other purposes, they shall be cleaned thoroughly and, if necessary, sanitized before the manufacture of biological substances is resumed. Areas used for processing animal tissue materials and microorganisms must be separated from premises used for manufacturing sterile biological products and have completely separate ventilation systems and separate staff.

(e) If certain products are to be produced on a campaign basis, the layout and design of the premises and equipment shall permit effective decontamination by fumigation, where necessary, as well as cleaning and sanitizing after the production campaign.

(f) Seed lots and cell banks used for the production of biological products should be

stored separately from other material. Access should be restricted to authorized personnel.

(g) Live organisms shall be handled in equipment that ensures that cultures are maintained in a pure state and are not contaminated during processing.

(h) Products such as killed vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers on the same premises as other sterile biological products, providing that adequate decontamination measures are taken after filling, if appropriate, sterilization and washing.

(i) Spore-forming organisms shall be handled in facilities dedicated to this group of products until the inactivation process is accomplished. For Bacillus anthracis, Clostridium botulinum and Clostridium tetani, strictly dedicated facilities should be utilized for each individual product. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product should be processed at a time.

(j) Dedicated facilities and equipment shall be used for the manufacture of medicinal products derived from human blood or plasma.

(k) All containers of biological substances, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross-contamination should be prevented by adoption of some or all of the following measures:

(i) processing and filling in segregated areas;
(ii) avoiding manufacture of different products at the same time, unless they are effectively segregated;
(iii) containing material transfer by means of airlocks, air extraction, clothing change 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 (especially by centrifugation and blending);
(vii) excluding pathological specimens sent in for diagnosis from areas used for manufacturing biological substances;
(viii) using containers that are sterilized or are of documented low “bioburden”.

(a) Positive-pressure areas should be used to process sterile products, but negative pressure is acceptable in specific areas where pathogens are processed. In general, any organisms to be pathogenic should be handled within specifically designed areas under negative pressures, in accordance with containment requirements for the product concerned.

(i) Air-handling units should be dedicated to the processing area concerned. Air from operations involving pathogens shall not be recirculated and, in the case

of organisms in a group above Risk Group 2 (3), shall be exhausted through sterilizing filters that are regularly checked for performance.

(ii) Specific decontamination systems should be considered for effluent when infectious and potentially infectious materials are used for production.

(iii) Pipework, valves and vent filters shall be properly designed to facilitate cleaning and sterilization. Valves on fermentation vessels shall be completely steam-sterilizable. Air-vent filters shall be hydrophobic and shall be validated for their designated use.

(iv) Small stocks of substances that have to be measured or weighed during the production process (e.g. buffers) may be kept in the production area, provided that they are not returned to the general stocks. Otherwise, dry materials used to formulate buffers, culture media, etc should be weighed and put into solution in a contained area outside the purification and aseptic areas in order to minimize contamination of the product.

Section 1.25 Animal Quarters and Care

(a) Animals are used for the manufacture and control of a number of biological products. Animals shall be accommodated in separate buildings with self-contained ventilation systems. The buildings' design and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin. Facilities for animal care shall include isolation units for quarantine of incoming animals and provision for vermin-free food storage. Provision shall also be made for animal inoculation rooms, which shall be separate from the postmortem rooms. There shall be facilities for the disinfection of cages, if possible by steam, and an incinerator for disposing of waste and of dead animals.

(b) The health status of animals from which starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in animal quarters must be provided with special clothing, changing facilities and showers. Where monkeys are used for the production or quality control of biological products, special consideration is required, as laid down in the revised Requirements for Biological Substances No. 7 (Requirements for Polio-myelitis Vaccine (Oral)) (5).

Section 1.26 Production

(a) Standard operating procedures shall be available and maintained up to date for all manufacturing operations.

(i) The source, origin and suitability of starting materials should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.

(ii) Where sterilisation of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation).

(iii) In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture of propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.

(iv) The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the marketing authorisation dossier. Scaling up of the process should not change this fundamental relationship.

(v) Seed lots and cell banks should be adequately characterised and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks should be established, stored and used in such a way as to minimise the risks of contamination or alteration.

(vi) Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.

(vii) Evidence of the stability and recovery of the seeds and banks should be documented. Storage containers should be hermetically sealed, clearly labeled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded.

(viii) Only authorised personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimise the risks of total loss.

(ix) All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to the stock.

(x) The growth promoting properties of culture media should be demonstrated.

(xi) Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure

that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.

(xii) Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live microorganisms is necessary.

(xiii) If possible, media should be sterilised in situ. In-line sterilising filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters should be used where possible.

(xiv) Careful consideration should be given to the validation of any necessary virus removal or inactivation undertaken.

(xv) In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.

(xvi) A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilised or sanitised between batches. the use of the same equipment at different stages of processing should be discouraged. Acceptance criteria, life span and sanitization or sterilisation method of columns should be defined.

Section 1.27 Labelling

(a) All products shall be clearly identified by labels. The labels used must remain permanently attached to the containers under all storage conditions and an area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labeling (for example a capillary tube), it should be in a labeled package.

(b) The information given on the label on the container and the label on the package shall be approved by the national control authority.

(c) The label on the container shall show:-
- (i) the name of the drug product;
- (ii) a list of the active ingredients and the amount of each present, with a statement of the net contents, e.g. number of dosage units, weight or volume;
- (iii) the batch or final lot number assigned by the manufacturer;
- (iv) the expiry date;
- (v) recommended storage conditions or handling precautions that may be necessary;
- (vi) directions for use, and warnings and precautions that may be necessary;
- (vii) the nature and amount of any substance used in the preparation of the biological product that is likely to give rise to an adverse reaction in some recipients;

(viii) the name and address of the manufacturer or the company and/or the person responsible for placing the drug on the market.

(a) The label on the package shall, in addition to the information shown on the label on the container, show at least the nature and amount of any preservative or additive in the product.

(i) The leaflet in the package should provide instructions for the use of the product, and mention any contraindications or potential adverse reactions.

Lot Processing Records (Protocols) and Distribution Records

(a) Processing records of regular production lots must provide a complete account of the manufacturing history of each lot of a biological preparation, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the licensed procedures.

(b) A separate processing record should be prepared for each lot of biological product, and should include the following information:

(i) the name and dosage of the product;
(ii) the date of manufacture;
(iii) the lot identification number;
(iv) the complete formulation of the lot, including identification of seed or starting materials;
(v) the batch number of each component used in the formulation;
(vi) the yield obtained at different stages of manufacture of the lot;
(vii) a duly signed record of each step followed, precautions taken and special observations made throughout the manufacture of the lot;
(viii) a record of all in-process control tests and of the results obtained;
(ix) a specimen of the label;
(x) identification of packaging materials, containers and closures used;
(xi) a dated signature of the expert responsible for approving the manufacturing operations;
(xii) an analytical report, dated and signed by the responsible expert, showing whether the lot complies with the specifications described in the standard operating procedure registered with the national control authority;
(xiii) a record of the decision regarding the release or rejection of the lot by the quality-control department and, if the lot is rejected, a record of its disposal or utilization.

(a) The records shall be of a type approved by the national control authority. They shall be retained for at least two years after the expiry date of a lot or batch of a biological product and be available at all times for inspection by the national control authority.

(i) Records must make it possible to trace all steps in the manufacture and testing of a lot, and should include records of sterilization of all apparatus and materials

used in its manufacture. Distribution records must be kept in a manner that permits rapid recall of any particular lot, if necessary.

Section 1.28 Quality Control

1.28.1 The quality-assurance and/or quality-control department should have the following principal duties:

(a) to prepare detailed instructions for each test and analysis;
(b) to ensure adequate identification and segregation of test samples to avoid mix-up and cross-contamination;
(c) to ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
(d) to release or reject raw materials and intermediate products, if necessary;
(e) to release or reject packaging and labeling materials and the final containers in which drugs are to be placed;
(f) to release or reject each lot of finished preparation;
(g) to evaluate the adequacy of the conditions under which raw materials, intermediate products and finished biological preparations are stored;
(h) to evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;
(i) to establish expiry dates on the basis of the validity period related to specified storage conditions;
(j) to establish and, when necessary, revise control procedures and specifications; and
(k) to be responsible for the examination of returned preparations to determine whether such preparations should be released; reprocessed or destroyed; adequate records of the distribution of such preparations should be maintained.

1.28.2 A manufacture's quality-control laboratory shall be separated from the production area and ideally should be in a separate building. The control laboratory should be designed and equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, preparation of records and performance of the necessary tests.

(a) In-process controls play a special important role in ensuring the consistent quality of biological products. Tests that are crucial for quality control but that cannot be carried out on the finished product shall be performed at an appropriate stage of production.

(b) Performance of all qualitative and quantitative tests mentioned in the specifications for starting materials may be replaced by a system of certificates issued by the producer of the starting material, provided that:
(i) there is a history of reliable production,
(ii) the producer is regularly audited, and
(iii) at least one specific identity test is conducted by the manufacturer of the final product.

(c) Samples of intermediate and final products shall be retained in sufficient amount and under appropriate storage conditions to allow the repetition or confirmation of a batch control. However, reference samples of certain starting materials, e.g. components of culture media, need not necessarily be retained.
(d) Certain operations require the continuous monitoring of data during a production process, for example monitoring and recording of physical parameters during fermentation.
(e) Special consideration needs to be given to the quality-control requirements arising from production of biological products by continuous culture.

Annex 3 Manufacture of veterinary medicinal products other than immunologicals

Section 1.29 Manufacture of Premixes for Medicated Feeding Stuffs

For the purposes of these paragraphs,
a *medicated feeding stuff* is any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties (e.g. medical diagnosis, restoration, correction or modification of physiological functions in animals):

a *pre-mix for medicated feeding stuffs* is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feeding stuffs.

(a) The manufacture of premixes for medicated feeding stuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimize this risk (point 3.5) and should also be subject to a regular pest control program.

(b) Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning, for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

(c) Parts of the process likely to have a significant adverse influence on the stability of the active ingredients) (e.g. use of steam in pellet manufacture) should be carried out in a uniform manner from batch to batch.

(d) Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimize the risk of contamination of other manufacturing areas.

Section 1.30 The Manufacture of Ectoparasiticides

(a) In derogation from point 3.7, ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorization, may be produced and filled on a campaign basis in pesticide specific areas. However, other categories of veterinary medicinal products should not be produced in such areas.

(b) Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

Section 1.31 The Manufacture of Veterinary Medicinal Products

Containing Penicillins

(a) The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity been recorded in horses and dogs, there are other materials which are toxic to certain species, e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities (point 3.7) may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

Retention of Samples *(point 1.4(h) and point 7.10)*

(a) It is recognized that because of the large volume of certain veterinary medicinal products in their final packaging, in particular premixes, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.

(b) In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

Section 1.32 Sterile Veterinary Medicinal Products

(a) Where this has been accepted by the competent authorities, terminally sterilized veterinary medicinal products may be manufactured in a clean area of a lower grade than the grade required in the annex on "Sterile preparations", but at least in a grade D environment.

Annex 4 Manufacture of immunological veterinary medical products

Section 1.33 Principle

The manufacture of immunological veterinary medicinal products has special characteristics which should be taken into consideration when implementing and assessing the quality assurance system.

Due to the large number of animal species and related pathogenic agents, the variety of products manufactured is very wide and the volume of manufacture is often low; hence, work on a campaign basis is common. Moreover, because of the very nature of this manufacture (cultivation steps, lack of terminal sterilization, etc.), the products must be particularly well protected against contamination and cross-contamination. The environment also must be protected especially when the manufacture involves the use of pathogenic or exotic biological agents and the worker must be particularly well protected when the manufacture involves the use of biological agents pathogenic to man.

These factors, together with the inherent variability of immunological veterinary medicinal products and the relative inefficiency in particular of final product quality control tests in providing adequate information about products, means that the role of the quality assurance system is of the utmost importance. The need to maintain control over all of the following aspects of GMP, as well as those outlined in this Guide, cannot be overemphasized. In particular, it is important that the data generated by the monitoring of the various aspects of GMP (equipment, premises, product etc.) are rigorously assessed and informed decisions, leading to appropriate action, are made and recorded.

Section 1.34 Personnel

(a) All personnel (including those concerned with cleaning and maintenance) employed in areas where immunological products are manufactured should be given training in and information on hygiene and microbiology. They should receive additional training specific to the products with which they work.

(b) Responsible personnel should be formally trained in some or all of the following fields: bacteriology, biology, biometry, chemistry, immunology, medicine, parasitology, pharmacy, pharmacology, virology and veterinary medicine and should also have an adequate knowledge of environmental protection measures.

(c) Personnel should be protected against possible infection with the biological agents used in manufacture. In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with the agent or with experimental animals.

(d) Where relevant, the personnel should be vaccinated and subject to medical examination.

(e) Adequate measures should be taken to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. Dependent on the type of biological agent, such measures may include complete change of clothes and

compulsory showering before leaving the production area.

(f) For immunological products, the risk of contamination or cross-contamination by personnel is particularly important.

Prevention of contamination by personnel should be achieved by a set of measures and procedures to ensure that appropriate protective clothing is used during the different stages of the production process.

Prevention of cross-contamination by personnel involved in production should be achieved by a set of measures and procedures to ensure that they do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination. In the course of a working day, personnel should not pass from areas where contamination with live microorganisms is likely or where animals are housed to premises where other products or organisms are handled. If such a passage is unavoidable, clearly defined decontamination procedures, including change of clothing and shoes, and, where necessary, showering, should be followed by staff involved in any such production.

Personnel entering a contained area where organisms had not been handled in open circuit operations in the previous twelve hours to check on cultures in sealed, surface decontaminated flasks would not be regarded as being at risk of contamination, unless the organism involved was an exotic.

Section 1.35 Premises

(a) Premises should be designed in such a way as to control both the risk to the product and to the environment. This can be achieved by the use of containment, clean, clean/contained or controlled areas.

(b) Live biological agents should be handled in contained areas. The level of containment should depend on the pathogenicity of the microorganism and whether it has been classified as exotic.

(c) Inactivated biological agents should be handled in clean areas. Clean areas should also be used when handling non-infected cells isolated from multicellular organisms and, in some cases, filtration-sterilized media.

(d) Open circuit operations involving products or components not subsequently sterilized should be carried out within a laminar air flow work station (grade A) in a grade B area.

(e) Other operations where live biological agents are handled (quality control, research and diagnostic services, etc.) should be appropriately, contained and separated if production operations are carried out in the same building. The level of containment should depend on the pathogenicity of the biological agent and whether they have been classified as exotic. Whenever diagnostic activities are carried out, there is the risk of introducing highly pathogenic organisms. Therefore, the level of containment should be adequate to cope with all such risks. Containment may also be required if quality control or other activities are carried out in buildings in close proximity to those

used for production.

(f) Containment premises should be easily disinfected and should have the following characteristics:

(i) The absence of direct venting to the outside;

(ii) a ventilation with air at negative pressure. Air should be extracted through HEPA filters and not be recirculated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the recirculated air through the normal supply HEPAs for that area). However, recycling of air between areas may be permissible provided that it passes through two exhaust HEPAs, the first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail;

(iii) air from manufacturing areas used for the handling of exotic organisms should be vented through 2 sets of HEPA filters in series, and that from production areas not recirculated;

(iv) a system for the collection and disinfection of liquid effluents including contaminated condensate from sterilizers, biogenerators, etc. Solid wastes, including animal carcasses, should be disinfected, sterilized or incinerated as appropriate. Contaminated filters should be removed using a safe method;

(v) changing rooms designed and used as air locks, and equipped with washing and showering facilities if appropriate. Air pressure differentials should be such that there is no flow of air between the work area and the external environment or risk of contamination of outer clothing worn outside the area;

(vi) an air lock system for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or risk of contamination of equipment within the lock. The air lock should be of a size which enables the effective surface decontamination of materials being passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective.

(vii) in many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.

(g) Equipment passes and changing rooms should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time. Changing rooms should be supplied with air filtered to the same standard as that for the work area, and extracts to produce an adequate air circulation independent of that of the work area. Equipment passes should normally be ventilated in the same way, but unventilated passes, or those equipped with supply air only, may be acceptable.

(h) Production operations such as cell maintenance, media preparation, virus culture, etc. likely to cause contamination should be performed in separate areas. Animals and animal products should be handled with appropriate precautions.

(i) Production areas where biological agents particularly resistant to disinfection (e.g. spore-forming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.

(j) With the exception of blending and subsequent filling operations, one biological agent only should be handled at a time within an area.

(k) Production areas should be designed to permit disinfection between campaigns, using validated methods.

(l) Production of biological agents may take place in controlled areas provided it is carried out in totally enclosed and heat sterilized equipment, all connections being also heat sterilized after making and before breaking. it may be acceptable for connections to be made under local laminar air flow provided these are few in number and proper aseptic techniques are used and there is no risk of leakage. The sterilization parameters used before breaking the connections must be validated for the organisms being used. Different products may be placed in different biogenerators, within the same area, provided that there is no risk of accidental cross-contamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.

(m) Animal houses where animals intended or used for production are accommodated, should be provided with the appropriate containment and/or clean area measures, and should be separate from other animal accommodation.

(n) Animal houses where animals used for quality control, involving the use of pathogenic biological agents, are accommodated, should be adequately contained.

(o) Access to manufacturing areas should be restricted to authorized personnel. Clear and concise written procedures should be posted as appropriate.

(p) Documentation relating to the premises should be readily available in a plant master file.

(q) The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) so that the designation and conditions of use of all the rooms are correctly identified as well as the biological agents which are handled in them. The flow of people and product should also be clearly marked.

