

TANZANIA FOOD AND DRUGS AUTHORITY



GOOD MANUFACTURING PRACTICE GUIDELINES FOR VETERINARY MEDICINAL PRODUCTS

(Made under section 51 of the Tanzania Food, Drugs and Cosmetics Act, Cap 219)

FIRST EDITION

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ABBREVIATIONS

API	-	Active Pharmaceutical Ingredient
CFU	-	Colony Forming Units
DNA	-	Deoxyribonucleic acid
DQ	-	Design Qualification
GCP	-	Good Clinical Practice
GEP	-	Good Engineering Practices
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
HEPA	-	High Efficiency Particulate Air
HVAC	-	Heating Ventilation and Air-Conditioning
INN	-	International Non Proprietary name
IQ	-	Installation Qualification
ISO	-	International Standard for Standardization
OQ	-	Operational Qualification
PIC/S	-	Pharmaceutical Inspection Convention Scheme
PQ	-	Performance Qualification
PV	-	Process Validation
RNA	-	Ribonucleic acid
SOP	-	Standard Operating Procedures
TFDA	-	Tanzania Food and Drugs Authority
VMP	-	Validation Master Plan
WHO	-	World Health Organization
WPU	-	Water for Pharmaceutical Use

FOREWORD

TFDA was established under the Tanzania Food, Drugs and Cosmetics Act, Cap 219 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of food, medicines, cosmetics and medical devices. The Authority has a legal responsibility of ensuring that all veterinary medicinal products manufactured and used in the country meet the prescribed standards for the intended use. The Authority has also been given mandate by section 51 of the Act to prescribe requirements for manufacturing medicinal products.

In order to streamline and effectively control veterinary medicinal products, this first edition of the *Good Manufacturing Practice Guidelines for Veterinary Medicinal Products* has been developed by TFDA.

The Guidelines provide up to date technical guidance on minimal requirements for manufacturing veterinary medicinal products. Its aim is to improve manufacturing practices for veterinary medicinal products in and outside the country as well as outlining a framework of requirements that manufacturers should follow when manufacturing products intended to be marketed in the country. These Guidelines can also be used as a training tool for veterinary medicinal products industry personnel, GMP auditors and training institutions.

These Guidelines gives the principles and application of GMP to include standards and/or requirements for premises, equipment, personnel, storage, quality management system, quality controls, documentation, validations, manufacturing processes as well as packaging and labeling requirements.

It is therefore anticipated that all manufacturers will cooperate with the Authority to achieve this legal obligation by adhering to GMP standards and manufacture veterinary medicinal products of acceptable quality.

The expectation of TFDA is that the Guidelines will enable consistent and uniform procedures for the manufacturing and documentation of veterinary medicinal products so that they can consistently meet safety and quality standards. Nevertheless we welcome new ideas, opinions and suggestions in this context that will assist in improvement of the Guidelines.

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- g. Tan Veterina Ltd
- h. Farmers centre Ltd

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ADMINISTRATIVE AND SUPPLEMENTARY INFORMATION

Regulation of veterinary medicinal products involves among other things, inspection of pharmaceutical plants to verify compliance to GMP. GMP is that part of quality assurance which ensures that products are consistently produced and controlled to meet quality standards appropriate for the intended use and as required by marketing authorization. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

In order to achieve this goal, TFDA GMP inspectors will be provided with a Manual containing sufficient working tools needed for observing, investigating and reaching conclusions in a particular inspection.

With respect to these Guidelines there are four types of inspection as indicated below;

- a) Routine inspection
- b) Concise inspection
- c) Follow-up inspection
- d) Special inspection

Routine Inspection

Routine inspection is a full review of all aspects and components of GMP within a facility. Routine inspection is conducted under the following circumstances:

- a) To a newly established manufacturing facility or a manufacturer who has expressed interest of expanding manufacturing activities e.g. introduction of new products.
- b) When there is modification to manufacturing methods or processes; or changes in premises and/or equipment.
- c) When GMP certification has expired.

This type of inspection should be announced.

Concise Inspection

Concise inspection is the evaluation of limited aspects relating to GMP compliance within a facility. A limited number of GMP requirements are selected by the inspector to serve as indicators of the overall GMP compliance by the manufacturer. The inspector also has to identify and evaluate any significant changes that could have been introduced by the manufacturer since the last inspection. Collectively, the selected indicators and the changes identified indicate the manufacturer's attitude toward GMP.

A concise inspection is conducted under the following circumstances:

- a) Where a manufacturer has a consistent record of compliance with GMP through routine inspections in the past.

- b) Where a sample of aspects can be taken as a good indication of the overall level of compliance with GMP.

However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, a more comprehensive or full GMP inspection should be performed soon after the concise inspection.

These inspections can be announced or unannounced.

Follow-up Inspection

A follow up inspection is also referred to as a re-inspection or a reassessment of the manufacturing facilities. It is performed specifically to monitor the result of corrective actions of the manufacturer following a previous inspection. Depending on the nature of the defects and the work required, the follow-up inspection could be carried out within the agreed timeframe after the previous inspection. The follow-up inspection is limited to specified GMP non compliances that have been observed.

A follow up inspection shall be unannounced.

Special Inspection

A special inspection is undertaken to do spot checks which could focus on one product, a group of related products, or specific operations e.g. mixing, or labeling.

Special inspection is conducted under the following circumstances:

- a) When there are complaints about a specific product that suggest there may be defects.
- b) When there is a product recall due to events such as adverse drug reactions.
- c) To gather specific information, or to investigate specific operations of the manufacturing processes.

The inspection shall be unannounced.

FREQUENCY OF INSPECTIONS

The frequency of inspection of local and foreign manufacturers shall be as follows:

Local Pharmaceutical Manufacturers

Local manufacturers shall be inspected once a year or after 2 years depending on the type of inspection to be performed.

Foreign Pharmaceutical Manufacturers

Foreign manufacturers shall be inspected once after 3 years. A manufacturer may be inspected more than once within 3 years, depending on the type of inspection to be performed.

CLASSIFICATION OF GMP INSPECTION NON-COMPLIANCE OBSERVATIONS

Non-compliance observations will be classified as “critical”, “major” and “minor” observation as detailed below;

Critical observation means an observation describing a situation that will most likely result in a non-compliant product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.

Major observation means an observation describing a situation that may have an impact on the product but is not as significant as a critical observation. It may have an indirect impact in the strength, identity, purity or safety of the product. There is reduced usability of the product without a probability of causing harm to the target animal species. Observation of a major deficiency puts a question mark on the reliability of the firm’s quality assurance system.

Minor observation means an observation describing a situation that is a departure from GMP but has no significant impact on the product quality. It has low probability of affecting the quality or usability of the product.

INTRODUCTION

Manufacture of veterinary medicinal products involve operations of purchase of materials, production, quality control, release, storage, shipment of finished products and the related controls. Such operations need to be carried out according to Good Manufacturing Practices (GMP) that forms an important part of a comprehensive system of quality assurance. Adherence to GMP ensures that veterinary medicinal products are manufactured to meet quality standards required for their intended use.

In order to protect the animals and public against health hazards associated with the use of medicines and cope with advancement in pharmaceutical sciences and technology, TFDA has developed GMP guidelines for veterinary medicinal products.

This guideline highlights in detail the principles of GMP that should be followed by all companies involved in any aspect of manufacturing of veterinary medicinal products for veterinary use. The guidelines targets both local and foreign manufacturers who intend to obtain marketing authorization in Tanzania and shall form the basis for licensing pharmaceutical manufacturers in the country. This is in line with the requirements of the Tanzania Food, Drugs and Cosmetics Act, Cap 219.

The document is divided into chapters and annexes. Chapter one (1) to fifteen (15) delineate the principles, general considerations and requirements for quality management, personnel, sanitation and hygiene, premises, equipment, material, documentation, good practices in production, good practices in quality control, contract production and analysis, complaints and product recalls, self-inspection and quality audits, qualification and validation, heating, ventilation and air conditioning (HVAC) system and water treatment.

Annex one (1) of the document illuminates GMP requirements for the production of sterile veterinary medicinal products. This additional guidance has been provided to minimize the risks of microbiological, particulate and pyrogen contamination during manufacturing of sterile veterinary medicinal products.

Annex two (2) outlines GMP requirements for the production of veterinary biological products. Unlike conventional pharmaceutical products which are normally produced and controlled by means of reproducible chemical and physical techniques, biological products are manufactured with biological materials and processes, such as cultivation of cells or extraction of materials from living organisms. As such materials and processes display inherent variability and the range and nature of manufacturing by-products in biological products are likewise variable. For such products, including vaccines, hormones and enzymes, full adherence to the GMP guidelines is recommended for all production steps, including those from which active ingredients are produced.

The requirements set forth in these guidelines should be considered as minimum and they are not meant to replace other legal controls, but rather to complement or supplement them.

GLOSSARY

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

Act:

Means the Tanzania Food, Drugs and Cosmetics Act, Cap 219

Action limit:

Means established criteria, requiring immediate follow-up and corrective action if exceeded.

Active pharmaceutical ingredient (API):

Means any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Airlock:

Means 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 use either by people or for goods and/or equipment.