(r) The animal species accommodated in the animal houses or otherwise on the site should be identified.

(s) The activities carried out in the vicinity of the site should also be indicated.

(t) Plans of contained and/or clean area premises, should describe the ventilation system indicating inlets and outlets, filters and their specifications, the number of air changes per hour, and pressure gradients. They should indicate which pressure gradients are monitored by pressure indicator.

Section 1.36 Equipment

a) The equipment used should be designed and constructed so that it meets the particular requirements for the manufacture of each product. Before being put into operation the equipment should be qualified and validated.

b) Where appropriate, the equipment should ensure satisfactory primary containment of the biological agents.

c) Where appropriate, the equipment should be designed and constructed as to allow easy and effective decontamination and/or sterilization.

d) Closed equipment used for the primary containment of the biological agents should be designed and constructed as to prevent any leakage or the formation of droplets and aerosols.

e) Inlets and outlets for gases should be protected so as to achieve adequate containment e.g. by the use of sterilizing hydrophobic filters.

f) The introduction or removal of material should take place using a sterilizable closed system, or possibly in an appropriate laminar air flow.

g) Equipment where necessary should be properly sterilized before use, preferably by pressurized dry steam. other methods can be accepted if steam sterilization cannot be used because of the nature of the equipment. It is important not to overlook such individual items as bench centrifuges and water baths.

h) Equipment used for purification, separation or concentration should be sterilized or disinfected at least between use for different products. The effect of the sterilization methods on the effectiveness and validity of-the equipment should be studied in order to determine the life span of the equipment.

i) All sterilization procedures should be validated.

j) Equipment should be designed so as to prevent any mix-up between different organisms or products. Pipes, valves and filters should be identified as to their function.

k) Separate incubators should be used for infected and non infected containers and also generally for different organisms or cells. Incubators containing more than one organism or cell type will only be acceptable if adequate steps are taken to seal,

surface decontaminate and segregate the containers. Culture vessels, etc. should be individually labelled. The cleaning and disinfection of the items can be particularly difficult and should receive special attention.

l) Equipment used for the storage of biological agents or products should be designed and used in such a manner as to prevent any possible mix-up. All stored items should be clearly and unambiguously labelled and in leak-proof containers. Items such as cells and organisms seed stock should be stored in dedicated equipment.

m) Relevant equipment, such as that requiring temperature control, should be fitted with recording and/or alarm systems.

n) To avoid breakdowns, a system of preventive maintenance, together with trend analyses of recorded data, should be implemented.

o) The loading of freeze driers requires an appropriate clean/contained area.

p) Unloading freeze driers contaminate the immediate environment. Therefore, for single-ended freeze driers, the clean room should be decontaminated before a further manufacturing batch is introduced into the area, unless this contains the same organisms, and double door freeze driers should be sterilized after each cycle unless opened in a clean area.

q) Sterilization of freeze driers should be done in accordance with item 23. In case of campaign working, they should at least be sterilized after each campaign.

Section 1.37 Animals and Animal Houses

(a) Animal houses should be separated from the other production premises and suitably designed.

(b) The sanitary status of the animals used for production should be defined, monitored, and recorded. Some animals should be handled as defined in specific monographs (e.g. Specific Pathogens Free flocks).

(c) Animals, biological agents, and tests carried out should be the subject of an identification system so as to prevent any risk of confusion and to control all possible hazards.

Section 1.38 Disinfection - Waste Disposal

(a) Disinfect ion and/or wastes and effluents disposal may be particularly important in the case of manufacture of immunological products. Careful consideration should therefore be given to procedures and equipment aiming at avoiding environmental contamination as well as to their validation and qualification.

Section 1.39 Production

(a) Because of the wide variety of products, the frequently large number of stages

involved in the manufacture of immunological veterinary medicinal products and the nature of the biological processes, careful attention must be paid to adherence to validated operating procedures, to the constant monitoring of production at all stages and to in-process controls.

Additionally, special consideration should be given to starting materials, media and the use of a seed lot system.

Section 1.40 Starting Materials

(a) The suitability of starting materials should be clearly defined in written specifications. These should include details of the supplier, the method of manufacture, the geographical origin and the animal species from which the materials are derived. The controls to be applied to starting materials must be included. Microbiological controls are particularly important.

(b) The results of tests on starting materials must comply with the specifications. Where the tests take a long time (e.g. eggs from SPF flocks) it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product is conditional upon satisfactory results of the tests on starting materials.

(c) Special attention should be paid to knowledge of the supplier's quality assurance system in assessing the suitability of a source and the extent of quality control testing required.

(d) Where possible, heat is the preferred method for sterilizing starting materials. If necessary, other validated methods, such as irradiation, may be used.

Media

(a) The ability of media to support the desired growth should be properly validated in advance.

(b) Media should preferably be sterilized in situ or in line. Heat is the preferred method. Gases, media, acids, alkalis, defoaming agents and materials introduced into sterile biogenerators should themselves be sterile.

(c) Seed lot and cell bank system

(d) In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of immunological veterinary medicinal products obtained by microbial, cell or tissue culture, or propagation in embryos and animals, should be based on a system of seed lots and/or cell banks.

(e) The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the dossier of authorisation for marketing.

(f) Seed lots and cell banks should be adequately characterized and tested for contaminants. Acceptance criteria for new seed lots should be established. Seed lots and cell banks should be established, stored and used in such a way as to minimize the risks of contamination, or any alteration. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus or cell lines) should be handled simultaneously in the same area or by the same person.

(g) Establishment of the seed lot and cell bank should be performed in a suitable environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it and the external environment.

(h) The origin, form and storage conditions of seed material should be described in full. Evidence of the stability and recovery of the seeds and banks should be provided. Storage containers should be hermetically sealed, clearly labelled and stored at an appropriate temperature. Storage conditions should be properly monitored. An inventory should be kept and each container accounted for.

(i) Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination errors. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimize the risk of total loss.

(j) Operating principles

(k) The formation of droplets and the production of foam should be avoided or minimized during manufacturing processes. centrifugation and blending procedures which can lead to droplet formation should be carried out in appropriate contained or clean/contained areas to prevent transfer of live organisms.

(l) Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures should be available for each organism. Where different strains of single bacteria species or very similar viruses are involved, the process need be validated against only one of them, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

(m) Operations involving the transfer of materials such as sterile media, cultures or product should be carried out in pre-sterilized closed systems wherever possible. Where this is not possible, transfer operations must be protected by laminar airflow work stations.

(n) Addition of media or cultures to biogenerators and other vessels should be carried out under carefully controlled conditions to ensure that contamination is not introduced. Care must be taken to ensure that vessels are correctly connected when addition of cultures takes place.

(o) When necessary, for instance when two or more fermentors are within a single area,

sampling and addition ports, and connectors (after connection, before the flow of product, and again before disconnection) should be sterilized with steam. In other circumstances, chemical disinfection of ports and laminar air flow protection of connections may be acceptable.

(p) Equipment, glassware, the external surfaces of product containers and other such materials must be disinfected before transfer from a contained area using a validated method (see 47 above). Batch documentation can be a particular problem. only the absolute minimum required to allow operations to GMP standards should enter and leave the area. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork must be adequately disinfected through an equipment pass, or the information transferred out by such means as photocopy or fax.

(q) Liquid or solid wastes such as the debris after harvesting eggs, disposable culture bottles, unwanted cultures or biological agents, are best sterilized or disinfected before transfer from a contained area. However, alternatives such as sealed containers or piping may be appropriate in some cases.

(r) Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only materials concerned with production are introduced. There should be a system which ensures that materials entering a room are reconciled with those leaving so that accumulation of materials within the room does not occur.

(s) Heat stable articles and materials entering a clean area or clean/contained area should do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an airlock with interlocked doors where they are disinfected. Sterilization of articles and materials elsewhere is acceptable provided that they are double wrapped and enter through an airlock with the appropriate precautions.

(t) Precautions must be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators. Containers in incubators should be carefully and clearly labelled.

(u) With the exception of blending and subsequent filling operations (or when totally enclosed systems are used) only one live biological agent may be handled within a production room at any given time. Production rooms must be effectively disinfected between the handling of different live biological agents.

(v) Products should be inactivated by the addition of inactivant accompanied by sufficient agitation. The mixture should then be transferred to a second sterile vessel, unless the container is of such a size and shape as to be easily inverted and shaken so as to wet all internal surfaces with the final culture/ inactivant mixture.

(w) Vessels containing inactivated product should not be opened or sampled in areas

containing live biological agents. All subsequent processing of inactivated products should take place in clean areas grade A-B or enclosed equipment dedicated to inactivated products.

(x) Careful consideration should be given to the validation of methods for sterilization, disinfection, virus removal and inactivation.

(y) Filling should be carried out as soon as possible following production. Containers of bulk product prior to filling should be sealed, appropriately labelled and stored under specified conditions of temperature.

(z) There should be a system to assure the integrity and closure of containers after filling.

(aa) The capping of vials containing live biological agents must be performed in such a way that ensures that contamination of other products or escape of the live agents into other areas or the external environment does not occur.

(bb) For various reasons there may be a delay between the filling of final containers and their labelling and packaging. Procedures should be specified for the storage of unlabelled containers in order to prevent confusion and to ensure satisfactory storage conditions. Special attention should be paid to the storage of heat labile or photosensitive products. Storage temperatures should be specified.

(cc) For each stage of production, the yield of product should be reconciled with that expected from that process. Any significant discrepancies should be investigated.

Section 1.41 Quality Control

(a) In-process controls play a special important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for the quality (e.g. virus removal) but which cannot be carried out on the finished product should be performed at an appropriate stage of production.

(b) It may be necessary to retain samples of intermediate products in sufficient amount and under appropriate storage conditions to allow repetition or confirmation of a batch control.

(c) There may be a requirement for the continuous monitoring of data during a production process, for example monitoring of physical parameters during fermentation.

(d) Continuous culture of biological products is a common practice and special consideration needs to be given to the quality control requirements arising from this type of production method.

Annex 5 Qualification and validation

Section 1.42 Principle

(a) This Annex describes the principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

Section 1.43 Planning for validation

(a) All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

(b) The VMP should be a summary document which is brief, concise and clear.

(c) The VMP should contain data on at least the following:
- (i) validation policy;
- (ii) organizational structure of validation activities;
- (iii) summary of facilities, systems, equipment and processes to be validated;
- (iv) documentation format: the format to be used for protocols and reports;
- (v) planning and scheduling;
- (vi) change control;
- (vii) reference to existing documents.

(d) In case of large projects, it may be necessary to create separate validation master plans.

Section 1.44 Documentation

(a) A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

(b) A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

(c) After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.

Section 1.45 Qualification

1.45.1 Design qualification

(a) The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).

(b) The compliance of the design with GMP should be demonstrated and documented.

1.45.2 Installation qualification

(a) Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.

(b) IQ should include, but not be limited to the following:

(i) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;

(ii) collection and collation of supplier operating and working instructions and maintenance requirements;

(iii) calibration requirements;

(iv) verification of materials of construction.

1.45.3 Operational qualification

(a) Operational qualification (OQ) should follow Installation qualification.

(b) OQ should include, but not be limited to the following:

(i) tests that have been developed from knowledge of processes, systems and equipment;

(ii) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.

(a) The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

(a) Performance qualification

(a) Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.

(b) PQ should include, but not be limited to the following:

(i) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;

(ii) tests to include a condition or set of conditions encompassing upper and lower operating limits.

(a) Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

(b) Qualification of established (in-use) facilities, systems and equipment

(a) Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

Section 1.46 Process validation

General

(a) The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and revalidation.

(b) Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).

(c) Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.

(d) Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

Prospective validation

(a) Prospective validation should include, but not be limited to the following:
- (i) short description of the process;
- (ii) summary of the critical processing steps to be investigated;
- (iii) list of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status
- (iv) finished product specifications for release;
- (v) list of analytical methods, as appropriate;
- (vi) proposed in-process controls with acceptance criteria;
- (vii) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
- (viii) sampling plan;
- (ix) methods for recording and evaluating results
- (x) functions and responsibilities;
- (xi) proposed timetable.

(b) Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the

process.

(c) Batches made for process validation should be the same size as the intended industrial scale batches.

(d) If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and (where applicable) the marketing authorisation.

Concurrent validation

(a) In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.

(b) The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

(c) Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation

(a) Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

(b) Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

(c) The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

(d) Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

(e) For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

Section 1.47 Cleaning validation

(a) Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carryover of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.

(b) Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

(c) Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.

(d) For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a “worst case” approach can be carried out which takes account of the critical issues.

(e) Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

(f) "Test until clean" is not considered an appropriate alternative to cleaning validation.

(g) Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

Section 1.48 Change control

(a) Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.

(b) All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, requalification and re-validation should be determined.

Section 1.49 Revalidation

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

Section 1.50 Glossary

Definitions of terms relating to qualification and validation which are not given in the glossary of the current NDA-GMP Guide, but which are used in this Annex, are given below.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

Cleaning Validation

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.

Concurrent Validation

Validation carried out during routine production of products intended for sale.

Design qualification (DQ)

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Process Validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Prospective Validation

Validation carried out before routine production of products intended for sale.

Retrospective Validation

Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

Re-Validation

A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Risk analysis

Method to assess and characterise the critical parameters in the functionality of an equipment or process.

Simulated Product

A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

System

A group of equipment with a common purpose.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

Annex 6 Computerized systems

Section 1.51 Principle

The introduction of computerised systems into systems of manufacturing, including storage, distribution and quality control does not alter the need to observe the relevant principles given elsewhere in the Guide. Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance. Consideration should be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

Section 1.52 Personnel

It is essential that there is the closest co-operation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilises computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of computerised system.

Section 1.53 Validation

The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether it is prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and changing.

Section 1.54 System

(a) Attention should be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.

(b) A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.

(c) The software is a critical component of a computerised system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of Quality Assurance.

(d) The system should include, where appropriate, built-in checks of the correct entry and processing of data.

(e) Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results. If a manual system is being replaced, the two should be run in parallel for a time, as part of this testing and validation.

(f) Data should only be entered or amended by persons authorised to do so. Suitable methods of deterring unauthorised entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. There should be a defined procedure for the issue, cancellation, and alteration of authorisation to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorised persons.

(g) When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.

(h) The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alteration to an entry of critical data should be authorised and recorded with the reason for the change. Consideration should be given to the system creating a complete record of all entries and amendments (an "audit trail").

(i) Alterations to a system or to a computer program should only be made in accordance with a defined procedure which should include provision for validating, checking, approving and implementing the change. Such an alteration should only be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded. Every significant modification should be validated.

(j) For quality auditing purposes, it should be possible to obtain meaningful printed copies of electronically stored data.

(k) Data should be secured by physical or electronic means against willful or accidental damage, and this in accordance with item 5.8 of the Guide. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.

(l) Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.

(m) There should be available adequate alternative arrangements for systems which need to be operated in the event of a breakdown. The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them. For example, information required to effect a recall must be available at short notice.

(n) The procedures to be followed if the system fails or breaks down should be defined

and validated. Any failures and remedial action taken should be recorded.

(o) A procedure should be established to record and analyse errors and to enable corrective action to be taken.

(p) When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency. (see chapter 8)

(q) When the release of batches for sale or supply is carried out using a computerized system, the system should recognize that only an Authorized Person can release the batches and it should clearly identify and record the person releasing the batches.

Annex 7 Water for pharmaceutical use

1.1 Scope

The guidance contained in this document is intended to provide information about the available specifications for water for pharmaceutical use (WPU), guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms, and to provide guidance on the good manufacturing practice (GMP) regarding the design, installation and operation of pharmaceutical water systems. Although the focus of this document is on water for pharmaceutical applications, the guidelines may also be relevant to other industrial or specific uses where the specifications and practices can be applied.

The GMP guidance for WPU contained in this document is intended to be supplementary to the general GMP guidelines for pharmaceutical products pub- lished by WHO (WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4).

This document refers to available specifications, such as the pharmacopoeias and industry guidance for the use, production, storage and distribution of water in bulk form. In order to avoid confusion it does not attempt to duplicate such material. Note: This document does not cover waters for administration to patients in their formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.

The guidance provided in this document can be used in whole or in part as appropriate to the application under consideration. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer will be expected to decide which option to choose in accordance with the related marketing authorization submitted to the national drug regulatory authority.

1.2 Background to water requirements and uses

Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health.

Different grades of water quality are required depending on the route of administration of the pharmaceutical products. One source of guidance about different grades of water is the European Medicines Agency (EMEA) Note for guidance on quality of water for pharmaceutical use (CPMP/QWP/158/01).

Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Unlike

other product and process ingredients, water is usually drawn from a system on demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is, there- fore, essential. Additionally, certain microbiological tests may require periods of incubation and, therefore, the results are likely to lag behind the water use. Control of the microbiological quality of WPU is a high priority. Some types of microorganism may proliferate in water treatment components and in the storage and distribution systems. It is very important to minimize microbial contamination by routine sanitization and taking appropriate measures to prevent microbial proliferation.

1.3 Applicable guides

In addition to the specific guidance provided in this document, the Bibliography lists some relevant publications that can serve as additional background material when planning, installing and using systems intended to provide WPU.

2. General requirements for pharmaceutical water systems

Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination (e.g. with dust and dirt).

The use of the systems following installation, commissioning, validation and any unplanned maintenance or modification work should be approved by the quality assurance (QA) department. If approval is obtained for planned preventive maintenance tasks, they need not be approved after implementation. Water sources and treated water should be monitored regularly for quality and for chemical, microbiological and, as appropriate, endotoxin contamination. The performance of water purification, storage and distribution systems should also be monitored. Records of the monitoring results and any actions taken should be maintained for an appropriate length of time.

Where chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed to ensure that the sanitizing agent has been effectively removed.

3. Water quality specifications

3.1 General

(a) The following requirements concern water processed stored and distributed in bulk form. They do not cover the specification of waters formulated for patient administration. Pharmacopoeias include specifications for both bulk and dosage-form waters.

(b) Pharmacopoeial requirements for WPU are described in national and inter- national pharmacopoeias and limits for various contaminants are given. Com- panies wishing to supply multiple markets should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

3.2 Drinking-water

(a) Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.

(b) Drinking-water is unmodified except for limited treatment of the water derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required to render it safe for human consumption (drinking). Typical treatment includes softening, removal of specific ions, particle reduction and antimicrobial treatment. It is common for drinking-water to be derived from a public water supply that may be a combination of more than one of the natural sources listed above. It is also common for public water- supply organizations to conduct tests and guarantee that the drinking-water delivered is of potable quality.

(c) Drinking-water quality is covered by the WHO drinking-water guidelines, standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

(d) If drinking-water is used directly in certain stages of pharmaceutical manufacture or is the feed-water for the production of higher qualities of WPU, then testing should be carried out periodically by the water user's site to confirm that the quality meets the standards required for potable water.

3.3 Purified water

(a) Purified water (PW) should be prepared from a potable water source as a minimum-quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation.

3.4 Highly purified water

(a) Highly purified water (HPW) should be prepared from potable water as minimum-quality feed-water. HPW is a unique specification for water found only in the European Pharmacopoeia. This grade of water must meet the same quality standard as water for injections (WFI) including the limit for endotoxins, but the water-treatment methods are not considered to be as reliable as distillation. HPW may be prepared by combinations of methods such as reverse osmosis, ultrafiltration and deionization.

3.5 Water for injections

(a) Water for injections (WFI) should be prepared from potable water as a minimum-quality feed-water. WFI is not sterile water and is not a final dosage form. It is an intermediate bulk product. WFI is the highest quality of pharmacopoeial WPU.

(b) Certain pharmacopoeias place constraints upon the permitted purification techniques as part of the specification of the WFI. The International Pharmacopoeia and the European Pharmacopoeia, for example, allow only distillation as the final purification step.

3.6 Other grades of water

(a) When a specific process requires a special non-pharmacopoeial grade of water, this should be specified and should at least satisfy the pharmacopoeial requirements of the grade of WPU required for the type of dosage form or process step.

4. Application of specific waters to processes and dosage forms

(a) Product licensing authorities define the requirement to use the specific grades of WPU for different dosage forms or for different stages in washing, prepara- tion, synthesis, manufacturing or formulation.

(b) The grade of water used should take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used.

(c) HPW can be used in the preparation of products when water of high quality

(d) (i.e. very low in microorganisms and endotoxins) is needed, but the process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeial monographs for WFI.

(e) WFI should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections. WFI should also be used for the final rinse after cleaning of equipment and components that come into contact with injectable products as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

(f) When steam comes into contact with an injectable product in its final container, or equipment for preparing injectable products, it should conform with the specification for WFI when condensed.

5. Water purification methods

5.1 General considerations

(a) The specifications for WPU found in compendia (e.g. pharmacopoeias) are generally not prescriptive as to permissible water purification methods other than those for WFI (refer to section 3.5).

(b) The chosen water purification method, or sequence of purification steps, must be appropriate to the application in question. The following should be considered when selecting the water treatment method:

(i) the water quality specification;
(ii) the yield or efficiency of the purification system;
(iii) feed-water quality and the variation over time (seasonal changes);
(iv) the reliability and robustness of the water-treatment equipment in operation;
(v) the availability of water-treatment equipment on the market;
(vi) the ability to adequately support and maintain the water purification equipment; and
(vii) the operation costs.

(c) The specifications for water purification equipment, storage and distribution systems should take into account the following:

(i) the risk of contamination from leachates from contact materials;
(ii) the adverse impact of adsorptive contact materials;
(iii) hygienic or sanitary design, where required;
(iv) corrosion resistance;
(v) freedom from leakage;
(vi) configuration to avoid proliferation of microbiological organisms;
(vii) tolerance to cleaning and sanitizing agents (thermal and chemical);
(viii) the system capacity and output requirements; and
(ix) the provision of all necessary instruments, test and sampling points to allow all the relevant critical quality parameters of the complete system to be monitored.

(d) The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

(i) the space available for the installation;
(ii) structural loadings on buildings;
(iii) the provision of adequate access for maintenance; and
(iv) the ability to safely handle regeneration and sanitization chemicals.

5.2 Production of drinking-water

(a) Drinking-water is derived from a raw water source such as a well, river or reser- voir. There are no prescribed methods for the treatment of raw water to produce potable drinking-water from a specific raw water source.

(b) Typical processes employed at a user plant or by a water supply authority include:
- (i) filtration;
- (ii) softening;
- (iii) disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection);
- (iv) iron (ferrous) removal;
- (v) precipitation; and
- (vi) reduction of specific inorganic/organic materials.

(c) The drinking-water quality should be monitored routinely. Additional testing should be considered if there is any change in the raw-water source, treatment techniques or system configuration. If the drinking-water quality changes significantly, the direct use of this water as a WPU, or as the feed-water to downstream treatment stages, should be reviewed and the result of the review documented.

(d) Where drinking-water is derived from an "in-house" system for the treatment of raw water, the water-treatment steps used and the system configuration should be documented. Changes to the system or its operation should not be made until a review has been completed and the change approved by the QA department.

(e) Where drinking-water is stored and distributed by the user, the storage systems must not allow degradation of the water quality before use. After any such storage, testing should be carried out routinely in accordance with a defined method. Where water is stored, its use should ensure a turnover of the stored water sufficient to prevent stagnation.

(f) The drinking-water system is usually considered to be an "indirect impact system" and does not need to be qualified.

(g) Drinking-water purchased in bulk and transported to the user by tanker presents special problems and risks not associated with potable water delivered by pipeline. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.

(h) Equipment and systems used to produce drinking-water should be able to be drained and sanitized. Storage tanks should be closed with appropriately protected vents, allow for visual inspection and for being drained and sanitized. Distribution pipe work should be able to be drained, or flushed, and sanitized.

(i) Special care should be taken to control microbiological contamination of sand filters,

carbon beds and water softeners. Once microorganisms have infected a system, the contamination can rapidly form biofilms and spread throughout the system. Techniques for controlling contamination such as back- flushing, chemical or thermal sanitization and frequent regeneration should be considered. Additionally, all water-treatment components should be maintained with continuous water flow to inhibit microbial growth.

5.3 Production of purified water

(a) There are no prescribed methods for the production of PW in the pharma- copoeias. Any appropriate qualified purification technique or sequence of tech- niques may be used to prepare PW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used. Distillation can also be used.

(b) The following should be considered when configuring a water purification system:
- (i) the feed-water quality and its variation over seasons;
- (ii) the required water-quality specification;
- (iii) the sequence of purification stages required;
- (iv) the energy consumption;
- (v) the extent of pretreatment required to protect the final purification steps;
- (vi) performance optimization, including yield and efficiency of unit treatment-process steps;
- (vii) appropriately located sampling points designed in such a way as to avoid potential contamination; and
- (viii) unit process steps should be provided with appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

(c) Ambient-temperature PW systems are especially susceptible to microbio- logical contamination, particularly when equipment is static during periods of no or low demand for water. It is essential to consider the mechanisms for microbi- ological control and sanitization. The following techniques should be considered:

- (i) maintenance of flow through water-purification equipment at all times;
- (ii) control of temperature in the system by pipeline heat exchange or plant- room cooling to reduce the risk of microbial growth (guidance value <25°C);
- (iii) provision of ultraviolet disinfection;
- (iv) selection of water-treatment components that can be thermally sanitized; and/or
- (v) application of chemical sanitization (including agents such as ozone).

5.4 Production of highly purified water

(a) There are no prescribed methods for the production of HPW in any major phar- macopoeia, including the European Pharmacopoeia. Any appropriate qualified purification technique or sequence of techniques may be used to prepare HPW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used.

The guidance provided in section 5.3 for PW is equally applicable to HPW.

5.5 Production of water for injections

(a) The pharmacopoeias prescribe or limit the permitted final water purification stage in the production of WFI. Distillation is the preferred technique; it is con- sidered a more robust technique based on phase change, and in some cases, high temperature operation of the process equipment.

(b) The following should be considered when designing a water purification system:
  (i) the feed-water quality;
  (ii) the required water quality specification;
  (iii) the optimum generator size to avoid over-frequent start/stop cycling;
  (iv) blow-down and dump functions; and
  (v) cool-down venting to avoid contamination ingress.

6 Water purification, storage and distribution systems

(a) This section applies to WPU systems for PW, HPW and WFI. The water storage and distribution should work in conjunction with the purification plant to ensure consistent delivery of water to the user points, and to ensure optimum operation of the water purification equipment.

6.1 General

(a) The storage and distribution system should be considered as a key part of the whole system, and should be designed to be fully integrated with the water purification components of the system.

(b) Once water has been purified using an appropriate method, it can either be used directly or, more frequently, it will be fed into a storage vessel for subse- quent distribution to points of use. The following text describes the require- ments for storage and distribution systems.

(c) The storage and distribution system should be configured to prevent recon- tamination of the water after treatment and be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained.

6.2 Materials that come into contact with systems for water for pharmaceutical use

(a) This section applies to generation equipment for PW, HPW and WFI, and the associated storage and distribution systems.

(b) The materials that come into contact with WPU, including pipework, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives.

  (i) Compatibility. All materials used should be compatible with the temperature

and chemicals used by or in the system.

(ii) Prevention of leaching. All materials that come into contact with WPU should be non-leaching at the range of working temperatures.

(iii) Corrosion resistance. PW, HPW and WFI are highly corrosive. To prevent failure of the system and contamination of the water, the materials selected must be appropriate, the method of jointing must be carefully controlled, and all fittings and components must be compatible with the pipework used. Appropriate sanitary-specification plastics and stainless steel materials are acceptable for WPU systems. When stainless steel is used it should be at least grade 316 L. The system should be passivated after initial installation or after modification. When accelerated passivation is undertaken, the system should be thoroughly cleaned first, and the passivation process should be undertaken in accordance with a clearly defined documented procedure.

(iv) Smooth internal finish. Once water has been purified it is susceptible to microbiological contamination, and the system is subject to the formation of biofilms when cold storage and distribution is employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices are frequently sites where corrosion can commence. The internal finish should have an arithmetical average surface roughness of not greater than 0.8 micrometre arithmetical mean roughness (Ra). When stainlesssteel is used, mechanical and electropolishing techniques may be employed. Electropolishing improves the resistance of the stainless steel material to surface corrosion.

(v) Jointing. The selected system materials should be able to be easily jointed by welding in a controlled manner. The control of the process should include as a minimum, qualification of the operator, documentation of the welder set-up, work-session test pieces, logs of all welds and visual inspection of a defined proportions of welds.

(vi) Design of flanges or unions. Where flanges or unions are used, they should be of a hygienic or sanitary design. Appropriate checks should be carried out to ensure that the correct seals are used and that they are fitted and tight- ened correctly.

(vii) Documentation. All system components should be fully documented and be supported by original or certified copies of material certificates.

(viii) Materials. Suitable materials that may be considered for sanitary elements of the system include 316 L (low carbon) stainless steel, polypropylene, polyvinylidenedifluoride and perfluoroalkoxy. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equip- ment designed for less pure water such as ion exchangers and softeners.

6.3 System sanitization and bioburden control

(a) Water treatment equipment, storage and distribution systems used for PW, HPW and WFI should be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for san- itizing or sterilizing the system after intervention for maintenance or modifica- tion. The techniques employed should be considered during the design of the system and their performance proven during the commissioning and qualifica- tion activities.

(b) Systems that operate and are maintained at elevated temperatures, in the range of 70–80°C, are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed or the temperature requirements for the water in use, then special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants (see section 6.5.3 for guidance).

6.4 Storage vessel requirements

(a) The water storage vessel used in a system serves a number of important purposes. The design and size of the vessel should take into consideration the following.

6.4.1 Capacity

(a) The capacity of the storage vessel should be determined on the basis of the following requirements.
  (i) It is necessary to provide a buffer capacity between the steady-state generation rate of the water-treatment equipment and the potentially variable simultaneous demand from user points
  (ii) The water treatment equipment should be able to operate continuously for significant periods to avoid the inefficiencies and equipment stress that occur when the equipment cycles on and off too frequently.
  (iii) The capacity should be sufficient to provide short-term reserve capacity in the event of failure of the water-treatment equipment or inability to produce water due to a sanitization or regeneration cycle. When determining the size of such reserve capacity, consideration should be given to providing sufficient water to complete a process batch, work session or other logical period of demand.

6.4.2 Contamination control considerations

(a) The following should be taken into account for the efficient control of contamination.
  (i) The headspace in the storage vessel is an area of risk where water droplets and air can come into contact at temperatures that encourage the proliferation of microbiological organisms. The water distribution loop should be configured to ensure that the headspace of the storage vessel is effectively wetted by a flow of water. The use of spray ball or distributor devices to wet the surfaces should be considered.

(ii) Nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harboured.

(iii) Vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should be bacteria-retentive, hydrophobic and ideally be configured to allow in situ testing of integrity. Offline testing is also acceptable. The use of heated vent filters should be considered to prevent condensation within the filter matrix that might lead to filter blockage and to microbial grow-through that could contaminate the storage vessels.

(iv) Where pressure-relief valves and bursting discs are provided on storage vessels to protect them from over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to prevent accidental loss of system integrity.

6.5 Requirements for water distribution pipework

(a) The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled.

(b) Filtration should not usually be used in distribution loops or at takeoff user points to control biocontamination. Such filters are likely to conceal system contamination.

6.5.1 Temperature control and heat exchangers

(a) Where heat exchangers are employed to heat or cool WPU within a system, precautions should be taken to prevent the heating or cooling utility from contaminating the water. The more secure types of heat exchangers of the double tube plate or double plate and frame configuration should be considered. Where these types are not used, an alternative approach whereby the utility is maintained and monitored at a lower pressure than the WPU may be considered. Where heat exchangers are used they should be arranged in continually circulating loops or subloops of the system to avoid unacceptable static water in systems.

(b) When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

6.5.2 Circulation pumps

(a) Circulation pumps should be of a sanitary design with appropriate seals that prevent contamination of the system. Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

6.5.3 Biocontamination control techniques

(a) The following control techniques may be used alone or more commonly in combination.

(i) Maintenance of continuous turbulent flow circulation within water distribution

systems reduces the propensity for the formation of biofilms. The maintenance of the design velocity for a specific system should be proven during the system qualification and the maintenance of satisfactory performance should be monitored. During the operation of a distribution system, short- term fluctuations in the flow velocity are unlikely to cause contamination problems provided that cessation of flow, flow reversal or pressure loss does not occur.

(ii) The system design should ensure the shortest possible length of pipework.
(iii) For ambient temperature systems, pipework should be isolated from adjacent hot pipes.
(iv) Deadlegs in the pipework installation greater than 1.5 times the branch diameter should be avoided.
(v) Pressure gauges should be separated from the system by membranes.
(vi) Hygienic pattern diaphragm valves should be used.
(vii) Pipework should be laid to falls to allow drainage.
(viii) The growth of microorganisms can be inhibited by:
(ix) ultraviolet radiation sources in pipework;
(x) maintaining the system heated (guidance temperature 70–80°C);
(xi) sanitizing the system periodically using hot water (guidance temperature >70°C);
(xii) sterilizing or sanitizing the system periodically using superheated hot water or clean steam; and
(xiii) routine chemical sanitization using ozone or other suitable chemical agents. When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water. Ozone can be effectively removed by using ultraviolet radiation.

7 Operational considerations

7.1 Start-up and commissioning of water systems

(a) Planned, well-defined, successful and well-documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system setup, controls loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

7.2 Qualification

(a) WPU, PW, HPW and WFI systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

(b) This guidance does not define the standard requirements for the conventional validation stages DQ, IQ and OQ, but concentrates on the particular PQ approach

that should be used for WPU systems to demonstrate their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

(c) **Phase1**: A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation. The following should be included in the testing approach.

(i) Undertake chemical and microbiological testing in accordance with a defined plan.
(ii) Sample the incoming feed-water daily to verify its quality.
(iii) Sample after each step in the purification process daily.
(iv) Sample at each point of use and at other defined sample points daily.
(v) Develop appropriate operating ranges.
(vi) Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
(vii) Demonstrate production and delivery of product water of the required quality and quantity.
(viii) Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
(ix) Verify provisional alert and action levels.
(x) Develop and refine test-failure procedure.

(d) **Phase 2**: A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purposes during this phase. The approach should also:

(i) demonstrate consistent operation within established ranges; and
(ii) demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

(e) **Phase 3**: Phase 3 typically runs for 1 year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features.

(i) Demonstrate extended reliable performance.
(ii) Ensure that seasonal variations are evaluated.
(iii) The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

7.3 Continuous system monitoring

(a) After completion of phase 3 of the qualification programme for the WPU system, a system review should be undertaken. Following this review, a routine monitoring plan

should be established based on the results of phase 3.

(b) Monitoring should include a combination of online instrument monitoring of parameters such as flow, pressure, temperature, conductivity and total organic carbon, and offline sample testing for physical, chemical and microbiological attributes. Offline samples should be taken from points of use and specific sample points. Samples from points of use should be taken in a similar way to that adopted when the water is being used in service.