Alert limit:

Means established criteria giving early warning of potential drift from normal conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Alert limit:

Means limit 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:

Means condition where the installation is complete with all services connected and functioning but with no production equipment, materials, or personnel present.

At-rest:

Means condition where the installation is complete with equipment installed and operating in a manner agreed up on by the customer and supplier, but with no personnel present.

Authority:

Means the Tanzania Food and Drugs Authority, or the acronym “TFDA” established under section 4(1) of the Act.

Authorized person:

Means a person recognized by the Authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the Act.

Batch (or lot):

Means a defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. 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. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity.

The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch number (or lot number):

Means a distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

Batch records:

Means 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:

Means any product that has completed all processing stages up to, but not including, final packaging.

Calibration:

Means a 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.

Change Control

Means 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.

Clean area:

Means 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.

Cleaning Validation:

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

Commissioning:

Means 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.

Concurrent Validation:

Means validation carried out during routine production of products intended for sale.

Consignment (or delivery):

Means quantity of pharmaceutical(s), 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.

Containment:

Means a process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

Contamination:

Means undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

Critical operation:

Means an operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Critical parameter or component:

Means processing parameter (such as temperature or humidity) that affects the quality of a product, or a component may have a direct impact on the quality of the product.

Cross-contamination:

Means contamination of a starting material, intermediate product or finished product with another starting material or product during production.

Design condition:

Means condition related to the specified range or accuracy of a controlled variable used by the designer as a basis to determine the performance requirements of an engineered system.

Design Qualification (DQ):

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

Finished product:

Means finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

In-process control:

Means 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 (IQ):

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

Intermediate product:

Means partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-volume parenterals:

Means sterile solutions intended for parenteral application with a volume of 100ml or more in one container of the finished dosage form.

Manufacture:

Means purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

Manufacturer:

Means a company that carries out operations such as production, packaging, repackaging, labeling and re-labelling of pharmaceuticals.

Marketing authorization (product license, registration certificate):

Means a legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeia or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

Master formula:

Means 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:

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

Medicated feedingstuff:

Means 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 as a medicinal

Non-critical parameter or component:

Means 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.

Operating range:

Means a range of validated critical parameters within which acceptable products can be manufactured.

Operational condition:

Means condition related 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):

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

Packaging:

Means filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Packaging material:

Means any material, including printed material, employed in the packaging of a pharmaceutical, but 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.

Performance Qualification (PQ)

Means 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.

Pharmaceutical product:

Means any material or product intended for human or veterinary use 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 the exporting state and/or the importing state.

Pre-mix for medicated feedingstuffs:

Means any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

Pressure cascade:

Means a process whereby air flows from one area, which is maintained at the highest pressure to another area at a lower pressure.

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.

Production:

Means all operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and re-labelling, to completion of the finished product.

Prospective Validation:

Means validation carried out during the development stage by means of a risk analysis of the production process which is broken down into individual steps; these are then evaluated on the basis of the past experience to determine whether they lead to critical situations.

Qualification:

Means action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification.

Quarantine:

Means 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:

Means a comparison between the theoretical quantity and the actual quantity.

Recovery:

Means 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. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Relative humidity:

Means 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.

Reprocessing:

Means subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally

necessary for biological drugs and, in such cases, are validated and pre-approved as part of the marketing authorization.

Retrospective validation:

Means examination of past experience of production on the assumption that composition, procedures and equipment remain unchanged

Re-Validation:

Means 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.

Reworking:

Means subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

Risk analysis:

Means a method to assess and characterize the critical parameters in the functionality of an equipment or process.

Self-contained area:

Means premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Shipping/dispatch:

Means assembly, packing for shipment, and sending of ordered medicinal products for clinical trials.

Simulated Product:

Means 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.

Specification:

Means a list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard operating procedure (SOP):

Means an authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (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:

Means any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Unidirectional airflow:

Means 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 Master Plan (VMP):

Means 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).

Validation:

Means action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Veterinary medicinal product:

Means any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to animals.

Worst Case:

Means 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 or process failure.

CHAPTER 1: QUALITY MANAGEMENT SYSTEM

Principle:

A quality system should be developed and implemented as a means by which stated policies and objectives will be achieved. It should define the organizational structure, functions, responsibilities, procedures, instructions, processes and resources for implementing the quality management system.

In manufacturing of veterinary products the overall intention and direction of an organization regarding quality should be among the main goals of the facility as stated in the quality policy statement. The achievement of 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.

The manufacturer of veterinary products must assume responsibility for the quality of the products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place animals and consumers of animal products at risk due to inadequate safety, quality or efficacy.

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.

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 veterinary products. Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

General:

- 1.1 Manufacturers of veterinary medicines and vaccines shall have a documented quality policy describing the overall intention regarding quality.
- 1.2 Manufacturers shall institute and implement quality management system which includes;
 - 1.2.1 An appropriate infrastructure or quality system encompassing the organizational structure, procedures, processes and resources.
 - 1.2.2 Systematic actions necessary to ensure adequate confidence that the product and documentation will satisfy given requirements for quality.

Quality Assurance

- 1.3 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.
- 1.4 The system of quality assurance appropriate to the manufacture of veterinary products should ensure that:
 - 1.4.1 Veterinary products are designed and developed in a way that takes account of the requirements of GMP, GLP and GCP;
 - 1.4.2 Production and control operations are clearly specified in a written form and GMP requirements are adopted;
 - 1.4.3 Managerial responsibilities are clearly specified in job descriptions and exercised;
 - 1.4.4 Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
 - 1.4.5 All necessary controls on starting materials, intermediate products and bulk products and other in-process controls, calibrations, and validations are carried out;
 - 1.4.6 The finished product is correctly processed and checked, according to the defined procedures;
 - 1.4.7 Veterinary products are not sold or supplied before the authorized persons have certified that each production batch has been and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of veterinary products;
 - 1.4.8 Satisfactory arrangements should exist to ensure, veterinary products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;
 - 1.4.9 There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;
 - 1.4.10 Deviations are reported, investigated and recorded;
 - 1.4.11 There is a system for approving changes that may have an impact on product quality;

1.4.12 Regular evaluations of the quality of veterinary products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement

1.4.13 And there is a system for quality risk management (QRM)

Good Manufacturing Practices (GMP)

1.5 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 aims at lowering risks, 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. It is required that:

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

1.5.2 Qualification and validation are performed where applicable;

1.5.3 All necessary resources are provided, including:

1.5.3.1 Appropriately qualified and trained personnel;

1.5.3.2 Adequate premises and space;

1.5.3.3 Suitable equipment and services;

1.5.3.4 Appropriate materials, containers and labels

1.5.3.5 Approved procedures and instructions;

1.5.3.6 Suitable storage and transport;

1.5.3.7 Adequate personnel, laboratories and equipment for in- process Controls under the responsibility of the production management

1.5.4 Instructions and procedures are written in clear and unambiguous language specifically applicable to the facilities provided;

1.5.5 Operators are trained to carry out procedures correctly;

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

- 1.5.7 Records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- 1.5.8 The proper storage and distribution of the veterinary products minimizes any risk to their quality;
- 1.5.9 A system is available to recall any batch of product from sale or supply;
- 1.5.10 Complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.
- 1.5.11 Manufacturer should establish a system of conducting periodic internal self inspections. A report should be made at the completion of each self inspection. Corrective and preventive actions should be established and implemented.

Quality Control (QC)

1.6 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications, testing and with the organization, documentation and release procedures which ensure that necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that;

- 1.6.1 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;
- 1.6.2 samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by quality control department;
- 1.6.3 test methods must be well documented and validated/ verified;
- 1.6.4 records must be made, manually and/or by recording instruments which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
- 1.6.5 the finished products contain ingredients complying with the qualitative and quantitative composition of the marketing authorization, are of the purity required, and are enclosed within their proper container and correctly labeled.
- 1.6.6 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.

- 1.6.7 Sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Product Quality Review (PQR)

- 1.7 Manufacturers should conduct regular, periodic or rolling quality reviews of all products, including export-only products with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished products to highlight any trends and to identify any product and process improvement. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:
- 1.7.1 Review of starting materials and packaging materials used for the product, especially those from new sources;
 - 1.7.2 A review of critical in-process controls and finished product results;
 - 1.7.3 A review of all batches that failed to meet established specification(s) and their investigation;
 - 1.7.4 A review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant corrective and preventive actions taken;
 - 1.7.5 A review of all changes made to the processes or analytical methods;
 - 1.7.6 A review of dossier variations submitted, granted or refused;
 - 1.7.7 A a review of the results of the stability monitoring programme and any adverse trends;
 - 1.7.8 A review of all quality-related returns, complaints and recalls and the investigations performed at the time;
 - 1.7.9 A review of adequacy of any other previous corrective actions on product process or equipment;
 - 1.7.10 For new dossiers and variations to the dossiers, a review of post marketing commitments;
 - 1.7.11 The manufacturer and marketing authorization holder, where different, should evaluate the results of this review and an assessment should be made whether corrective and preventive action or any revalidation should be undertaken. Reasons for such corrective actions should be documented.
 - 1.7.12 Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified. Where the marketing authorization holder is not the manufacturer, there should be a

technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification, together with the marketing authorization holder, should ensure that the quality review is performed in a timely manner and is accurate.