(c) Tests should be carried out to ensure that the selected pharmacopoeia specification has been satisfied, and should include, as appropriate, determination of conductivity, pH, heavy metals, nitrates, total organic carbon, total viable count, presence of specific pathogens and endotoxins.

(d) Monitoring data should be subject to trend analysis.

7.4 Maintenance of water systems

(a) WPU systems should be maintained in accordance with a controlled, documented maintenance programme that takes into account the following:

(i) defined frequency for system elements;
(ii) the calibration programme;
(iii) SOPs for specific tasks;
(iv) control of approved spares;
(v) issue of clear maintenance plan and instructions;
(vi) review and approval of systems for use upon completion of work; and
(vii) record and review of problems and faults during maintenance.

7.5 System reviews

(a) WPU (PW, HPW and WFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, operations and maintenance. The review should consider matters such as:

(i) changes made since the last review;
(ii) system performance;
(iii) reliability;
(iv) quality trends;
(v) failure events;
(vi) investigations;
(vii) out-of-specifications results from monitoring;
(viii) changes to the installation;
(ix) updated installation documentation;
(x) log books; and
(xi) the status of the current SOP list.

8.0 Inspection of water systems

(a) WPU (PW, HPW and WFI) systems are likely to be the subject of regulatory inspection from time to time. Users should consider conducting routine audit and self-inspection of established water systems. This GMP guidance can be used as the basis of inspection. The following list identifies items and a logical sequence for a WPU system inspection or audit:

(i) a sampling and monitoring plan with a drawing of all sample points;
(ii) the setting of monitoring alert and action levels;
(iii) monitoring results and evaluation of trends;
(iv) inspection of the last annual system review;
(v) review of any changes made to the system since the last audit and check that the change control has been implemented;
(vi) review of deviations recorded and their investigation;
(vii) general inspection of system for status and condition;
(viii) review of maintenance, failure and repair logs; and
(ix) checking calibration and standardization of critical instruments.

(b) For an established system that is demonstrably under control, this scope of review should prove adequate.

(c) For new systems, or systems that display instability or unreliability, the fol- lowing should also be reviewed:

(i) performance qualification;
(ii) operational qualification; and
(iii) Installation qualification.

Annex 8 Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. A well designed HVAC system will also provide comfortable conditions for operators. These guidelines mainly focus on recommendations for systems for manufacturers of solid dosage forms. The guidelines also refer to other systems or components which are not relevant to solid dosage form manufacturing plants, but which may assist in providing a comparison between the requirements for solid dosage- form plants and other systems.

(a) HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross-contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system. In view of these critical aspects, the design of the HVAC system should be considered at the concept design stage of a pharmaceutical manufacturing plant.

(b) Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

(c) This document aims to give guidance to pharmaceutical manufacturers and inspectors of pharmaceutical manufacturing facilities on the design, installation, qualification and maintenance of the HVAC systems. These guidelines are intended to complement those provided in Good manufacturing practices for pharmaceutical products (1) and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements set out in the parent guide.

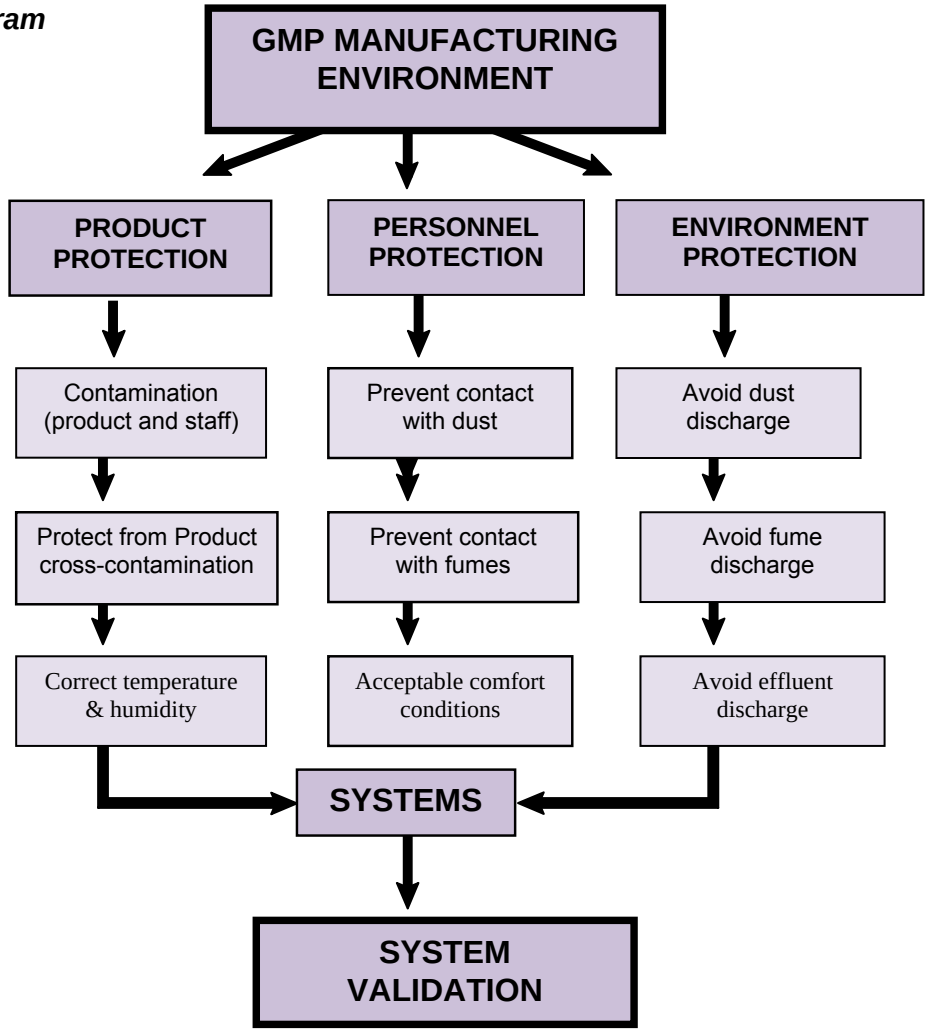
2. Scope

(a) These guidelines focus primarily on the design and good manufacturing practices (GMP) requirements for HVAC systems for facilities for the manufacture of solid dosage forms. Most of the system design principles for facilities manufacturing solid dosage forms also apply to other facilities such as those manufacturing liquids, creams and ointments. These guidelines do not cover requirements for manufacturing sites for the production of sterile pharmaceutical products.

(b) These guidelines are intended as a basic guide for use by GMP inspectors. They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation.

(c) Many manufacturers have their own engineering design and qualification standards and requirements may vary from one manufacturer to the next.

Figure 1: The guidelines address the various system criteria according to the sequence set out in this diagram



GMP, Good Manufacturing Practice

Design parameters should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standards and ensuring that product quality and safety are not compromised. The three primary aspects addressed in this manual are the roles that the HVAC system plays in product protection, personnel protection and environmental protection (Fig. 1).

3 Glossary

The definitions given below apply to terms used in these guidelines. They may have different meanings in other contexts

Acceptance criteria

Measurable terms under which a test result will be considered acceptable.

Action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

Air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

Airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (PAL, personnel airlock; MAL, material airlock).

Alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

As-built

Condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present.

At-rest

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.

Central air-conditioning unit (see air-handling unit)

Change control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

Clean area (clean room)[1]

An area (or room) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the intro- duction, generation and retention of contaminants within the area.

Commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

Containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

Contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during pro- duction, sampling, packaging or repackaging, storage or transport.

Critical parameter or component

A processing parameter (such as temperature or humidity) that affects the quality of a product, or a component that may have a direct impact on the quality of the product.

Cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

Design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

[1] *Note: Clean area standards, such as ISO 14644-1 provide details on how to classify air cleanliness by means of particle concentrations, whereas the GMP standards provide a grading for air cleanliness in terms of the condition (at-rest or operational), the permissible microbial concentrations, as well as other factors such as gowning requirements. GMP and clean area standards should be used in conjunction with each other to define and classify the different manufacturing environments.*

Design qualification (DQ)

DQ is the documented check of planning documents and technical specifications for conformity of the design with the process, manufacturing, GMP and regulatory requirements.

Direct impact system

A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice (GEP) and, in addition, are subject to qualification practices.

Facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

Good engineering practice (GEP)

Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.

Indirect impact system

This is a system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to GEP only.

Infiltration

Infiltration is the ingress of contaminated air from an external zone into a clean area.

Installation qualification (IQ)

IQ is documented verification that the premises, HVAC system, supporting utilities and equipment have been built and installed in compliance with their approved design specification.

No-impact system

This is a system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned according to GEP only.

Non-critical parameter or component

A processing parameter or component within a system where the operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

Normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

Operating limits

The minimum and/or maximum values that will ensure that product and safety requirements are met.

Operating range

Operating range is the range of validated critical parameters within which acceptable products can be manufactured.

Operational condition

This condition relates to carrying out room classification tests with the normal production process with equipment in operation, and the normal staff present in the room.

Operational qualification (OQ)

OQ is the documentary evidence to verify that the equipment operates in accordance with its design specifications in its normal operating range and performs as intended throughout all anticipated operating ranges.

Oral solid dosage (OSD)

Usually refers to an OSD plant that manufactures medicinal products such as tablets, capsules and powders to be taken orally.

Performance qualification (PQ)

PQ is the documented verification that the process and/or the total process related to the system performs as intended throughout all anticipated operating ranges.

Point extraction

Air extraction to remove dust with the extraction point located as close as possible to the source of the dust.

Pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

Qualification

Qualification is the planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

Relative humidity

The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

Standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Turbulent flow

Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

Unidirectional airflow (UDAF)

Unidirectional airflow is a rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent flow). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

Validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

Validation Master Plan (VMP)

VMP is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

4 Protection

4.1 Product and personnel

4.1.1 Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils and equipment are exposed to the environment, should be classified as “clean areas”.

4.1.2 The achievement of a particular clean area classification depends on a number of criteria that should be addressed at the design and qualification stages. A suitable balance between the different criteria will be required in order to create an efficient clean area.

4.1.3 Some of the basic criteria to be considered should include:

(a) building finishes and structure
(b) air filtration
(c) air change rate or flushing rate
(d) room pressure
(e) location of air terminals and directional airflow
(f) temperature
(g) humidity
(h) material flow
(i) personnel flow
(j) equipment movement
(k) process being carried out
(l) outside air conditions
(m)occupancy
(n) type of product.

4.1.4 Air filtration and air change rates should ensure that the defined clean area classification is attained.

4.1.5 The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters. Primarily the air change rate should be set to a level that will achieve the required clean area classification.

4.1.6 Air change rates normally vary between 6 and 20 air changes per hour and are normally determined by the following considerations:

(a) level of protection required
(b) the quality and filtration of the supply air
(c) particulates generated by the manufacturing process
(d) particulates generated by the operators
(e) configuration of the room and air supply and extract locations
(f) sufficient air to achieve containment effect
(g) sufficient air to cope with the room heat load
(h) Sufficient air to maintain the required room pressure.

4.1.7 In classifying the environment, the manufacturer should state whether this is achieved under “as-built” (Fig. 2), “at-rest” (Fig. 3) or “operational” (Fig. 4) conditions.

Figure 2. "As-built" condition

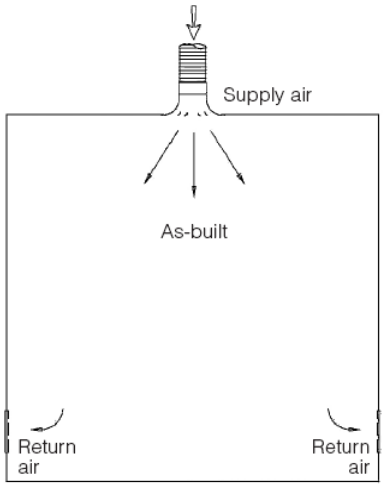


Figure 3. "At-rest" condition

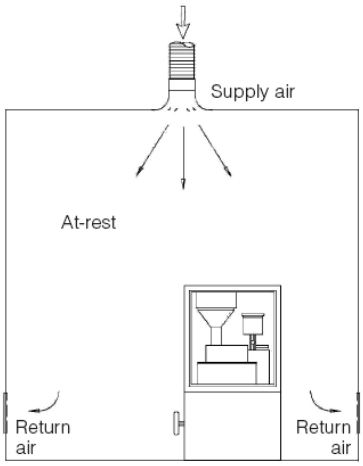
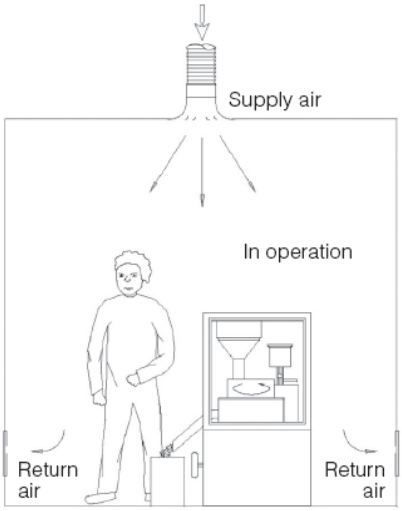


Figure 4: "Operational" Condition



4.1.8 Room classification tests in the “as-built” condition should be carried out on the bare room, in the absence of any equipment or personnel.

4.1.9 Room classification tests in the “at-rest” condition should be carried out with the equipment operating where relevant, but without any operators. Because of the amounts of dust usually generated in a solid dosage facility most clean area classifications are rated for the “at-rest” condition.

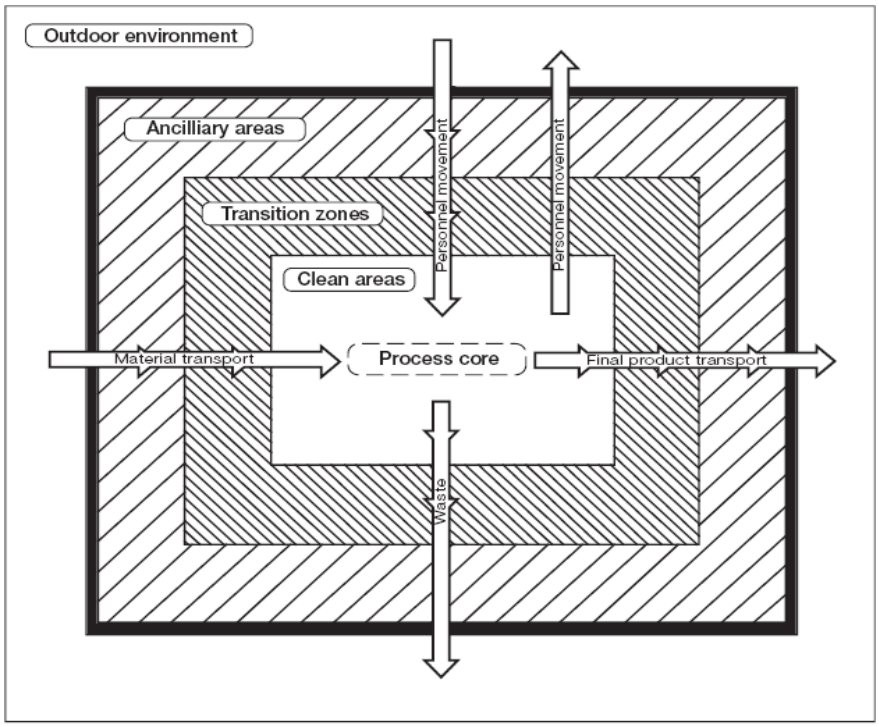
4.1.10 Room classification tests in the “operational” condition should be carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally a room that is tested for an “operational” condition should be able to be cleaned up to the “at-rest” clean area classification after a short clean-up time. The clean-up time should be determined through validation and is generally of the order of 20 minutes.

4.1.11 Materials and products should be protected from contamination and cross-contamination during all stages of manufacture (see also section 5.5 for cross-contamination control). Note: contaminants may result from inappropriate premises (e.g. poor design, layout or finishing), poor cleaning procedures, contaminants brought in by personnel, and a poor HVAC system.

4.1.12 Airborne contaminants should be controlled through effective ventilation.

4.1.13 External contaminants should be removed by effective filtration of the supply air. (See Fig. 5 for an example of a shell-like building layout to enhance containment and protection from external contaminants.)

Figure 5. Shell-like containment control concept



Note: The process core is regarded as the most stringently controlled clean zone which is protected by being surrounded by clean areas of a lower classification.

4.1.14 Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow. (See Figs 6 and 7 for examples of methods for the flushing of airborne contaminants.)

4.1.15 Airborne particulates and the degree of filtration should be considered critical parameters with reference to the level of product protection required.

4.1.16 The level of protection and air cleanliness for different areas should be determined according to the product being manufactured, the process being used and the product's susceptibility to degradation (Table 1).

4.2 Air filtration

Note: The degree to which air is filtered plays an important role in the prevention of contamination and the control of cross-contamination.

4.2.1 The type of filters required for different applications depend on the quality of the ambient air and the return air (where applicable) and also on the air change rates. Table 2 gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should deter- mine and prove the appropriate use of filters.

Figure 6. Turbulent dilution of dirty air

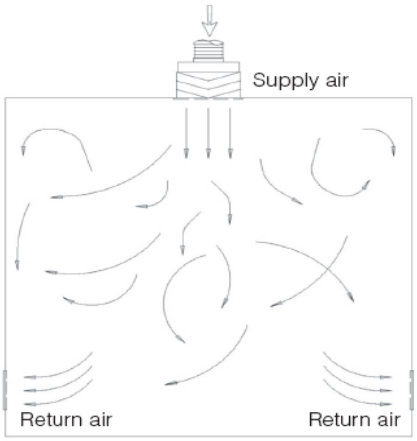


Figure 7. Unidirectional displacement of dirty air

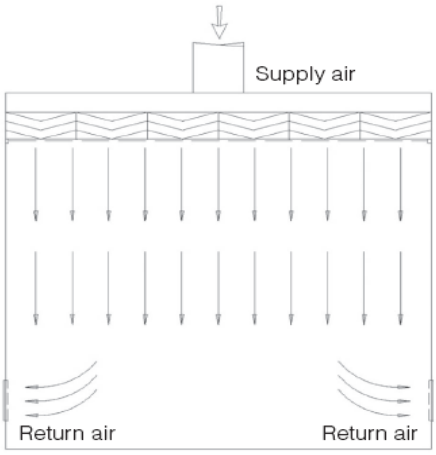


Table 1. Examples of levels of protection

Level	Condition	Example of area
Level 1	General Area	with normal housekeeping and maintenance, e.g. ware- housing, secondary packing
Level 2	Protected Area	in which steps are taken to protect the exposed pharmaceutical starting material or product from contamination or degradation, e.g. manufacturing, primary packing, dispensing
Level 3	Controlled Area	in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product

Table 2. Levels of protection and recommended filtration

Level of Protection	Example of area
Level 1	Primary filters only (e.g. EN779 G4 filters)
Levels 2 and 3	Production facility operating on 100% outside air: primary plus secondary filters (e.g. EN779 G4 plus F8 filters)
Levels 2 and 3	Production facility operating on recirculated 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)

Note: The filter classifications referred to above relate to the EN1822 and EN779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes H10 to U16).

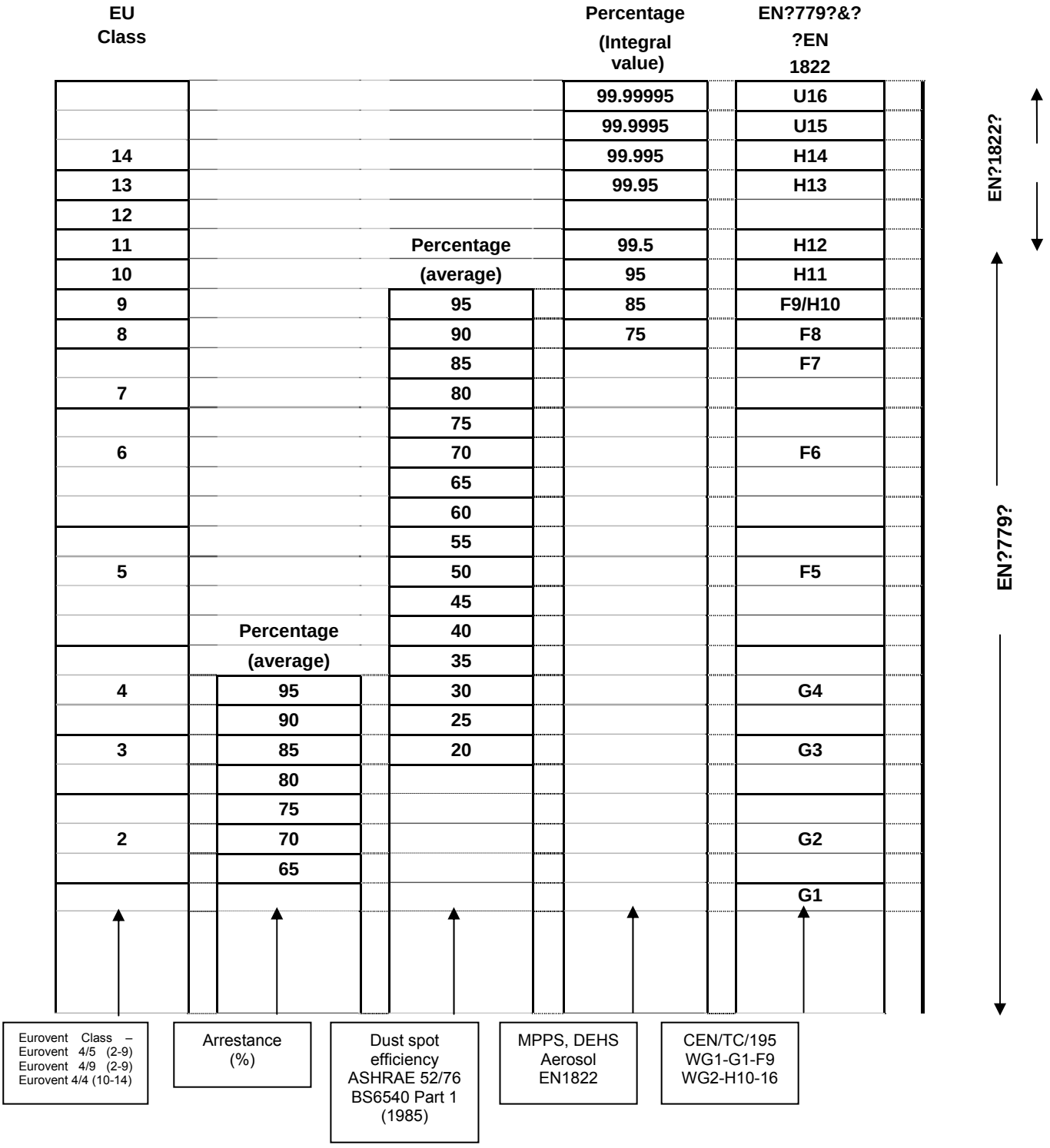
4.2.2 Filter classes should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (as different test methods each result in a different value for the same filter) (Fig. 8).

4.2.3 In selecting filters, the manufacturer should have considered other factors, such as particularly contaminated ambient conditions, local regulations and specific product requirements. Good prefiltration extends the life of the more expensive filters downstream.

4.2.4 Materials for components of an HVAC system should be selected with care so that they do not become the source of contamination. Any component with the potential for liberating particulate or microbial contamination into the air stream should be located upstream of the final filters.

4.2.5 Ventilation dampers, filters and other services should be designed and positioned so that they are accessible from outside the manufacturing areas (service voids or service corridors) for maintenance purposes.

Figure 8. Comparison of filter test standards



EN, European norm (Euronorm); EU, European Union.

This figure gives a rough comparison between the different filter standards (filter classes should always be connected to the standard test method

4.2.6 Personnel should not be a source of contamination.

4.2.7 Directional airflow within production or packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation.

4.2.8 HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread.

4.2.9 Supply air diffusers of the high induction type (e.g. those typically used for office-type air-conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect. (See Figs 9–11 for illustrations of the three types of diffuser.)

4.2.10 Whenever possible, air should be exhausted from a low level in rooms to help provide a flushing effect.

4.3 Unidirectional airflow

4.3.1 Unidirectional airflow (UDAF) should be used where appropriate to provide product protection by supplying a clean air supply over the product, minimizing the ingress of contaminants from surrounding areas.

Figure 9. Induction diffuser (not recommended)

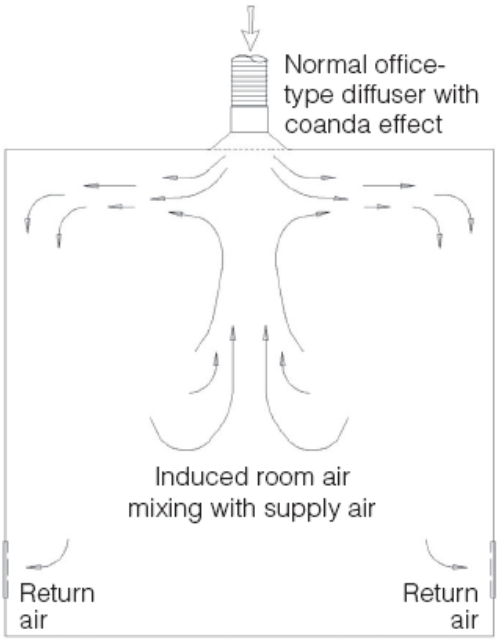


Figure 10. Perforated plate diffuser (recommended)

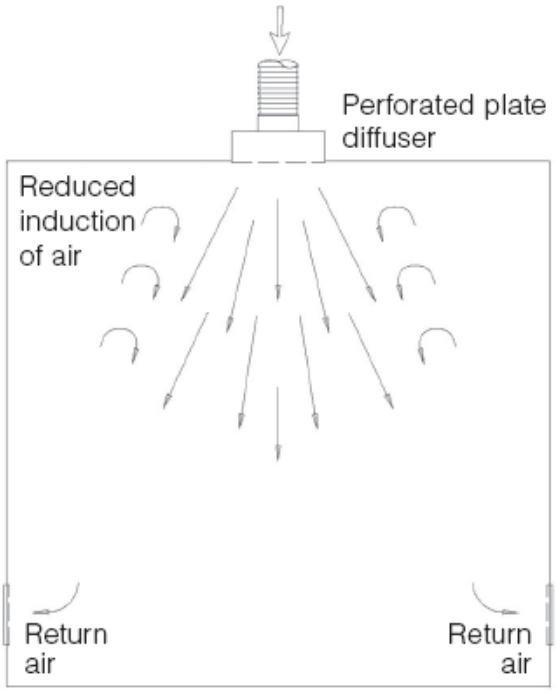
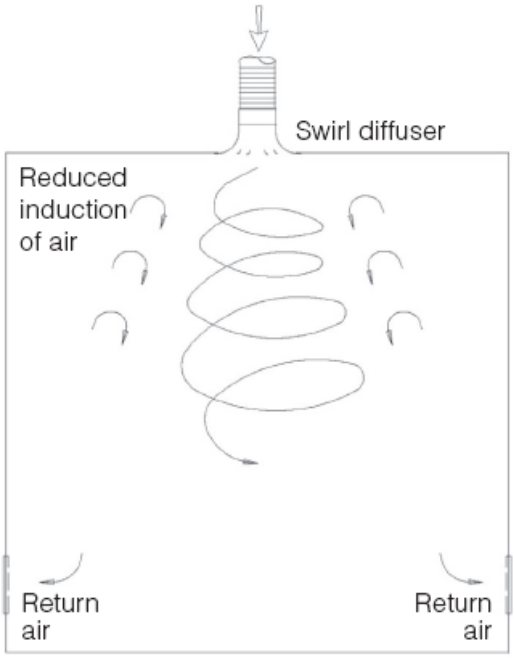


Figure 11. Swirl diffuser (recommended)



4.3.2 Where appropriate, the unidirectional airflow should also provide pro- tection to the operator from contamination by the product.

4.3.3 Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for the further processing of the product.

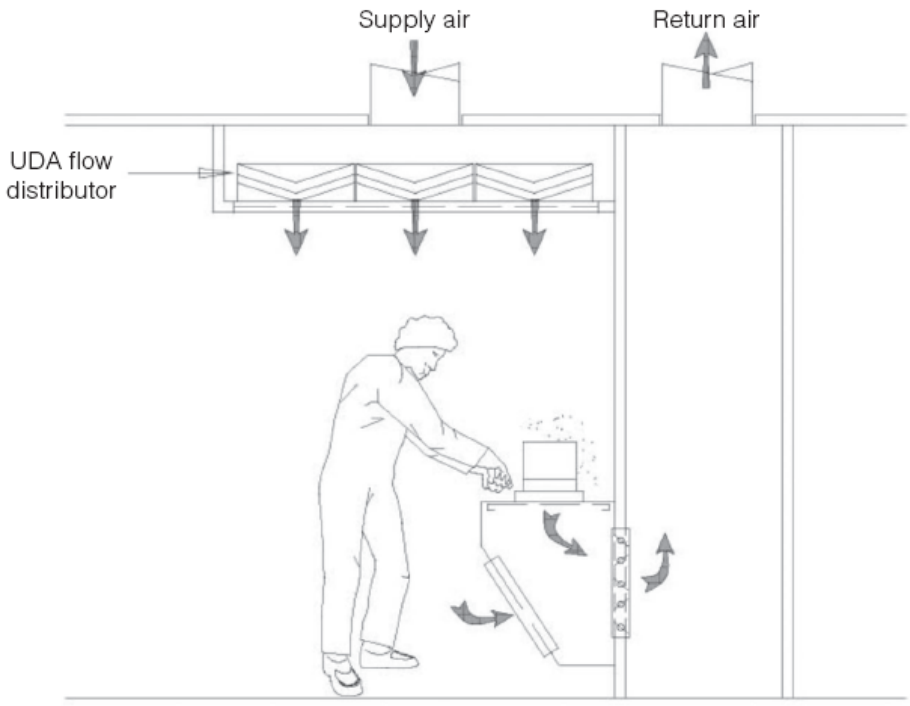
4.3.4 In a weighing booth situation, the aim of the design using UDAF should be to provide dust containment.

4.3.5 A dispensary or weighing booth should be provided with unidirectional airflow for protection of the product and operator.

4.3.6 The source of the dust and the position in which the operator normally stands should be determined before deciding on the direction of unidirectional flow.

Example: In Fig. 12 the dust generated at the weighing station is immediately extracted through the perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the product from contamination by the operator by means of the vertical unidirectional airflow stream.

Figure 12. Operator protection at weighing station



UDA, Unidirectional air.

4.3.7 The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent inaccuracies during weighing, provided that sufficient airflow is maintained to provide containment.

4.3.8 The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product (Fig. 13).

4.3.9 Once the system has been designed and qualified with a specific layout for operators and processes, this should be maintained in accordance with an SOP.

4.3.10 There should be no obstructions in the path of a unidirectional flow air stream that may cause the operator to be exposed to dust.

Fig. 14 illustrates the incorrect use of a weighing scale which has a solid back. The back of the weighing scale should not block the return air path as this causes air to rise vertically, resulting in a hazardous situation for the operator.

Fig. 15 illustrates a situation where an open bin is placed below a vertical unidirectional flow distributor. The downward airflow should be prevented from entering the bin, and then being forced to rise again, as this would carry dust up towards the operator's face.

Fig. 16 shows that a solid worktop can sometimes cause deflection of the vertical unidirectional airflow resulting in a flow reversal. A possible solution would be to have a 100 mm gap between the back of the table and the wall, with the air being extracted here.

4.3.11 The manufacturer should select either vertical or horizontal unidirectional flow (Fig. 17) and an appropriate airflow pattern to provide the best protection for the particular application.

4.4 Infiltration

4.4.1 Air infiltration of unfiltered air into a pharmaceutical plant should not be the source of contamination.

4.4.2 Manufacturing facilities should be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure to prevent the escape of harmful products to the outside (such as penicillin and hormones), special precautions should be taken.