- 1.7.13 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of a pharmaceutical product. It can both be applied proactively and retrospectively. The quality risk management system should ensure that: evaluation of the risk is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; and The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk

CHAPTER 2: PERSONNEL

Principle:

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of products and active ingredients rely upon people. For this reason there must be sufficient qualified and trained personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

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 so as to present any risk to quality.
- 2.2 The manufacturer should have an organizational chart showing the names of key personnel, as well as their areas of responsibility and lines of authority. 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 and records of those delegations should be kept. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of GMP.
- 2.3 Operators' verbal and written communication skills should be sufficient for them to respond to training, accept and implement instructions exactly and, where their duties require it, fill out forms correctly.
- 2.4 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.
- 2.5 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

- 2.6 Key personnel include the head of production, the head of quality control and the authorized person. 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.
- 2.7 Key personnel responsible for supervising the manufacture and quality control of veterinary products should possess a basic degree of scientific education and practical experience. Their education should include the study of an appropriate combination of:

- 2.7.1 Pharmaceutical sciences and technology;
 - 2.7.2 Chemistry (analytical or organic) or biochemistry;
 - 2.7.3 Microbiology;
 - 2.7.4 Veterinary medicine;
 - 2.7.5 Pharmacology and toxicology;
 - 2.7.6 Other related Sciences.
- 2.8 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 judgment, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.
- 2.9 The heads of the production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:
- 2.9.1 Authorization of written procedures and other documents, including amendments;
 - 2.9.2 Monitoring and control of the manufacturing environment;
 - 2.9.3 Plant hygiene;
 - 2.9.4 Process validation and calibration of analytical apparatus;
 - 2.9.5 Training, including the application and principles of quality assurance;
 - 2.9.6 Approval and monitoring of suppliers of materials;
 - 2.9.7 Approval and monitoring of contract manufacturers;
 - 2.9.8 Designation and monitoring of storage conditions for materials and products;
 - 2.9.9 Performance and evaluation of in-process controls;
 - 2.9.10 Retention of records;
 - 2.9.11 Monitoring of compliance with GMP requirements;

- 2.9.12 Inspection, investigation and taking of samples in order to monitor factors that may affect product quality.
- 2.10 The head of the production generally has the following responsibilities:
 - 2.10.1 To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
 - 2.10.2 To approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
 - 2.10.3 To ensure that the production records are evaluated and signed by a designated person;
 - 2.10.4 To check the maintenance of the department, premises, and equipment;
 - 2.10.5 To ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
 - 2.10.6 To ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.
- 2.11 The head of the quality control generally has the following responsibilities:
 - 2.11.1 To approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation with their specifications;
 - To evaluate batch records;
 - 2.11.2 To ensure that all necessary testing is carried out;
 - 2.11.3 To approve sampling instructions, specifications, test methods and other quality control procedures;
 - 2.11.4 To approve and monitor analyses carried out under contract;
 - 2.11.5 To check the maintenance of the department, premises and equipment;
 - 2.11.6 To ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out;
 - 2.11.7 To ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.
 - 2.11.8 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.

- 2.12 The authorized person will also be involved in other activities, including the following:
 - 2.12.1 Implementation (and, when needed, establishment) of the quality system;
 - 2.12.2 Participation in the development of the company's quality manual;
 - 2.12.3 Supervision of the regular internal audits or self-inspections;
 - 2.12.4 Oversight of the quality control department;
 - 2.12.5 Participation in external audit (vendor audit);
 - 2.12.6 Participation in validation programmes.
- 2.13 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.
- 2.14 The person responsible for approving a batch for release should always ensure that the following requirements have been met:
 - 2.14.1 The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
 - 2.14.2 The principal manufacturing and testing processes have been validated, if different;
 - 2.14.3 All the necessary checks and tests have been performed and Account taken of the production conditions and manufacturing records;
 - 2.14.4 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;
 - 2.14.5 Any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
 - 2.14.6 All necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines;
 - 2.14.7 Appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
 - 2.14.8 Approval has been given by the head of quality control;
 - 2.14.9 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).

- 2.15 Register of staff signatures and initials should be maintained. Entries should be updated at regular stated intervals and the previous records archived.
- 2.16 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.

Training

- 2.17 The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into production areas or into quality control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel whose activities could affect product quality.
- 2.18 Training programs should be appropriate to the identified needs of staff and be approved by the head of either Production or of Quality, as appropriate. The effectiveness of the training program should be monitored.
- 2.19 Training programs should include initial training in the basic principles of GMP. Continuing training should also be given including training in changes to the manufacturing process and procedures.

Training programs should specifically address the concept of quality assurance, as well as relevant aspects of sanitation and personal hygiene and its practical effectiveness should periodically be assessed. Training records of all internal and external training activities undertaken by individual staff should be kept.

- 2.20 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.
- 2.21 The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.
- 2.22 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.
- 2.23 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

CHAPTER 3: SANITATION AND HYGIENE

Principle:

Sanitation and hygiene should be practiced and maintained to avoid contamination and it should cover personnel, premises, equipment/apparatus, production materials and packaging materials.

General:

Personnel

- 3.1 Personnel engaging in manufacturing process and quality control should be healthy to perform their assigned duties.
- 3.2 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.
- 3.3 Personnel should maintain adequate cleanliness and be free from sources of microbiological contamination (for example; sores and wounds)
- 3.4 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.
- 3.5 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.
- 3.6 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.
- 3.7 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.
- 3.8 Smoking, eating, drinking, chewing, spitting and keeping 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. Relevant signs should be displayed at prominent positions at entry points to these areas.
- 3.9 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. contractor's employees, visitors, senior managers

and inspectors. The wearing of jewellery that may become detached or caught in machinery should be discouraged in manufacturing areas.

Premises

- 3.10 Adequate washing, cleaning, plumbing and toilets should be available to allow for sanitary operation, cleaning of facilities, equipment and utensils as well as personal cleanliness
- 3.11 Fixtures, ducts, pipes and drainages should be installed to prevent condensate or drip contamination
- 3.12 Suitable locker facilities should be provided at appropriate positions for the storage of employees' and personal belongings
- 3.13 Waste materials should not be allowed to accumulate, should be regularly collected in suitable receptacles for removal to collection points outside the production area
- 3.14 There should be adequate filth and pests control (examples of filth may include, any objectionable matter, contributed by animal contamination such as rodents, insects, bird matter or any other objectionable matter contributed by insanitary conditions)
- 3.15 Rodenticides, insecticides, fumigating agents and sanitizing materials must not contaminate equipment, raw materials, packaging materials, in-process materials or finished products

Equipment and Apparatus

- 3.16 The equipment should be maintained in clean and orderly condition, sanitized at appropriate times and stored in a manner that protects against splash, dust and other contaminants
- 3.17 There must be approved cleaning procedures for all equipment and apparatus and cleaning validation for the major manufacturing equipment and machines

CHAPTER 4: PREMISES

Principle:

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

General:

- 4.1 The layout and design of premises 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.
- 4.2 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.
- 4.3 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.
- 4.4 Premises should be designed to ensure the logical flow of materials and personnel.
- 4.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate cleaning and sanitation.
- 4.6 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.
- 4.7 Premises should be cleaned and, where applicable, disinfected according to written procedures. Records should be maintained.
- 4.8 Pipe work, electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the products during their manufacture and storage, or the accurate functioning of equipment.
- 4.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals.
- 4.10 Rest and refreshment rooms should be separated from manufacturing and quality control areas.
- 4.11 Appropriate changing rooms and toilets should be provided.
- 4.12 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.

- 4.13 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.
- 4.14 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Storage Areas

- 4.15 Storage areas should be of sufficient capacity to allow orderly storage of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.
- 4.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.
- 4.17 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow verification and cleaning of incoming materials.
- 4.18 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.
- 4.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.
- 4.20 Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.
- 4.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labeling and special attention should be paid to sampling and the safe and secure storage of these materials, preferably they should be stored under lock and key with restricted access.
- 4.22 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.)

Weighing Areas

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

Production Areas

- 4.24 In order to minimize the risk of serious medical hazards due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular veterinary products, such as highly sensitizing materials (e.g. Penicillin) or biological preparations (e.g. live microorganisms). The production of certain other highly active products such as some antibiotics, hormones and certain non-medicinal products should not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacturer of veterinary products.
- 4.25 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.
- 4.26 Where starting and primary packaging materials or intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be suitable for the class of product being manufactured. This will usually require surfaces that are nonporous, smooth, free from open joints, and do not shed particulate matter. They should also permit effective cleaning.
- 4.27 Joints between walls and floors should be easy to clean, adequately sealed and where appropriate, coved to form a smooth curve between the floor and wall.
- 4.28 Wherever possible, wood or wood-based material should be avoided as a material of construction or support for equipment or materials in production areas, especially where it may be wetted. If used, it should be sealed with a coating that is resistant to chipping, disinfectants and cleaning agents and that is easily cleaned.
- 4.29 The use of wood-based pallets should be avoided in production areas where there is a risk of contamination of the product.
- 4.30 Production areas should be effectively ventilated and allow, where necessary, control of air flow, temperature, humidity and filtration appropriate to the products handled, the operation undertaken and the external environment.
- 4.31 Production areas should be well lit, especially where visual on-line controls are carried out.
- 4.32 Drains should be of adequate size and designed 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.
- 4.33 Premises for the packaging of veterinary products should be specifically designed and laid out so as to avoid mix-ups or cross contamination.