4.4.3 The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structure is well sealed.

Figure 13. Operator protection by horizontal airflow

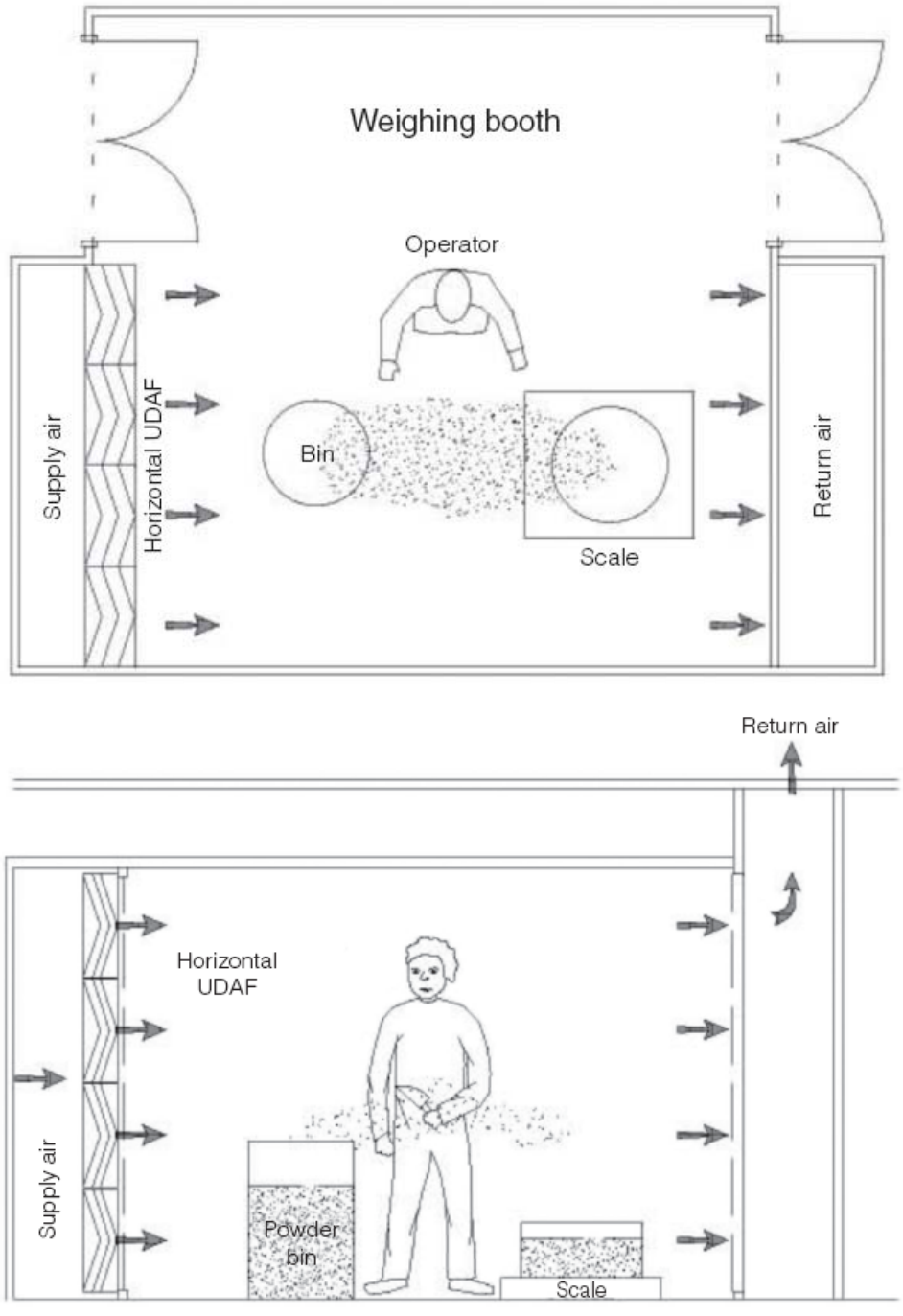
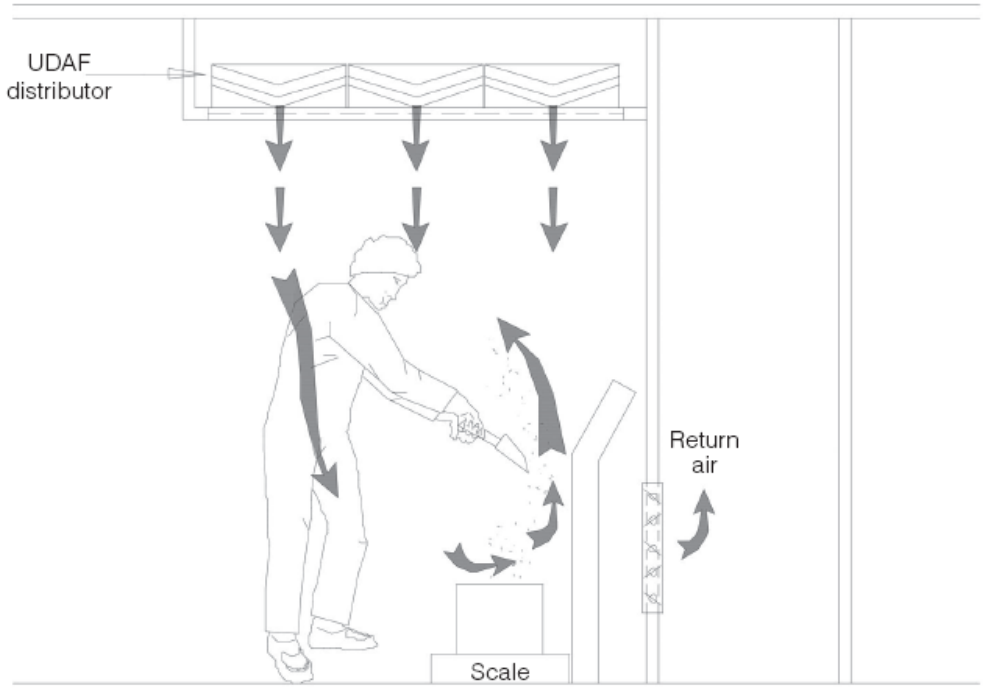


Figure 14. Operator subject to powder inhalation due to obstruction



UDAF, Unidirectional airflow.

Figure 15. Operator subject to powder contamination due to airflow reversal in bin

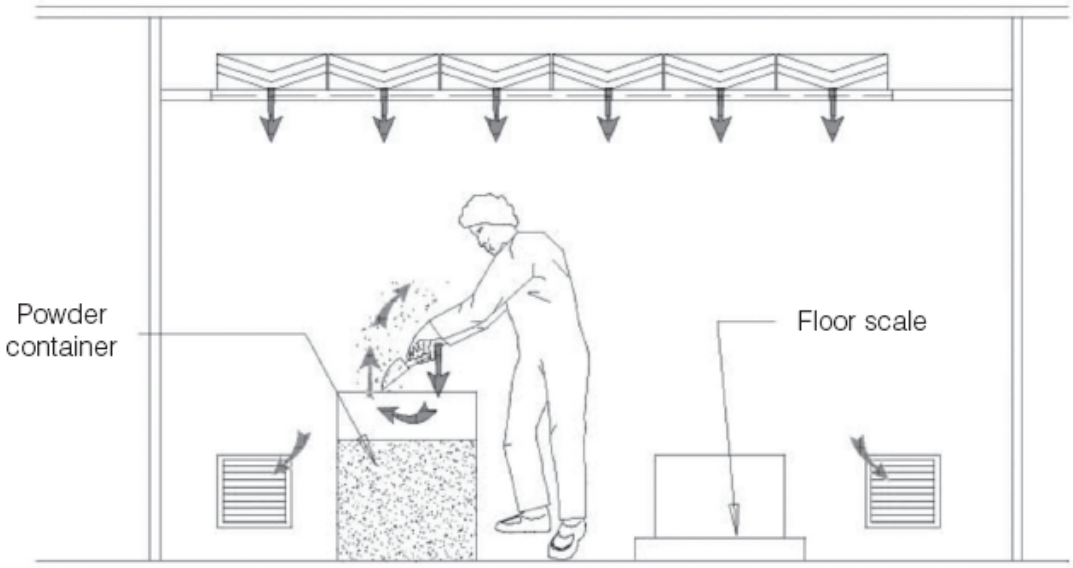
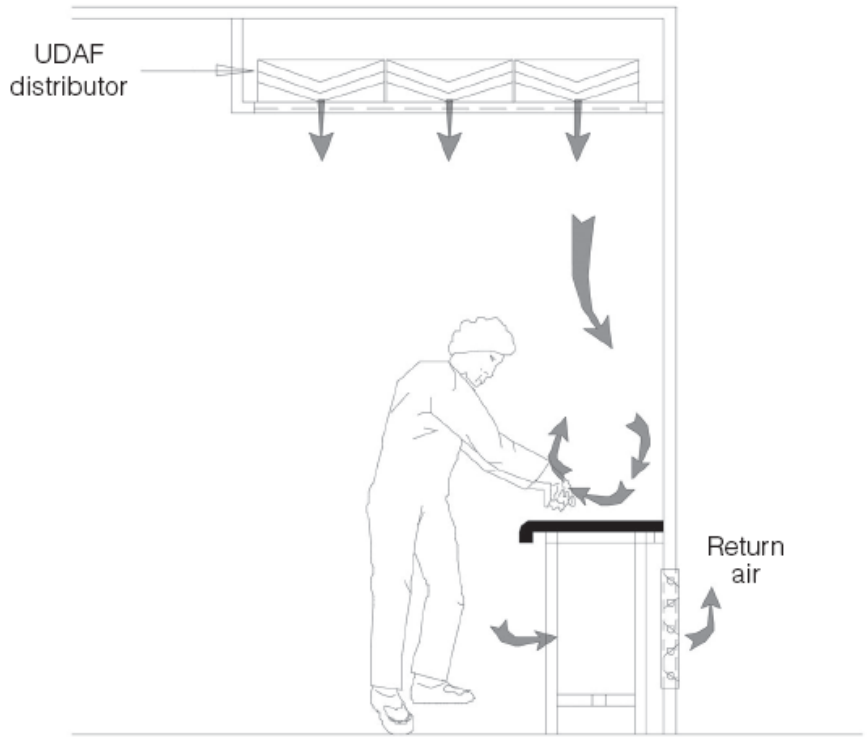
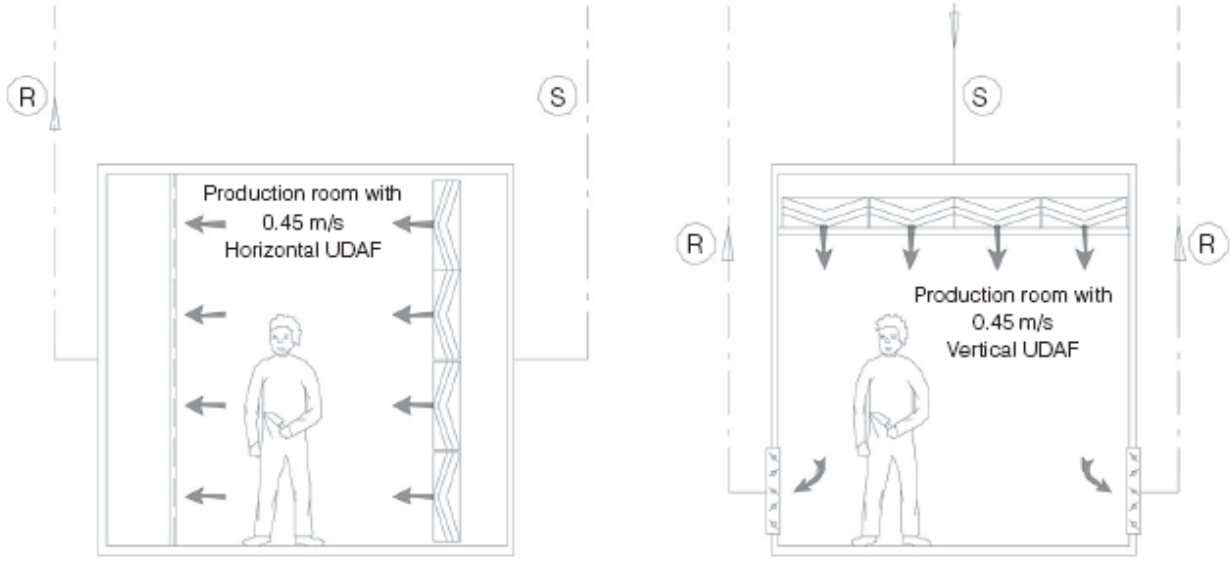


Figure 16. Operator subject to powder inhalation due to worktop obstruction



UDAF, Unidirectional airflow.

Figure 17. Diagram indicating horizontal and vertical unidirectional flow



UDAF, Unidirectional airflow.

4.4.4 Negative pressure zones should, as far as possible, be encapsulated by sur- rounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

4.5 Cross-contamination

4.5.1 Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another.

4.5.2 Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.

4.5.3 The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

4.5.4 Containment can normally be achieved by application of the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or the physical barrier concept.

4.5.5 The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used.

4.5.6 Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.

4.5.7 The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required.

4.5.8 Building structure should be given special attention to accommodate the pressure cascade design.

4.5.9 Airtight ceilings and walls, close fitting doors and sealed light fittings should be in place.

Displacement concept (low pressure differential, high airflow)

Note: This method of containment is not the preferred method, as the measurement and monitoring of airflow velocities in doorways is difficult. This concept should ideally be applied in production processes where large amounts of dust are generated.

4.5.10 Under this concept the air should be supplied to the corridor, flow through the doorway, and be extracted from the back of the cubicle. Normally the cubicle door should be closed and the air should enter the cubicle through a door grille, although the concept can be applied to an opening without a door.

4.5.11 The velocity should be high enough to prevent turbulence within the doorway resulting in dust escaping.

4.5.12 This displacement airflow should be calculated as the product of the door area and the velocity, which generally results in fairly large air quantities.

Pressure differential concept (high pressure differential, low airflow)

Note: The pressure differential concept may normally be used in zones where little or no dust is being generated. It may be used alone or in combination with other containment control techniques and concepts, such as a double door airlock.

4.5.13 The high pressure differential between the clean and less clean zones should be generated by leakage through the gaps of the closed doors to the cubicle.

4.5.14 The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems.

4.5.15 In considering room pressure differentials, transient variations, such as machine extract systems, should be taken into consideration.

Note: The most widely accepted pressure differential for achieving containment between two adjacent zones is 15 Pa, but pressure differentials of between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. For example, where a control tolerance of □3 Pa is specified, the implications of the upper and lower tolerances on containment should be evaluated.

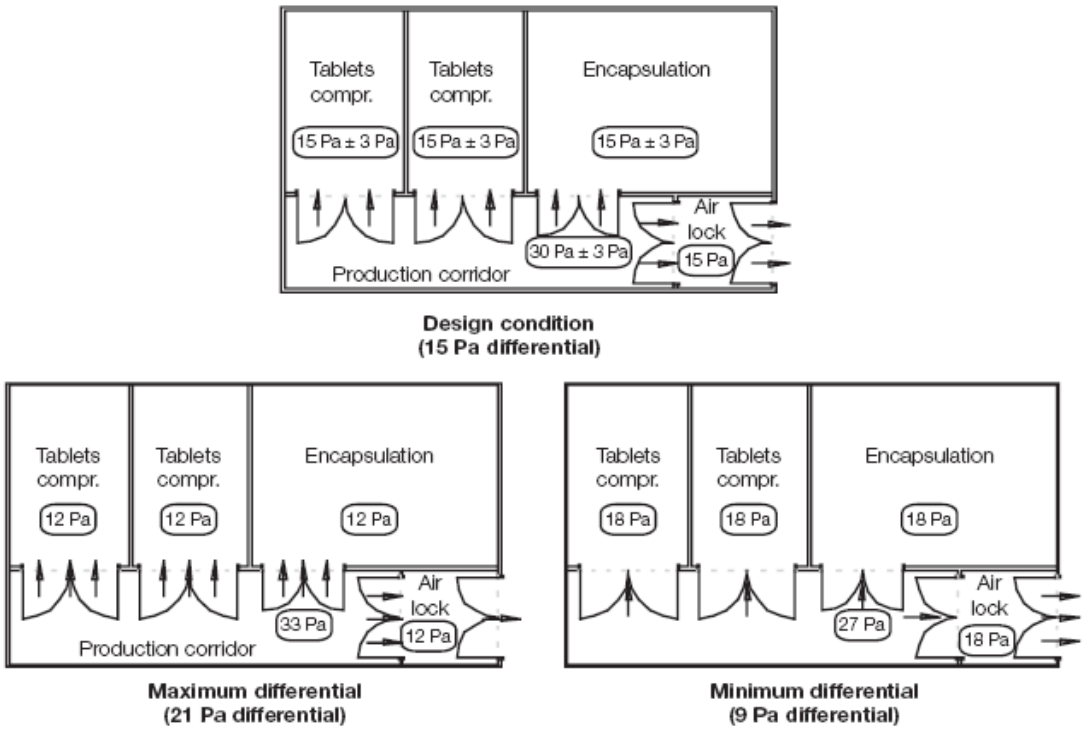
4.5.16 The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in no pressure cascade, if the first room is at the maximum tol- erance and the second room is at the minimum tolerance.

4.5.17 Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used.

4.5.18 The effect of room pressure tolerances are illustrated in Fig. 18.

4.5.19 The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis.

Figure 18. Examples of pressure cascades



4.5.20 Manual control systems, where used, should be set up during commissioning and should not change unless other system conditions change.

4.5.21 Airlocks can be important components in setting up and maintaining pressure cascade systems.

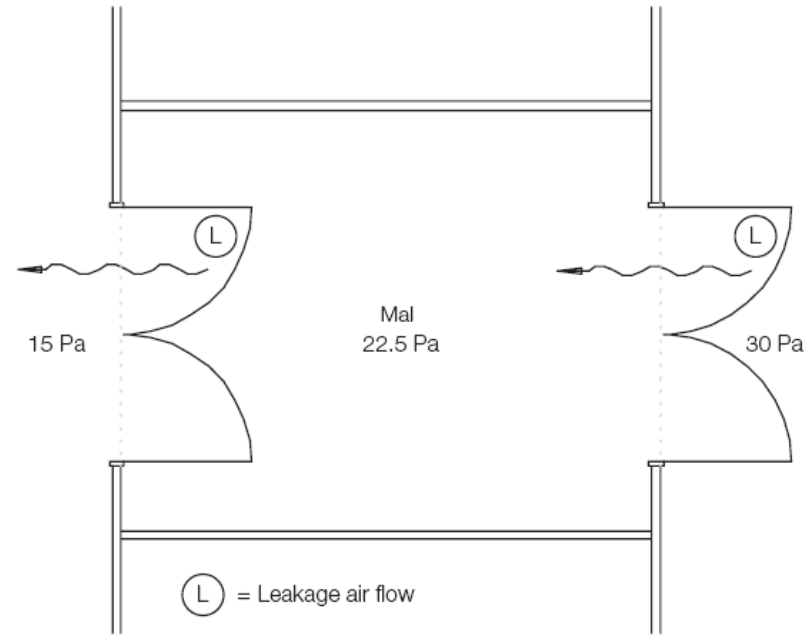
4.5.22 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figs 19–21).

(a) Cascade airlock: high pressure on one side of the airlock and low pressure on the other.
(b) Sink airlock: low pressure inside the airlock and high pressure on both outer sides.
(c) Bubble airlock: high pressure inside the airlock and low pressure on both outer sides.

4.5.23 Doors should open to the high pressure side, and be provided with self- closers. Door closer springs, if used, should be designed to hold the door closed and prevent the pressure differential from pushing the door open. Sliding doors are not recommended.