Quality Control Areas

- 4.34 Quality control laboratories should be separated from production areas. In the laboratory, areas where biological, microbiological or radioisotope test methods are employed should be separated from each other.
- 4.35 Quality 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), solvents, reagents and records.
- 4.36 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.
- 4.37 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.

CHAPTER 5: EQUIPMENT

Principle:

Equipment must be located, designed, constructed, adapted, and maintained to suit the intended purpose.

General:

- 5.1 The layout and design 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.
- 5.2 Equipment should be installed in such a way as to minimize any risk of error or contamination.
- 5.3 Equipment should be used in accordance with written instructions that are appropriate to the equipment and consistent with any operating instruction issued by the manufacturer.
- 5.4 Equipment should be uniquely identified. This identification should be traceable to all records pertaining to the equipment.
- 5.4 Fixed pipe work should be clearly labeled to indicate the contents and, where applicable, the direction of flow. Pipes should be adequately sloped for drainage and constructed without 'dead-legs'. There should be measures in place to ensure that materials transferred via pipelines are delivered to the correct destination.
- 5.5 All service piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.
- 5.6 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, preferably on a label attached to the instrument.
- 5.7 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations.
- 5.7 Production equipment should be thoroughly cleaned on a scheduled basis.
- 5.8 Laboratory equipment and instruments should be suited to the testing procedures undertaken.
- 5.9 Washing, cleaning and drying equipment should be designed and used so as not to be a source of contamination.

- 5.10 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.
- 5.11 Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labeled as defective to prevent use.
- 5.12 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.
- 5.13 Non-dedicated equipment should be cleaned according to validated cleaning procedures between productions of different pharmaceutical products to prevent cross-contamination.
- 5.14 Repair and maintenance operations should not present any hazard to the quality of the products.

CHAPTER 6: MATERIAL

Principle:

The main objective of a veterinary manufacturing plant is to produce finished products for animals' use from a combination of approved materials to meet specified requirements. Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labeling materials.

General:

- 6.1 No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product.
- 6.2 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.
- 6.3 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 expiry, first-out rule.
- 6.4 Water used in the manufacture of veterinary products should be suitable for its intended use.

Starting Materials

- 6.5 Purchase of starting materials is an important operation that should involve staff who has a particular and thorough knowledge of the products and suppliers.
- 6.6 Suppliers of starting materials should be approved and if possible starting materials should be purchased directly from producer/manufacturer. 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 critical 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 contractually agreed between the manufacturer and the supplier.
- 6.7 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.
- 6.8 Containers should be cleaned where necessary and labeled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.
- 6.9 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.

- 6.10 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- 6.11 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:
 - 6.11.1 The designated name of the product and the internal code reference where applicable;
 - 6.11.2 The batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
 - 6.11.3 The status of the contents (e.g. on quarantine, on test, released, rejected, to be returned);
 - 6.11.4 Where appropriate, an expiry date or a date beyond which retesting is necessary.
 - 6.11.5 When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.
- 6.12 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.
- 6.13 Only starting materials released by the quality control department and which are within their shelf-life should be used. It shall be ensured that shelf-life of formulation product shall not exceed with that of active raw materials used.
- 6.14 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.
- 6.15 Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 6.16 Materials dispensed for each batch of the final product should be kept together and conspicuously labeled as such.

Packaging Materials

- 6.17 The purchase, handling and control of primary and printed packaging materials should be as for starting materials.
- 6.18 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. Roll feed labels should be used wherever possible. 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 and reconciliation of the remaining labels should be done and documented.

- 6.19 Outdated or obsolete primary packaging material or printed packaging material should be destroyed as per the documented procedure and its disposal recorded.
- 6.20 All packaging materials to be used should be checked on delivery to the packaging section/department for quantity, identity and conformity with the packaging instructions.

Intermediate and Bulk Products

- 6.21 Intermediate and bulk products should be kept under appropriate conditions.
- 6.22 Intermediate and bulk products purchased should be handled on receipt by following the procedures for receiving starting materials.

Finished Products

- 6.23 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.

Rejected, Recovered, Reprocessed and Reworked Materials

- 6.24 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 in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.
- 6.25 The reworking or recovery 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 reworking or recovery. A reworked batch should be given a new batch number.
- 6.26 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.
- 6.27 The need for additional testing of any finished product that has been reprocessed reworked or into which a recovered product has been incorporated, should be considered by the quality control department.

Recalled Products

- 6.28 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.

Returned Goods

- 6.29 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or re-labeling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued 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. Any action taken should be appropriately recorded.

Reagents and Culture Media

- 6.30 There should be records for the receipt and preparation of reagents and culture media.
- 6.31 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 re-standardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.
- 6.32 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference Standards

- 6.33 Whenever official reference standards exist, these should preferably be used.
- 6.34 Official reference standards should be used only for the purpose described in the appropriate monograph.
- 6.35 Reference standards prepared by the producer should be tested, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.
- 6.35 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.
- 6.36 Reference standards should be properly labeled with at least the following information; Name of the material; Batch or lot number and control number; Date of preparation; Shelf-life; Potency and Storage conditions.

- 6.37 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.
- 6.38 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste Materials

- 6.39 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

CHAPTER 7: DOCUMENTATION

Principle:

Manufacturers of veterinary products must establish and maintain a system of documentation, document control and record keeping. The documents should aim to define specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a product for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation.

It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General:

- 7.1 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.
- 7.2 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.
- 7.3 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.
- 7.4 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. Superseded documents should be retained for a specific period of time.
- 7.5 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.
- 7.6 Any change 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.
- 7.7 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of veterinary products are traceable. Records should be retained for at least one year after the expiry date of the finished product.
- 7.8 Documents should be legible, readily identifiable and retrievable. They should not include superfluous data and, at the working level, should be written in the

imperative (i.e. as instructions rather than statements of what is desired). They should be laid out in an orderly fashion and be easy to check.

- 7.9 Data (and records for storage) 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 stored electronically 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.

Documents Required

Labels

- 7.10 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 colors to indicate status (e.g. quarantined, approved, rejected and cleaned).
- 7.11 All finished veterinary products should be identified by labeling, as required by the national legislation, bearing at least the following information:
- 7.11.1 The name of the product;
 - 7.11.2 A list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
 - 7.11.3 The batch number assigned by the manufacturer;
 - 7.11.4 The expiry date in an uncoded form;
 - 7.11.5 Any special storage conditions or handling precautions that may be necessary;
 - 7.11.6 Directions for use, and warnings and precautions that may be necessary;
 - 7.11.7 The name and address of the manufacturer or the company or the person responsible for placing the product on the market.
 - 7.11.8 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

Specifications and Testing Procedures

- 7.11 Testing procedures described in documents should be verified/validated in the context of available facilities and equipment before they are adopted for routine testing.
- 7.12 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.
- 7.13 Each specification should be approved, signed and dated, and maintained by quality control, quality assurance unit or documentation centre.
- 7.14 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.
- 7.15 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

Specifications for Starting and Packaging Materials

- 7.16 Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:
 - 7.16.1 The designated name (if applicable, the INN) and internal code
 - 7.16.2 The reference, if any, to a pharmacopoeia monograph; Qualitative and quantitative requirements with acceptance limits.
- 7.17 Depending on the company's practice other data may be added to the specification, such as:
 - 7.17.1 The supplier and the original producer of the materials;
 - 7.17.2 A specimen of printed materials;
 - 7.17.3 Directions for sampling and testing, or a reference to procedures;
 - 7.17.4 Storage conditions and precautions;
 - 7.17.5 The maximum period of storage before re-examination.
- 7.18 Packaging material should conform to specifications, and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

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

Specifications for Intermediate and Bulk Products

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

Specifications for Finished Products

- 7.21 Specifications for finished products should include:
- 7.21.1 The designated name of the product and the code reference, where applicable;
 - 7.21.2 The designated name(s) of the active ingredient(s) (if applicable, with the INN(s));
 - 7.21.3 The formula or a reference to the formula;
 - 7.21.4 A description of the dosage form and package details;
 - 7.21.5 Directions for sampling and testing or a reference to procedures;
 - 7.21.6 The qualitative and quantitative requirements, with acceptance limits;
 - 7.21.7 The storage conditions and precautions, where applicable;
 - 7.21.8 The shelf-life.

Master Formulae

- 7.22 A formally authorized master formula should exist for each product and batch size to be manufactured.
- 7.23 The master formula should include:
- 7.23.1 The name of the product, with a product reference code relating to its specification;
 - 7.23.2 A description of the dosage form, strength of the product and batch size;
 - 7.23.3 A list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);

- 7.23.4 A statement of the expected final yield with the acceptable limits and of relevant intermediate yields, where applicable;
- 7.23.5 A statement of the processing location and the principal equipment to be used;
- 7.23.6 The methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
- 7.23.7 Detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- 7.23.8 The instructions for any in-process controls with their limits;
- 7.23.9 Where necessary, the requirements for storage of the products, including the container, the labeling, and any special storage conditions;
- 7.23.10 Any special precautions to be observed.

Packaging Instructions

- 7.24. Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:
 - 7.24.1 The name of the product;
 - 7.24.2 A description of its pharmaceutical form, strength and, where applicable, method of application;
 - 7.24.3 The pack size expressed in terms of the number, weight or volume of the product in the final container;
 - 7.24.4 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;
 - 7.24.5 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;
 - 7.24.6 Special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
 - 7.24.7 A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

- 7.24.8 Details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

- 7.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)
- 7.26 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.
- 7.27 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:
- 7.27.1 The name of the product;
 - 7.27.2 The number of the batch being manufactured;
 - 7.27.3 The name of the person responsible for each stage of production, dates and times of commencement, significant intermediate stages, and of completion of production;
 - 7.27.4 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);
 - 7.27.5 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);
 - 7.27.6 Any relevant processing operation or event and the major equipment used;
 - 7.27.7 The in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
 - 7.27.8 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;
 - 7.27.9 Notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch Packaging Records

- 7.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)
- 7.29 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.
- 7.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:
- 7.30.1 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;
 - 7.30.2 The date(s) and time(s) of the packaging operations;
 - 7.30.3 The name of the responsible person carrying out the packaging operation;
 - 7.30.4 The initials of the operators of the different significant steps;
 - 7.30.5 The checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
 - 7.30.6 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;
 - 7.30.7 Whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
 - 7.30.8 Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
 - 7.30.9 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.

Standard Operating Procedures (SOPs) and Records

- 7.31 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:
 - 7.31.1 equipment assembly and validation;
 - 7.31.2 analytical apparatus and calibration;
 - 7.31.3 maintenance, cleaning and sanitization;
 - 7.31.4 personnel matters including qualification, training, clothing and hygiene;
 - 7.31.5 environmental monitoring;
 - 7.31.6 pest control;
 - 7.31.7 complaints;
 - 7.31.8 recalls;
 - 7.31.9 returns.
- 7.32 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.
- 7.33 The records of the receipts should include:
 - 7.33.1 The name of the material on the delivery note and the containers;
 - 7.33.2 The “in-house” name and/or code of material if different from (7.33.1);
 - 7.33.3 The date of receipt;
 - 7.33.4 The supplier’s name and, if possible, manufacturer’s name;
 - 7.33.5 The manufacturer’s batch or reference number;
 - 7.33.6 The total quantity, and number of containers received;
 - 7.33.7 The batch number assigned after receipt;
 - 7.33.8 Any relevant comment (e.g. state of the containers).
- 7.34 There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

- 7.35 Standard operating procedures should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.
- 7.36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.
- 7.37 The sampling instructions should include:
- 7.37.1 The method of sampling and the sampling plan;
 - 7.37.2 The equipment to be used;
 - 7.37.3 Any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
 - 7.37.4 The amount of sample(s) to be taken;
 - 7.37.5 Instructions for any required subdivision of the sample;
 - 7.37.6 The type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labeling;
 - 7.37.7 Any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.
- 7.38 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.
- 7.39 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.
- 7.40 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.
- 7.41 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.
- 7.42 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.
- 7.43 Analysis records should include at least the following data:
- 7.43.1 The name of the material or product and, where applicable, dosage form;

- 7.43.2 The batch number and, where appropriate, the manufacturer and/or supplier;
 - 7.43.3 References to the relevant specifications and testing procedures;
 - 7.43.4 Test results, including observations and calculations, and reference to any specifications (limits);
 - 7.43.5 Date(s) and reference number(s) of testing;
 - 7.43.6 The initials of the persons who performed the testing;
 - 7.43.7 The date and initials of the persons who verified the testing and the calculations, where appropriate;
 - 7.43.8 A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
- 7.44 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.
 - 7.45 Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.
 - 7.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.
 - 7.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.
 - 7.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

CHAPTER 8: GOOD PRACTICES IN PRODUCTION

Principle:

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

General:

- 8.1 Production should be performed and supervised by competent people.
- 8.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- 8.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.
- 8.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 8.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.
- 8.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being 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. In some cases it may be useful to record also the name of the previous product that has been processed.
- 8.7 Access to production premises should be restricted to authorized staff.
- 8.8 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 Microbial Contamination During Production

- 8.9 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).
- 8.10 Contamination of a starting material or of a product has to be avoided. Contamination may arise from uncontrolled release of dust, gases, particles,

vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated.

Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones 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.

- 8.11 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:
 - 8.11.1 Carrying out production in dedicated and self-contained areas (which may be required for products such as live vaccines, live bacterial preparations and certain other biologicals);
 - 8.11.2 Conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
 - 8.11.3 Providing appropriately designed airlocks, pressure differentials, and air supply (air velocity, air flow pattern and air changes) and extraction systems;
 - 8.11.4 Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
 - 8.11.5 Wearing protective clothing where products or materials are handled; using cleaning and decontamination procedures of known effectiveness;
 - 8.11.6 Using a "closed system" in production;
 - 8.11.7 Testing for residues;
 - 8.11.8 Using cleanliness status labels on equipment.
- 8.12 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.
- 8.13 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

Manufacture of veterinary medicinal products containing penicillins

- 8.14 The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity

have been recorded in horses and dogs, there are other materials which are toxic to certain species, e.g. the ionophore antibiotics in horses.

- 8.15 The manufacturing of penicillin and non-penicillin containing veterinary medicinal products may be carried out in the same facility provided that all necessary measures have been taken to avoid cross contamination and any risk to operator safety.

Manufacture of premixes for medicated feeding stuffs

- 8.16 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 and should also be subject to a regular pest control programme.
- 8.17 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.
- 8.18 Parts of the process likely to have a significant adverse influence on the stability of the active ingredient(s) (e.g. use of steam in pellet manufacture) should be carried out in a uniform manner from batch to batch.
- 8.19 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 minimise the risk of contamination of other manufacturing areas.

Manufacture of ectoparasiticides

- 8.20 Ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorisation, 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.
- 8.21 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 these guidelines.

Processing operations

- 8.22 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.
- 8.23 Intermediate and bulk products should be kept under appropriate conditions.

- 8.24 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
- 8.25 Any necessary in-process controls and environmental controls should be carried out and recorded.
- 8.26 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.
- 8.27 After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.
- 8.28 Time limits for storage of equipment after cleaning and before use should be stated and based on data.
- 8.29 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.
- 8.30 Any significant deviation from the expected yield should be recorded and investigated.
- 8.31 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.
- 8.32 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

Packaging operations

- 8.33 When the programme 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.
- 8.34 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 which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.
- 8.35 The name and batch number of the product being handled should be displayed at each packaging station or line.

- 8.36 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.
- 8.37 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.
- 8.38 The correct performance of any printing (e.g. 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.
- 8.39 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. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups.
- 8.40 Checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.
- 8.41 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 8.42 On-line control of the product during packaging should include at least checks on:
- 8.42.1 The general appearance of the packages;
 - 8.42.2 Whether the packages are complete;
 - 8.42.3 Whether the correct products and packaging materials are used;
 - 8.42.4 Whether any overprinting is correct;
 - 8.42.5 The correct functioning of line monitors.
- 8.43 Samples taken away from the packaging line should not be returned.
- 8.44 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.
- 8.45 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, satisfactorily accounted for, and recorded before release.
- 8.46 Upon completion of a packaging operation, any unused batch coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

CHAPTER 9: 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.

General:

9.1 Each manufacturer (the holder of a manufacturing authorization) should have a quality control function. The quality control function 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:

- 9.1.1 Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing of starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- 9.1.2 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;
- 9.1.3 Qualification and validation must be performed;
- 9.1.4 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;
- 9.1.5 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;
- 9.1.6 Records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

- 9.1.7 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 production together with the authorized person from quality control;
- 9.2 Quality control 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 labelling 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.
- 9.3 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.
- 9.4 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

- 9.5 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.
- 9.6 Samples should be representative of the batches of material from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (example beginning or end of a process) in accordance with the approved written procedure.
- 9.7 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.
- 9.8 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.
- 9.9 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.
- 9.10 Each sample container should bear a label indicating: the name of the sampled material; the batch or lot number; the number of the container from which the sample has been taken; the number of the sample; the signature of the person who has taken the sample and the date of sampling.

9.11 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test requirements: Starting and packaging materials

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

9.13 An identity test should be conducted on a sample from each container of starting material. However in exceptional circumstances appropriate sampling formula may be used.

9.14 Each batch (lot) of printed packaging materials must be examined following receipt.

9.15 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 and through on-site audits of the supplier's capabilities. Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information:

9.15.1 Identification (name and address) of the issuing supplier;

9.15.2 Signature of the competent official, and statement of his or her qualifications;

9.15.3 The name of the material tested;

9.15.4 The batch number of the material tested;

9.15.5 The specifications and methods used;

9.15.6 The test results obtained;

9.15.7 The date of testing.

In-process control

9.16 In-process control records should be maintained and form a part of the batch records.

Finished products

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

- 9.18 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch record review

- 9.19 Production and quality control records should be reviewed as part of the approval process of batch release. 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.