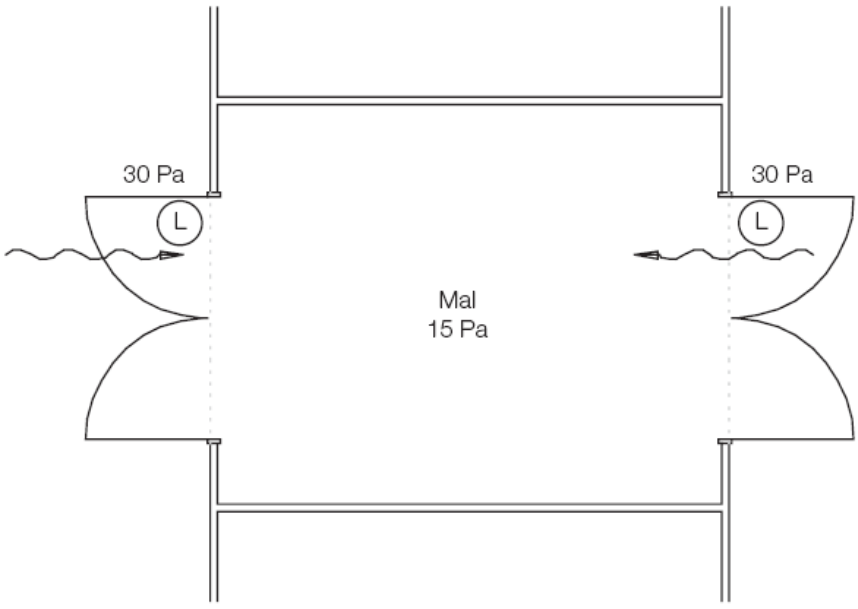
4.5.24 Central dust extraction systems should be interlocked with the appropriate air handling systems, to ensure that they operate simultaneously.

Figure 19. Example of cascade airlock



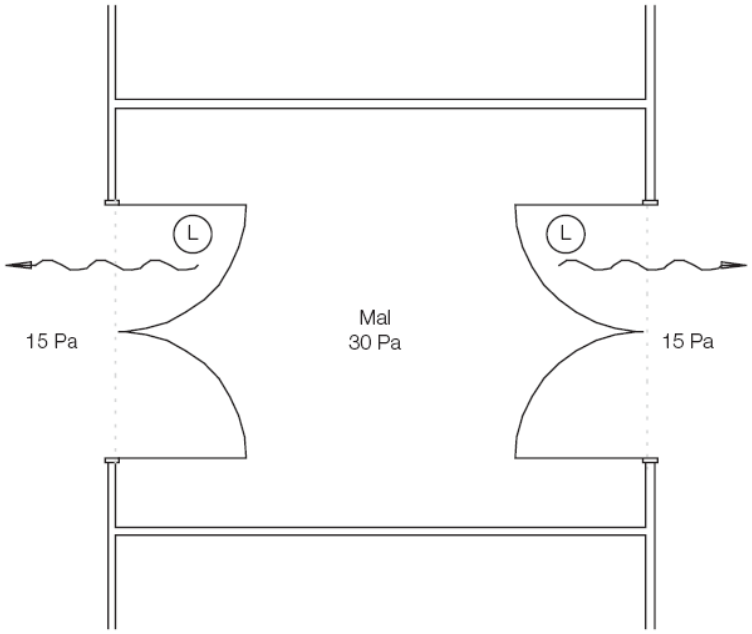
MAL, Material airlock.

Figure 20. Example of sink airlock



MAL, Material airlock.

Figure 21. Example of bubble airlock



MAL, Material airlock.

4.5.25 Room pressure imbalance between adjacent cubicles which are linked by common dust extraction ducting should be prevented.

4.5.26 Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting (this would normally occur only if the dust extraction system was inoperative).

Physical barrier concept

4.5.27 Where appropriate, an impervious barrier to prevent cross-contamination between two zones, such as barrier isolators or pumped transfer of materials, should be used.

4.5.28 Spot ventilation or capture hoods may be used as appropriate.

4.6 Temperature and relative humidity

4.6.1 Temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products, and to provide a comfortable environment for the operator where necessary.

4.6.2 Maximum and minimum room temperatures and relative humidity should be appropriate.

4.6.3 Temperature conditions should be adjusted to suit the needs of the oper- ators while wearing their protective clothing.

4.6.4 The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close.

4.6.5 Cubicles, or suites, in which products requiring low humidity are processed, should have well-sealed walls and ceilings and should also be sepa- rated from adjacent areas with higher humidity by means of suitable airlocks.

4.6.6 Precautions should be taken to prevent moisture migration that increases the load on the HVAC system.

4.6.7 Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.

4.6.8 Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.

4.6.9 Appropriate cooling media for dehumidification such as low temperature chilled water/glycol mixture or refrigerant should be used.

4.6.10 Humidifiers should be avoided if possible as they may become a source of contamination (e.g. Microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product-contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.

4.6.11 Where steam humidifiers are used, chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system.

4.6.12 Humidification systems should be well drained. No condensate should accumulate in air-handling systems.

4.6.13 Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used because of the potential risk of microbial contamination.

4.6.14 Duct material in the vicinity of the humidifier should not add contaminants to air that will not be filtered downstream.

4.6.15 Air filters should not be installed immediately downstream of humidifiers.

4.6.16 Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components.

4.6.17 When specifying relative humidity, the associated temperature should also be specified.

4.6.18 Chemical driers using silica gel or lithium chloride are acceptable, pro- vided that they do not become sources of contamination.

5.0 Dust control

5.1 Wherever possible, the dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed.

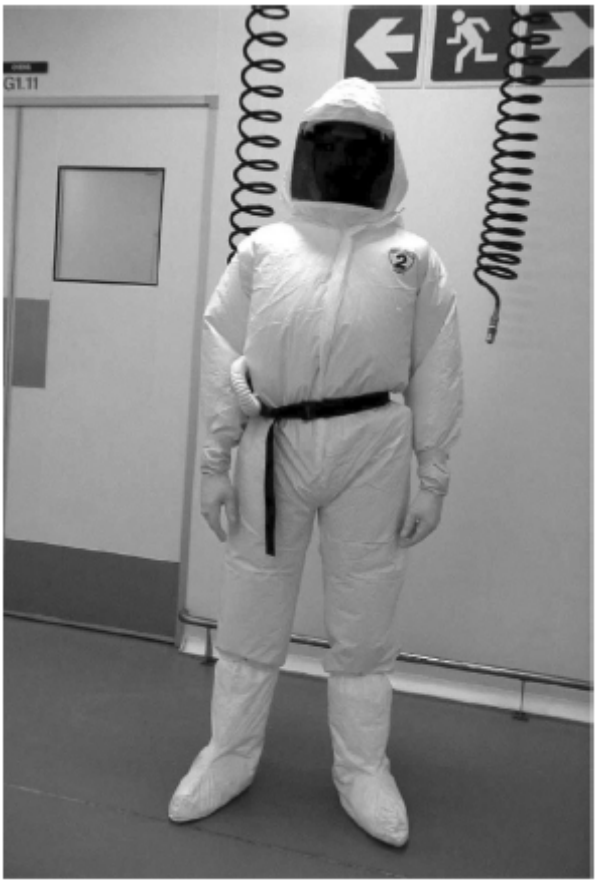
5.2 Point-of-use extraction should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.

5.3 Dust extraction ducting should be designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting.

5.4 The required transfer velocity should be determined: it is dependent on the density of the dust (the denser the dust, the higher the transfer velocity should be, e.g. 15–20 m/s).

5.5 Airflow direction should be carefully chosen, to ensure that the operator does not contaminate the product, and so that the operator is not put at risk by the product.

Figure 22. Protective garments



5.6 Dust-related hazards to which the operators may be subjected should be assessed. An analysis of the type of dust and toxicity thereof should be done and the airflow direction determined accordingly.

5.7 Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow should be used to assist in removing dust and vapours from the room.

5.8 Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers and extracted from the room at low level to help give a flushing effect in the room

5.9 The low-level extraction should assist in drawing air downwards and away from the operator's face. The extract grilles should be positioned strategically to draw air away from the operator, but at the same time to prevent the operator from contaminating the product.

5.10 When planning the system for the extraction of vapours, the density of the vapour should be taken into account. If the vapour is lighter than air, the extract grilles should be at a high level, or possibly at both high and low levels.

5.11 When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.

5.12 When working with exposed products such as hormones or highly potent products, operators should wear totally enclosed garments, as indicated in Fig. 22. Operators should also be equipped with an air-breathing system that provides a supply of filtered and conditioned air. The air supply to this type of breathing apparatus should normally be through an air compressor. Filtration, temperature and humidity need to be controlled to ensure operator safety and comfort.

5.13 The rates at which fresh air is supplied to the facility should comply with national, regional and/or international regulations, to provide operators with an acceptable level of comfort and safety and also to remove odours or fumes.

5.14 The rate of fresh airflow should also be determined by leakage from the building, for pressure control purposes.

6.0 Protection of the environment

6.1 Dust in exhaust air

6.1.1 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 should be provided with adequate filtration to prevent contamination of the ambient air.

6.1.2 Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN779 filter standards.

6.1.3 Where harmful substances such as penicillin, hormones, toxic powders and enzymes are manufactured, the final filters on the dust exhaust system should be HEPA filters with at least an H12 classification according to EN1822 filter standards, as appropriate.

6.1.4 For exhaust systems where the discharge contaminant is considered particularly hazardous, it may be necessary to install two banks of HEPA filters in series, to provide additional protection should the first filter fail.

6.1.5 When handling hazardous compounds, safe-change filter housings, also called “bag-in-bag-out” filters, should be used.

6.1.6 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading.

6.1.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

6.1.8 Exhaust filters should be monitored regularly to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in contamination of the ambient air.

6.1.9 Sophisticated computer-based data monitoring systems may be installed, with which preventive maintenance is planned by trend logging (This type of system is commonly referred to as a building management system (BMS), building automation system (BAS) or system control and data acquisition (SCADA) system.)

6.1.10 An automated monitoring system should be capable of indicating any out-of-specification condition without delay by means of an alarm or similar system.

6.1.11 Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they should usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow.

6.1.12 Alternative types of dust collectors (such as those operating with a mechanical shaker, requiring that the fan be switched off when the mechanical shaker is activated) should be used in such a manner that there is no risk of cross-contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.

6.1.13 Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required.

6.1.14 When wet scrubbers are used, the dust-slurry should be removed by a suitable drainage system.

6.1.15 The quality of the exhaust air should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

6.1.16 Where necessary, additional filtration may be provided downstream of the dust collector.

6.2 Fume removal

6.2.1 The systems for fume, dust and effluent control should 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.

6.2.2 Fumes should be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).

6.2.3 Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.

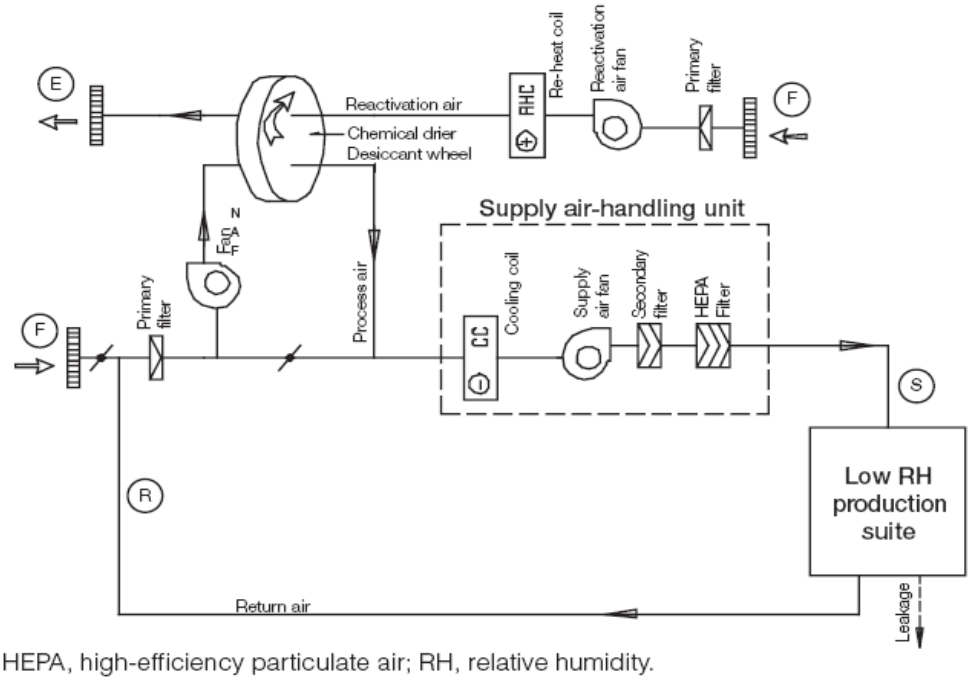
6.2.4 Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.

6.2.5 The type and quantity of the vapours to be removed should be known to enable the appropriate filter media, as well as the volume of media required to be determined.

7.0 HVAC systems and components

Note: The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters, provided the air is not recirculated. Many open product zones of OSD form facilities are capable of meeting ISO 14644-1 Class 8, "at-rest" condition, measured against particle sizes of 0.5 □m and 5 cm, but cleanliness may not be classified as such by manufacturers.

Figure 23. Air-handling system with chemical drying



HEPA, high-efficiency particulate air; RH, relative humidity.

7.1 General

7.1.1 There should be no failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan. Failure can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.

7.1.2 A schematic diagram of the airflow for a typical system serving a low humidity suite is represented in Fig. 23.

7.1.3 Air should be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated by means of passing hot air through one segment of the wheel).

7.1.4 The figure illustrates the chemical drier handling part of the fresh air/ return air mixture on a by-pass flow. The location of the chemical drier should be considered in the design phase. Examples of appropriate locations include:

(a) full flow of fresh/return air;
(b) partial handling of fresh/return air (by-pass airflow);
(c) return air only;
(d) fresh air only; or
(e) pre-cooled air with any of the above alternatives.

7.1.5 Possible additional components that may be required should be considered depending on the climatic conditions and locations. These may include items such as:

(a) frost coils on fresh air inlets in very cold climates to preheat the air;
(b) snow eliminators to prevent snow entering air inlets and blocking airflow;
(c) dust eliminators on air inlets in arid and dusty locations;
(d) moisture eliminators in humid areas with high rainfall; and
(e) fresh air pre-cooling coils for very hot or humid climates.

7.1.6 Appropriate alarm systems should be in place to alert personnel if a critical fan fails.

7.1.7 Low-level return or exhaust air grilles are usually preferred. However, where this is not possible, a higher air change rate may be needed to achieve a specified clean area classification, e.g. where ceiling return air grilles are used.

7.1.8 There may be alternative locations for return air. For example, referring to Fig. 24, room D (low-level return air) and room E (ceiling return air).

7.1.9 The airflow schematics of the two systems (Figs 24 and 25) indicate air-handling unit with return air or recirculated air, having a percentage of fresh air added. Fig. 25 is a schematic diagram of an air-handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow, for rooms A, B and C, respectively.

7.1.10 The airflow diagram in Fig. 24 is an example of a typical system with a lower clean

area classification.

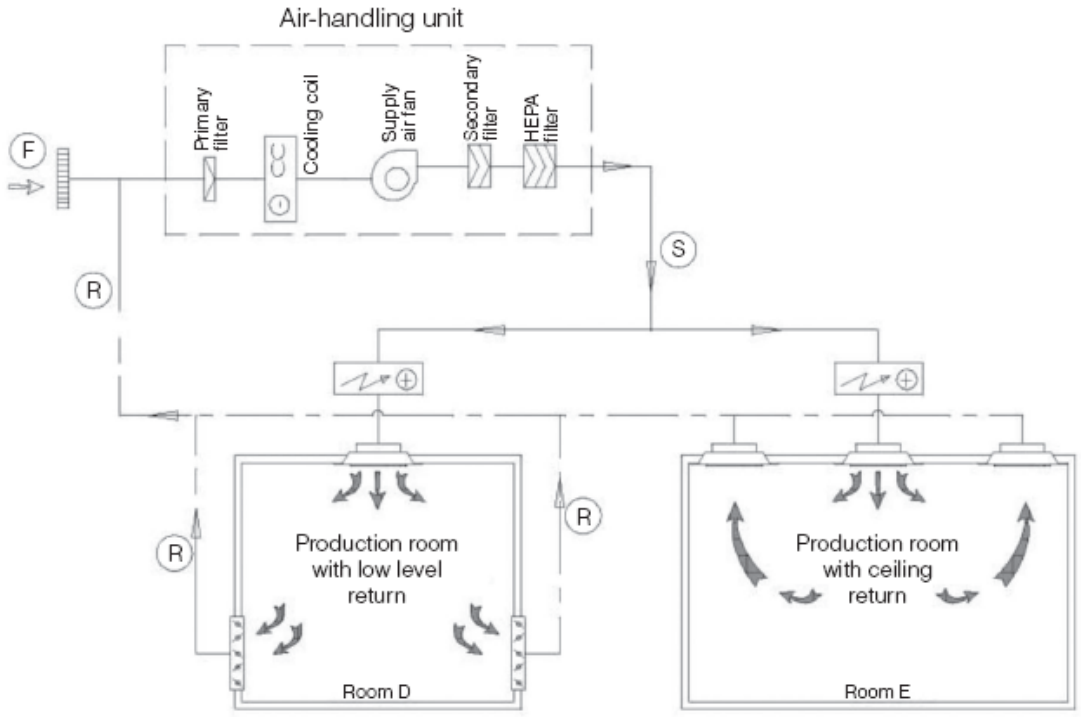
Note: There are two basic concepts of air delivery to pharmaceutical production facilities: a recirculation system, and a full fresh air system (100% outside air supply).