Retention of samples

- 9.20 Sufficient samples to permit at least two full re-examinations of starting materials and products must be retained for at least one year after the expiry date to permit future examination of the product if necessary. The retained product must be kept in its final pack under the recommended storage conditions. However it is recognized that because of the large volume of certain veterinary medicinal products in their final packaging it may not be feasible for manufacturers to retain samples from each batch in its final packaging. Nevertheless manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with these guidelines.

Stability studies

- 9.21 Quality control should evaluate the quality and stability of finished veterinary medicinal products and, when necessary, of starting materials and intermediate products.
- 9.22 Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.
- 9.23 A written programme for ongoing stability determination should be developed and implemented to include elements such as:
- 9.23.1 A complete description of the drug involved in the study;
 - 9.23.2 The complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
 - 9.23.3 Provision for the inclusion of a sufficient number of batches;
 - 9.23.4 The testing schedule for each drug;
 - 9.23.5 Provision for special storage conditions;
 - 9.23.6 A summary of all the data generated, including the evaluation and the conclusions of the study.

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

CHAPTER 10: 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.

General:

- 10.1 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.
- 10.2 The contract should permit the contract giver to audit the facilities of the contract acceptor.
- 10.3 In the case of contract analysis, the final approval for release must be given by the authorized person.

The Contract Giver

- 10.4 The contract giver is responsible for assessing the competence of the contract acceptor in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.
- 10.5 The contract giver should provide the contract acceptor 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 acceptor 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.
- 10.6 The contract giver should ensure that all processed products and materials delivered by the contract acceptor comply with their specifications or that the product has been released by the authorized person.

The Contract Acceptor

- 10.7 The contract acceptor 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.
- 10.8 The contract acceptor 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 acceptor 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 acceptor.

- 10.9 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The Contract

- 10.10 There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party.
- 10.11 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 and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.
- 10.12 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.
- 10.13 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.
- 10.14 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 acceptor should take samples at the premises of the manufacturer.
- 10.15 Manufacturing, analytical, 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.
- 10.16 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 procedure to be followed if the contract analysis shows that the tested product must be rejected.

CHAPTER 11: COMPLAINTS AND PRODUCT RECALLS

Principle:

Complaints

All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market complaints.

- 11.1 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.
- 11.2 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.
- 11.3 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.
- 11.4 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.
- 11.5 Immediate corrective actions should be taken to address the root cause of the problem, and actions should be taken to prevent it from recurring. There should be active follow-up of the implementation of corrective actions.
- 11.6 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- 11.7 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 11.8 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.
- 11.9 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.

Product Recalls

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 sales and marketing department. If this person is different from the authorized person, the latter should be made aware of any recall operation.

- 11.10 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 a hospital or pharmacy or any authorized drug outlet.
- 11.11 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.
- 11.12 The distribution records should be readily available to a person 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.
- 11.13 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including reconciliation between the delivered and recovered quantities of the products.
- 11.14 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.
- 11.15 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 12: 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 QC. The self-inspection programme should be designed to detect any shortcoming 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 authority 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

- 12.1 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:
 - 12.1.1 Personnel;
 - 12.1.2 Premises including personnel facilities;
 - 12.1.3 Maintenance of buildings and equipment;
 - 12.1.4 Storage of starting materials and finished products;
 - 12.1.5 Equipment;
 - 12.1.6 Production and in-process controls;
 - 12.1.7 QC;
 - 12.1.8 Documentation;
 - 12.1.9 Sanitation and hygiene;
 - 12.1.10 Validation and revalidation programmes;
 - 12.1.11 Calibration of instruments or measurement systems;
 - 12.1.12 Recall procedures;
 - 12.1.13 Complaints management;
 - 12.1.14 Labels control;
 - 12.1.15 Results of previous self-inspections and any corrective steps taken.

Self-inspection team

- 12.2 Management should appoint a self inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

- 12.3 The frequency at which self inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-inspection report

- 12.4 A report should be made at the completion of a self-inspection. The report should include:
- 12.4.1 Self-inspection findings;
 - 12.4.2 Evaluation and conclusions; and
 - 12.4.3 Recommended corrective actions.

Follow-up action

- 12.5 There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

- 12.6 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.

Vendors'/Suppliers' audits and approval

- 12.7 The person responsible for QC should have responsibility together with other relevant departments for approving vendor/suppliers who can reliably supply starting and packaging materials that meet established specifications.
- 12.8 Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a vendor's/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 13: QUALIFICATION AND VALIDATION

Principle:

Principles of qualification and validation are applicable to the manufacture of veterinary 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 facilities, equipment and 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.

PLANNING FOR VALIDATION

- 13.1 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.
- 13.2 The VMP should be a summary document which is brief, concise and clear.
- 13.3 The VMP should contain data on at least the following:
 - 13.3.1 Validation policy;
 - 13.3.2 Organizational structure of validation activities;
 - 13.3.3 Summary of facilities, systems, equipment and processes to be validated;
 - 13.3.4 Documentation format: the format to be used for protocols and reports;
 - 13.3.5 Planning and scheduling;
 - 13.3.6 Change control;
 - 13.3.7 Reference to existing documents.
- 13.4 In case of large projects, it may be necessary to create separate validation master plans.

DOCUMENTATION

- 13.5 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.
- 13.6 A report that cross-references the qualification and/or validation protocol should be prepared, summarizing 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.

- 13.7 After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorization.

QUALIFICATION

Design qualification

- 13.8 The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).
- 13.9 The compliance of the design with GMP should be demonstrated and documented.

Installation qualification

- 13.10 Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.
- 13.11 IQ should include, but not be limited to the following:
- 13.11.1 Installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
 - 13.11.2 Collection and collation of supplier operating and working instructions and maintenance requirements;
 - 13.11.3 Calibration requirements;
 - 13.11.4 Verification of materials of construction.

Operational qualification

- 13.12 Operational qualification (OQ) should follow Installation qualification.
- 13.13 OQ should include, but not be limited to the following:
- 13.13.1 Tests that have been developed from knowledge of processes, systems and equipment;
 - 13.13.2 Tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.
- 13.14 The completion of a successful Operational qualification should allow the finalization of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal “release” of the facilities, systems and equipment.

Performance qualification

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

13.16 PQ should include, but not be limited to the following:

13.16.1 Tests, using production materials, qualified substitutes or simulated product that have been developed from knowledge of the process and the facilities, systems or equipment;

13.16.2 Tests to include a condition or set of conditions encompassing upper and lower operating limits.

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

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

13.18 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.

PROCESS VALIDATION

13.19 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.

13.20 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).

13.21 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.

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

Prospective validation

13.23 Prospective validation should include, but not be limited to the following:

13.23.1 Short description of the process;

13.23.2 Summary of the critical processing steps to be investigated;

- 13.23.3 List of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status
 - 13.23.4 Finished product specifications for release;
 - 13.23.5 List of analytical methods, as appropriate;
 - 13.23.6 Proposed in-process controls with acceptance criteria;
 - 13.23.7 Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
 - 13.23.8 Sampling plan;
 - 13.23.9 Methods for recording and evaluating results
 - 13.23.10 Functions and responsibilities;
 - 13.23.11 Proposed timetable.
- 13.24 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.
- 13.25 Batches made for process validation should be the same size as the intended industrial scale batches.
- 13.26 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 authorization.

Concurrent validation

- 13.27 In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
- 13.28 The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.
- 13.29 Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation

- 13.30 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.
- 13.31 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. 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.
- 13.32 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.
- 13.33 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.

CLEANING VALIDATION

- 13.34 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.
- 13.35 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.
- 13.36 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.
- 13.37 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 utilizing a “worst case” approach can be carried out which takes account of the critical issues.
- 13.38 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.
- 13.39 “Test until clean” is not considered an appropriate alternative to cleaning validation.

13.40 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.

CHANGE CONTROL

13.41 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.

13.42 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 revalidation should be determined.

REVALIDATION

13.43 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.

CHAPTER 14: HEATING, VENTILATION AND AIR CONDITIONING (HVAC) SYSTEMS

Principle:

Heating, Ventilation and Air-Conditioning (HVAC) play an important role in ensuring the manufacture of quality veterinary products. A well designed HVAC system will also result in operator comfort.

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.

Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of veterinary products during their manufacture and storage, or the accurate functioning of equipment.

Protection of Product and Personnel:

- 14.1 Manufacturing areas where veterinary starting materials and products, utensils and equipment are exposed to the environment should be classified as “clean areas”.
- 14.2 The achievement of a particular clean area classification depends on a number of criteria which should be addressed at the design stage and qualification. There should be a balance between the different criteria in order to create an efficient clean area.
- 14.3 Some of the basic criteria to be considered should include:
 - 14.3.1 Building finishes and structure
 - 14.3.1.1 Air filtration
 - 14.3.1.2 Air change rate or flushing rate
 - 14.3.1.3 Room pressure
 - 14.3.1.4 Location of air terminals and directional airflow
 - 14.3.1.5 Temperature
 - 14.3.1.6 Humidity
 - 14.3.1.7 Material flow
 - 14.3.1.8 Personnel flow
 - 14.3.1.9 Equipment movement

- 14.3.1.10 Process being carried out
 - 14.3.1.11 Outside air conditions
 - 14.3.1.12 Occupancy
- 14.4 Air filtration and air change rates should ensure that the defined clean area classification is attained.
- 14.5 The air change rates should be determined by the manufacturer and designer, taking the various critical parameters into account. Primarily the air change rate should be set to a level that will achieve the required clean area classification.
- 14.6 Air change rates normally vary between 6 and 20 air changes per hour and are normally determined by the following considerations:
- 14.6.1 The quality and filtration of the supply air
 - 14.6.2 Particulates generated by the manufacturing process
 - 14.6.3 Particulates generated by the operators
 - 14.6.4 Configuration of the room and air supply and extract locations
 - 14.6.5 Sufficient air to achieve containment effect
 - 14.6.6 Sufficient air to cope with the room heat load
 - 14.6.7 Sufficient air to maintain the required room pressure
 - 14.6.8 Each clean area class should be specified as achieving the clean area classification under “as-built”, “at-rest” or “operational” conditions.
 - 14.6.9 Materials and products should be protected from contamination and cross-contamination through all stages of manufacture. Contaminants may result from inappropriate premises (e.g. design, layout, finishing), poor cleaning procedures, personnel, and a poor HVAC system.
 - 14.6.10 Contaminants should be removed through effective ventilation.
- 14.7 External contaminants should be removed by effective filtration of the supply air where 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.
- 14.8 Internal contaminants should be removed by dilution and flushing of contaminants in the room, or by displacement airflow.

Air Filtration:

- 14.9 Materials for components of an HVAC system should be selected with care so as not to 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.
- 14.10 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.
- 14.11 Personnel should not be a source of contamination. Airflows should be planned in conjunction with operator locations, so as to minimize operator contamination of the product and also to protect the operator from dust inhalation.
- 14.12 HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread.
- 14.13 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. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect.
- 14.14 Whenever possible, air should be exhausted from a low level in rooms.

Unidirectional Airflow:

- 14.15 Unidirectional airflow 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.
- 14.16 Sampling should be carried out in the same environmental condition that is required for the further processing of the product. In some cases, sampling cubicles located in warehouses are used. These cubicles should normally provide a unidirectional airflow screen to ensure that clean air is flowing over the container when it is opened.
- 14.17 The unidirectional flow velocity should not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent scale inaccuracies, provided that sufficient airflow is maintained to provide containment.
- 14.18 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.

Infiltration:

- 14.19 Manufacturing facilities should be maintained at a positive pressure relative to the outside, in order to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to ambient, in order to prevent the escape of harmful products to the outside (such as penicillin and hormones), then special precautions should be taken.
- 14.20 The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, and particular attention given to ensuring that the building structure is well sealed.
- 14.21 Negative pressure zones should, as far as possible, be encapsulated by surrounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

Cross-contamination:

- 14.22 Where different products are manufactured at the same time, in different areas/cubicles, in a multi-product oral solid dosage manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another.
- 14.23 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 air flow is from the clean corridor into the cubicles, resulting in dust containment.
- 14.24 The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.
- 14.25 Containment can normally be achieved by the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or physical barrier concept.
- 14.26 Where large amount of dust are generated in production process, displacement concept should preferably be used.
- 14.27 Where there is little or no dust is being generated on the production process the pressure differential concept, should preferably be used.
- 14.28 The choice of pressure cascade regime and choice of airflow direction should be considered in relation to the product and processing method used).
- 14.29 Highly potent products should be manufactured under a pressure cascade regime that is negative to atmospheric pressure. The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required.
- 14.30 Building structure should be given special attention because of the pressure cascade design.

- 14.31 Airtight ceilings and walls, close fitting doors and sealed light fittings should be in place.
- 14.32 Pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be verified and recorded on a regular basis. Based on a risk analysis, pressure control devices should be linked to an alarm system.
- 14.33 Where manual control systems are used, these should be set up during commissioning and should not change unless other system conditions change.
- 14.34 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.
- 14.35 Central dust extraction systems should be interlocked with the appropriate air handling systems, to ensure that they operate simultaneously.
- 14.36 Room pressure imbalance between adjacent cubicles which are linked by common dust extract ducting should be prevented.
- 14.37 Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting.

Temperature and Relative humidity:

- 14.38 Maximum and minimum temperature and relative humidity should be controlled, monitored and recorded where relevant, in order to ensure compliance with materials and product requirements, and to provide operator comfort where necessary.
- 14.39 The operating band or tolerance between the acceptable minimum and maximum temperatures should not be made too close.
- 14.40 Cubicles, or suites, processing products requiring low humidity, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher humidity, by means of suitable airlocks.
- 14.41 Humidifiers should be avoided if possible as these 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 humidification purposes.
- 14.42 Humidification systems should be well drained. No condensate should accumulate in air handling systems.

- 14.43 Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used due to the possible microbial contamination risk
- 14.44 Duct material in the vicinity of the humidifier should not add contaminants to air that will not be filtered downstream.
- 14.45 Final air filters should not be installed immediately downstream of humidifiers.
- 14.46 There should be insulation of cold surfaces in order to prevent condensation within the clean area or on air-handling components, where high humidity is required.
- 14.47 Chemical driers may be used to achieve conditions lower than 45% RH at a temperature of 22°C. Chemical driers or dehumidifiers employing a desiccant, such as silica gel or lithium chloride to remove the moisture from the air, should have desiccant wheels of the non-shedding type and should not support microbial growth.

Dust Control

- 14.48 Wherever possible, the dust or vapour contamination should be removed at source. Point extraction, as close as possible to the point where dust is generated, should be employed.
- 14.49 Point extraction should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extract hood.
- 14.50 Dust extraction ducting should be designed so as to have sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting.
- 14.51 The required transfer velocity should be determined as 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).
- 14.52 The low level extract should assist in drawing air down and away from the operator's face. The location of the extract grilles should be positioned strategically to draw air away from the operator, but at the same time prevent the operator from contaminating the product.
- 14.53 When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.
- 14.54 For products such as hormones or highly potent products, operators should wear totally enclosed garments, with an air breathing system.

Protection of the Environment:

Exhaust Air Dust:

- 14.55 Exhaust air discharge points on pharmaceutical 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 ambient contamination.
- 14.56 Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters having a filter classification of F9 according to EN779 filter standards.
- 14.57 Where harmful substances such as penicillin, hormones, toxic powders and enzymes are exhausted, the final filters should be HEPA filters with at least an H12 classification according to EN1822 filter standards, as appropriate.
- 14.58 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.
- 14.59 When handling hazardous compounds safe change filter housings, also called “bag-in bag-out” filters, should be used.
- 14.60 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and should be marked with the clean resistance and the change-out filter resistance.
- 14.61 Monitoring of filters should be done at regular intervals in order to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.
- 14.62 More sophisticated computer-based data monitoring systems may be installed, with preventive maintenance plans by trend logging.
- 14.63 An automated monitoring system should be capable of indicating any out-of-specification condition without delay by means of an alarm or similar system.
- 14.64 Mechanical shaker dust collectors should not be used for applications where continuous airflow is required.
- 14.65 When wet scrubbers are used, the dust-slurry should be passed to a suitable drainage system.
- 14.66 The exhaust air quality should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

Fume removal

- 14.67 Fume, dust and effluent control should be designed, installed and operated in a manner that these 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.
- 14.68 Removal of fumes should be by means of wet scrubbers or dry chemical scrubbers (deep bed scrubbers).
- 14.69 Wet scrubbers for fume removal should normally have various chemicals added to the water to increase the adsorption efficiency.
- 14.70 Deep bed scrubbers should be designed with activated carbon filters or chemical adsorption granular media. The chemical media for deep bed scrubbers should be specific to the effluent being treated.

HVAC Systems

Recirculation System

- 14.71 There should be no risk of contamination or cross-contamination (including fumes and volatiles) due to recirculation of air.
- 14.72 Depending on the airborne contaminants in the return air system it may usually 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.
- 14.73 HEPA filters may not be required where the air handling system is serving a single product facility and there is evidence that there is no possibility of cross-contamination.
- 14.74 Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.
- 14.75 HEPA filters may be located in the air handling unit or placed terminally.
- 14.76 Dust from highly toxic processes should never be re-circulated to the HVAC system.

Full Fresh Air Systems

- 14.77 The degree of filtration on the exhaust air should be determined dependent on the exhaust air contaminants and local environmental regulations.
- 14.78 Energy recovery wheels should normally not be used in multi-product facilities. When energy wheels are used these should not become a source of possible contamination.

14.79 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.

Commissioning, Qualification and Maintenance

Commissioning:

- 14.80 Commissioning should involve the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that the system meets all the requirements, as specified in the User Requirement Specification, and capacities as specified by the designer or developer.
- 14.81 The installation records of the system should provide documented evidence of all measured capacities of the system.
- 14.82 The data should include items such as the design and measured figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals.
- 14.83 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation
- 14.84 Training should be provided to personnel after installation of the system, and should include operation and maintenance.
- 14.85 Operating & Maintenance manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.
- 14.86 Commissioning should be a precursor to system qualification and validation.

Qualification:

- 14.87 The qualification of the HVAC system should be described in a validation master plan (VMP).
- 14.88 It should define the nature and extent of testing, the test procedures and protocols to be followed.
- 14.89 Stages of the qualification of the HVAC system should include design qualification, installation qualification, Operational qualification and performance qualification.
- 14.90 Critical and non-critical parameters should be determined by means of a risk analysis for all HVAC installation components, subsystems and controls.
- 14.91 All parameters that may affect the quality of the pharmaceutical product should be considered to be a critical parameter.