7.2 Recirculation system

7.2.1 There should be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

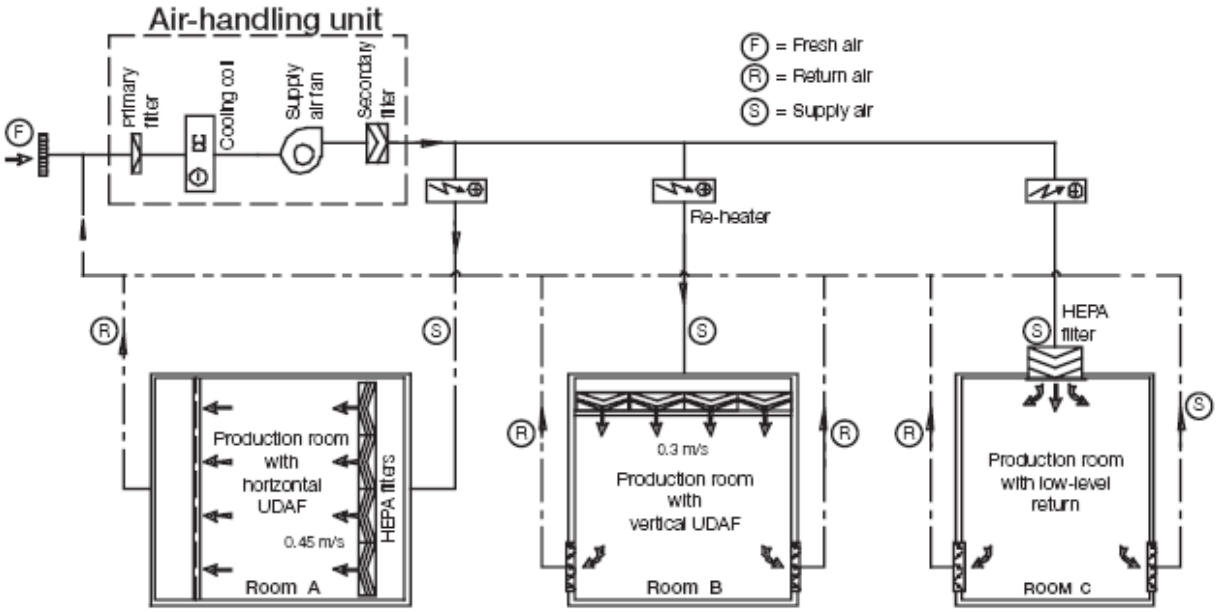
7.2.2 Depending on the airborne contaminants in the return-air system it may be acceptable to use recirculated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN1822 classification of H13.

Figure 24. Air-handling system with high-efficiency particulate air filters in air-handling unit



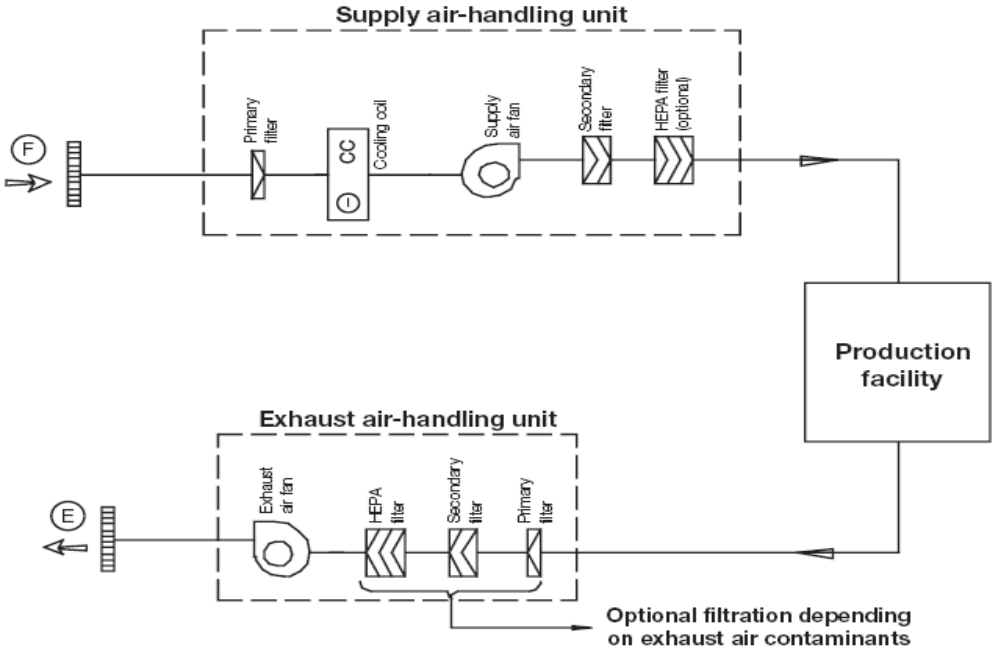
HEPA, high-efficiency particulate air

Figure 25. Horizontal unidirectional flow, vertical unidirectional flow and turbulent flow



UDAF, unidirectional airflow; HEPA, high-efficiency particulate air.

Figure 26. Full fresh-air system



7.2.3 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.

7.2.4 Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.

7.2.5 HEPA filters may be located in the air-handling unit or placed terminally.

7.2.6 Air containing dust from highly toxic processes should never be recirculated to the HVAC system.

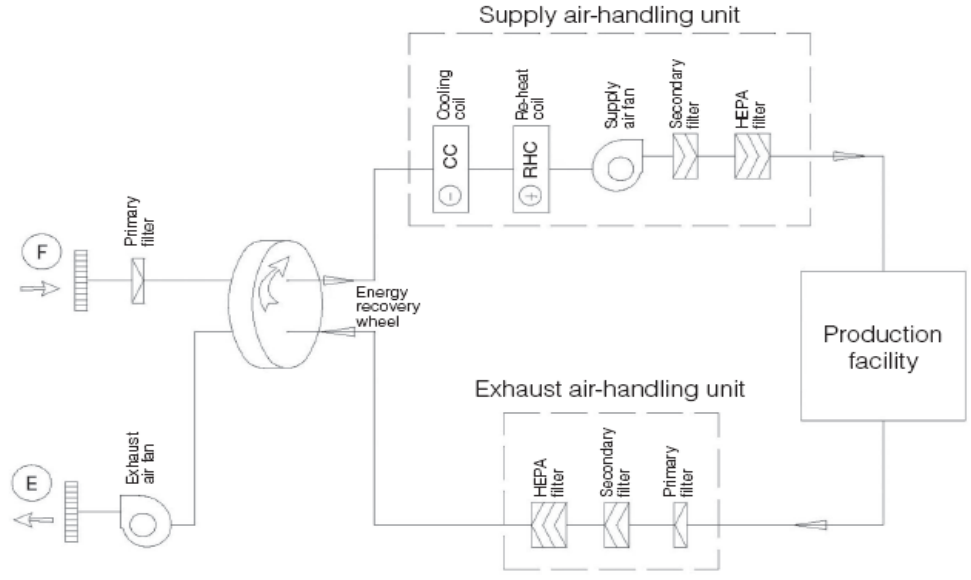
7.3 Full fresh-air systems

Fig. 26 indicates a system operating on 100% fresh air and would normally be used in a facility dealing with toxic products, where recirculation of air with contaminants should be avoided.

7.3.1 The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations.

7.3.2 Energy-recovery wheels should normally not be used in multiproduct facilities. When such wheels are used they should not become a source of possible contamination (see Fig. 27). Note: Alternatives to the energy-recovery wheels, such as crossover plate heat exchangers and water-coil heat exchangers, may be used in multiproduct facilities.

Figure 27. Full fresh-air system with energy recovery



HEPA, high-efficiency particulate air.

7.3.3 The potential for air leakage between the supply air and exhaust air as it passes through the wheel should be prevented. The relative pressures between supply and

exhaust air systems should be such that the exhaust air system operates at a lower pressure than the supply system.

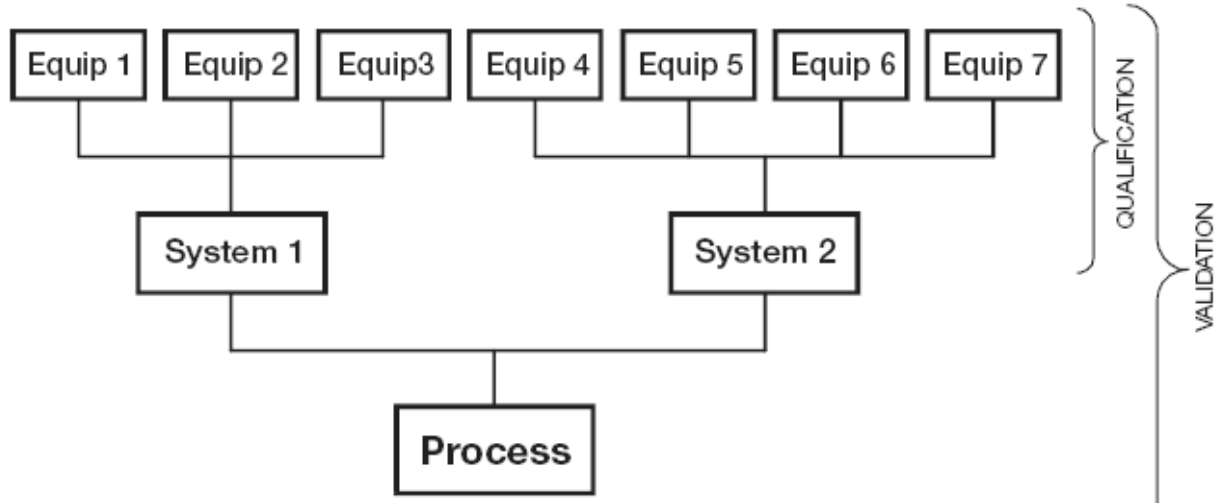
8.0 Commissioning, qualification and maintenance

8.1 Commissioning

8.1.1 Commissioning should include the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that it meets all the requirements, as specified in the user requirement specification (URS), and capacities as specified by the designer or developer.

8.1.2 The installation records of the system should provide documented evidence of all measured capacities of the system.

Figure 28. Qualification is a part of validation



Equip, equipment.

8.1.3 The data should include items such as the design and measurement figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).

8.1.4 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation.

8.1.5 Training should be provided to personnel after installation of the system, and should include operation and maintenance.

8.1.6 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.

8.1.7 Commissioning should be a precursor to system qualification and process validation.

8.2 Qualification

8.2.1 Validation is a many-faceted and extensive activity and is beyond the scope of these guidelines. Qualification and validation guidelines are included in: Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 937), Annex 4 (see also Fig. 28).

Manufacturers should qualify HVAC systems using a risk-based approach. The basic concepts of qualification of HVAC systems are set out below.

8.2.2 The qualification of the HVAC system should be described in a validation master plan (VMP).

8.2.3 It should define the nature and extent of testing and the test procedures and protocols to be followed.

8.2.4 Stages of the qualification of the HVAC system should include DQ, IQ, OQ and PQ.

8.2.5 Critical and non-critical parameters should be determined by means of a risk analysis for all HVAC installation components, subsystems and controls.

8.2.6 Any parameter that may affect the quality of the pharmaceutical product, or a direct impact component, should be considered a critical parameter.

8.2.7 All critical parameters should be included in the qualification process.
Note: A realistic approach to differentiating between critical and non-critical parameters is required, to avoid making the validation process unnecessarily complex.

Example:

(a) The humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemical drier or steam humidifier, which is producing the humidity controlled air, is further removed from the product and may not require operational qualification.

(b) A room cleanliness classification is a critical parameter and, therefore, the room air change rates and HEPA filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and secondary filters are non-critical parameters, and may not require operational qualification.

8.2.8 Non-critical systems and components should be subject to GEP and may not necessarily require qualification.

8.2.9 A change control procedure should be followed when changes are planned to the direct impact HVAC system, its components and controls that may affect critical parameters.

8.2.10 Acceptance criteria and limits should be defined during the design stage.

8.2.11 The manufacturer should define design conditions, normal operating ranges, operating ranges, and alert and action limits.

8.2.12 Design condition and normal operating ranges should be identified and set to realistically achievable parameters.

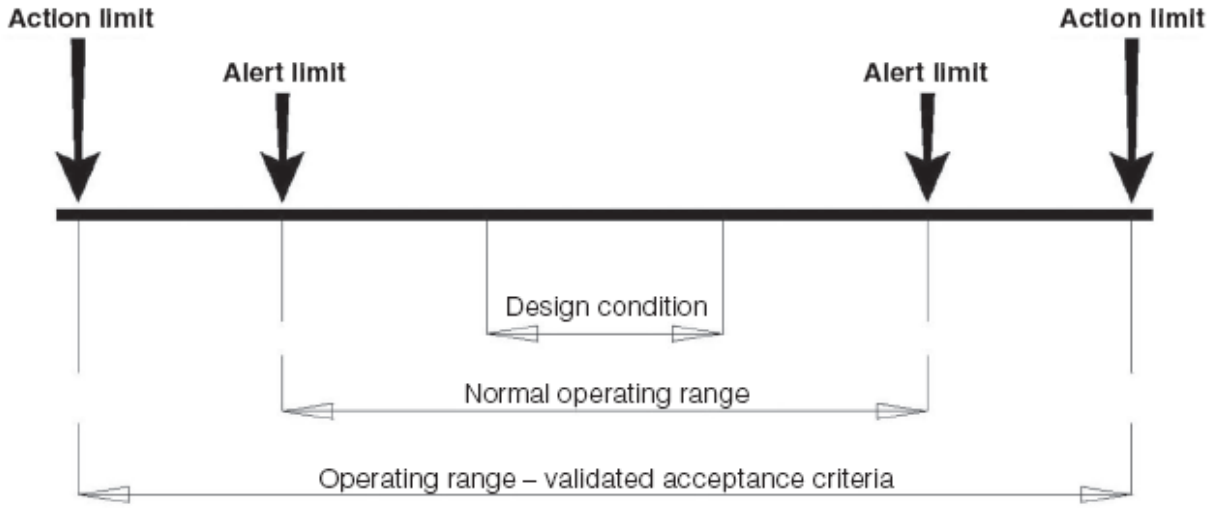
8.2.13 All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

8.2.14 Out-of-limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.

8.2.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Fig. 29.

8.2.16 A narrow range of relative humidities coupled with a wide range of temperatures is unacceptable as changes in temperature will automatically give rise to variations in the relative humidity.

Figure 29. System operating ranges



8.2.17 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include:

(a) temperature
(b) relative humidity
(c) supply air quantities for all diffusers
(d) return air or exhaust air quantities
(e) room air change rates
(f) room pressures (pressure differentials)
(g) room airflow patterns
(h) unidirectional flow velocities
(i) containment system velocities
(j) HEPA filter penetration tests
(k) room particle counts
(l) room clean-up rates
(m)microbiological air and surface counts where appropriate
(n) operation of de-dusting
(o) warning/alarm systems where applicable.

Table 3. Part A: schedule of tests to demonstrate compliance (for reference purposes only)

Schedule of tests to demonstrate continuing compliance			
Test parameter	**Clean room class**	**Max. time interval**	**Test procedure**
Particle count test (Verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure dif- ferential between different zones is recommended. In accordance with ISO 14644-3 Annex B5*
Airflow volume (To verify air change rates)	All classes	12 months	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13*
Airflow velocity (To verify laminar flow or containment conditions)	All Classes	12 Months	Air velocities for containment sys- tems and laminar flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4*

8.2.18 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered.

Note: Table 3 gives intervals for reference purposes only. The actual test periods may be more frequent or less frequent, depending on the product and process.

8.2.19 Periodic requalification of parameters should be done at regular intervals, e.g. annually.

8.2.20 Requalification should also be done when any change, which could affect system performance, takes place.

8.2.21 Clean-up or recovery times normally relate to the time it takes to “clean up” the room from one condition to another, e.g. the relationship between “at- rest” and “operational” conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an “operational” condition to an “at rest” condition.

Table 3. Part B: recommended optional strategic tests (ISO 14644)

Schedule of tests to demonstrate continuing compliance			
Test parameter	**Clean room class**	**Max. time interval**	**Test procedure**
Filter leakage tests (To verify filter integrity)	All classes	24 months	Filter penetration tests to be carried out by a recognized authority to demonstrate filter media and filter seal integrity. Only required on HEPA filters. In accordance with ISO 14644-3 Annex B6*
Containment leakage (To verify absence of cross-contamination)	All classes	24 months	Demonstrate that contaminant is maintained within a room by means of: • airflow direction smoke tests • room air pressures. In accordance with ISO 14644-3 Annex B4*
Recovery (To verify clean- up time)	All classes	24 months	Test to establish time that a clean room takes to return from a contaminated condition to the specified clean room condition. This should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*
Airflow visualization (To verify required airflow patterns)	All Classes	24 months	Tests to demonstrate airflows: • from clean to dirty areas • do not cause cross-contamination • uniformly from laminar flow units. Demonstrated by actual or video- taped smoke tests in accordance with ISO 14644-3 Annex B7*

8.3 Maintenance

8.3.1 There should be a planned preventive maintenance program, procedures and records for the HVAC system. Records should be kept.

8.3.2 Maintenance personnel should receive appropriate training.

8.3.3 HEPA filters should be changed either by a specialist or a trained person.

8.3.4 Any maintenance activity should be assessed critically to determine any impact on product quality including possible contamination.

8.3.5 Maintenance activities should normally be scheduled to take place outside production hours, and any system stoppage should be assessed with a view to the possible need for requalification of an area as a result of an interruption of the service.

Document Revision History

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
2006	0	Not on record-	Deus Mubangizi	First issue
5th April 2013	1	INS/GDL/001	Nasser Mbaziira, Kate Kikule, Peter Ssali.	Changed format, changed document numbering system, revised all sections and added Annexes in accordance with the current WHO GMP text 2007; and PICS- PE 009-07 parts 1, 2 and Annexes.

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