- 14.92 Systems and components, which are non-critical, should be subject to Good engineering practice and may not necessarily require full qualification.
- 14.93 A change control procedure should be followed when changes are planned to the HVAC system, its components and controls that may affect critical parameters.
- 14.94 Design condition and normal operating ranges should be set as wide as possible to set realistically achievable parameters.
- 14.95 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.
- 14.96 Out of limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.
- 14.97 A very tight relative humidity tolerance, but a wide temperature tolerance, should not be acceptable as variances between the maximum and minimum temperature condition will give an automatic deviation of the humidity condition.
- 14.98 For a pharmaceutical facility some of the typical HVAC system parameters that should be qualified may include:
- 14.98.1 Temperature;
 - 14.98.2 Relative humidity;
 - 14.98.3 Supply air quantities for all diffusers;
 - 14.98.4 Return air or exhaust air quantities;
 - 14.98.5 Room air change rates;
 - 14.98.6 Room pressures (pressure differentials);
 - 14.98.7 Room airflow patterns;
 - 14.98.8 Unidirectional flow velocities;
 - 14.98.9 Containment system velocities;
 - 14.98.10 HEPA filter penetration tests;
 - 14.98.11 Room particle counts;
 - 14.98.12 Room clean-up rates;
 - 14.98.13 Microbiological air and surface counts where appropriate;

14.98.14 Operation of dedusting;

14.98.15 Warning/alarm systems where applicable.

14.99 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. (Table below gives intervals for reference purposes only. The actual test periods may be more frequent or less frequent, depending on the product and process).

Schedule of Tests to Demonstrate Continuing Compliance

Test Parameter	Clean area Class	Max Time Interval	Test Procedure
Particle Count Test (Verification of Cleanliness)	All classes	6 Months	Dust particle counts to be carried out & result printouts produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air Pressure Difference (To verify non 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 differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5
Airflow Volume (To verify air change rates)	All Classes	12 Months	Air flow 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 unidirectional flow or containment conditions)	All Classes	12 Months	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4

14.100 Periodic re-qualification of parameters should be done at regular intervals, e.g. annually.

14.101 Re-qualification should also be done when any change, which could affect system performance, takes place.

14.102 The table below reflects permissible particle concentrations for various clean area classifications, as well as a comparison between different clean area standards. The ISO 14644 standard has superseded the US and BS standards, but these are given for comparative purposes only. ISO Classes Grades 1 to 4 are not applicable to pharmaceutical facilities, but are included for completeness of the table.

Controlled environment standards

ISO classification number (N)	Maximum concentration limits (particles/m ³ of air) for particle equal to and larger than the considered sizes shown below.						Approx Equivalent			
	0.1 μm	0.2 μm	0.3 μm	0.5 μm	1 μm	5 μm	American Federal Standard		BS5229 5 1989	EEC (GMP)
ISO class 1	10	2								
ISO Class 2	100	24	10	4			M1			
ISO Class 3	1,000	237	102	35	8		M1.5	1	(C)	
ISO Class 4	10,000	2,370	1,020	352	83		M2.5	10	(D)	
ISO Class 5 (U)	100,000	23,700	10,200	3,520	832	29	M3.5	100(U)	E	A
ISO class 5 (N)	100,000	23,700	10,200	3,520	832	20	M3.5	100(N)	F	B
ISO Class 6	1,000,000	237,000	102,000	35,200	8,320	293	M4.5	1,000	G or H	
ISO Class 7				352,000	83,200	2,930	M5.5	10,000	J	C
ISO Class 8				3,520,000	832,000	29,300	M6.5 M.7	100,000	K	D
ISO Class 9				35,200,000	8,320,000	293,000			L	

U= unidirectional flow, N = non-unidirectional or turbulent flow
Maintenance

- 14.103 There should be a planned preventive maintenance programme, procedures and records for the HVAC system. Records should be kept.
- 14.104 There should be appropriate training for maintenance personnel.
- 14.105 HEPA filters should be changed only by specialists or trained personnel.
- 14.106 Any maintenance activity should be critically assessed to determine any impact on product quality including possible contamination.
- 14.107 Maintenance activities should normally be scheduled to take place outside of production hours, and any system stoppage should be assessed with a view to possible re-qualification of an area that may be required as a result of an interruption of the service.

CHAPTER 15: WATER TREATMENT

Principle:

Water is essential to the production of medicinal products. Different limits for contaminants exist as set by regional and national authorities. GMP should be implemented as a principle of pharmaceutical production to ensure WPU complies with its specifications.

Every WPU production stage has a description of the fundamental functions of the processing components that make up the processing system input, processing itself and outputs, including a dynamic view of a system functionality, control and timing of starting and finishing.

These chapter present main recommendations and requirements specifications to ensure the GMP based WPU production.

General:

- 15.1 Water treatment systems should be designed, constructed, installed, maintained and adapted to ensure a consistently reliable production of water of an appropriate quality.
- 15.2 Water treatment system components, equipment, control and measuring instruments should be tagged.
- 15.3 Pipelines, valves, monitoring and measuring instruments should be marked and labelled and the direction of flow should be indicated.
- 15.4 All measuring instruments should be calibrated and the calibration recorded. It is recommended that the individual instruments be labelled as proof of calibration (date of calibration, done by, due date for calibration) where possible.
- 15.5 All water treatment systems components, including stills, should be subject to routine and planned maintenance, validation and monitoring. All maintenance, validation and monitoring operations should be documented.
- 15.6 The manufacturer should monitor all components of the water treatment system and processing stages to ensure that water complies with the required specification.
- 15.7 Water sources, treatment procedures, water treatment system efficiency, treated water quality for production, and microbiological or contamination with endotoxins monitoring results should be within limits in accordance with the specification (e.g. for WPU grade indicated in the pharmaceutical dossier of the finished product).
- 15.8 Water treatment systems should be separated from the “in-house” water treatment system.

Sources of Portable Water for Pharmaceutical Use

- 15.9 Although drinking water is used as feed water for preparing Water for Pharmaceutical Use (WPU), proper control methods, continuous monitoring and appropriate specifications for chemical and microbial quality of drinking water supply should be established and periodic testing conducted. To achieve high efficiency of the in-house water treatment processes the pre-treatment of feed water should be effective in removing different contaminants.
- 15.10 The risk assessment of contaminants should be conducted at two levels: firstly, for the contaminants themselves (which means the hazard they represent for the consumer or for the intended use); and secondly, for the probability of their presence or amount in a given case. The site, type of water supply and possible seasonal variations should be considered.
- 15.11 An important raw water source for factories is municipal (or civil) tap water or a combination of tap and well waters. Where municipal tap water is not available well water is an important source for drinking and pharmaceutical use.

Water purchased in bulk requires vendor assessment and authorized certification as for any other purchased starting or raw material. The delivery vehicle should be confirmed as acceptable for the delivery of potable water. Continuous environmental monitoring of water supply areas should be recommended.

Contaminants in Water and their Removal:

- 15.12 The main categories of contaminants in water may be minerals, heavy metals, various organic and microbial, biological settlements and contaminants from human beings, as well as the result of industrial and agricultural pollution of the environment. Prior to the decision making about the water supply for pharmaceutical manufacture a detailed analysis and monitoring of the site and environment of the source should be carried out.
- 15.13 Removal of turbidity and colloids is essential and usually the first step in water treatment. Filtration should normally be done to remove particulates (that may have been shed by softeners and downstream equipment) and micro organisms (algae, protozoa, bacteria).

Colloids which carry a slight electrical charge should be removed by flocculants after the filtering of suspended material. The aluminium content of flocculants like aluminium sulphate may become critical and should be under control especially in connection with WPU for haemodialysis processes.

Feed water pre-treatment processes technology should remove problem minerals such as calcium, magnesium (to avoid precipitation of these mineral salts on the heating surfaces of boilers), iron and manganese (to avoid discoloration of water and reactions with drug components, or actions catalysts in decomposition processes). A high content of calcium and magnesium salts can interfere with other water treatment processes and should be removed by softening equipment, followed by an ion exchanger or reverse osmosis units.

- 15.14 Gaseous dissolved contaminants in water such as carbon dioxide, hydrogen sulphide and phosphorus compounds (phosphates ions) may react with other mineral contaminants or metals, or change the pH of water and cause precipitation and therefore should be removed during the pre-treatment process by using effective methods.
- 15.15 Contamination with metal-ions such as copper, aluminium and heavy metals (lead, cadmium, arsenic, zinc, mercury, etc) could cause serious technical, chemical and health problems and, therefore, they should be removed up to the level allowed by legislation. The treatment methods should be validated and water tested periodically.
- 15.16 Biological contaminants in portable water should be removed during pre-treatment as their presence may result in biofilm formation.
- 15.17 Insufficient pre-treatment elimination for microorganism contaminants (insufficient filtration, adsorption or ion exchange) should be completed or corrected by appropriate treatment measures such as disinfection, heat or chemical treatment, in order to obtain potable water of acceptable quality.
- 15.18 Heat should be preferred to chemical disinfectants as the latter produce by-products.
- 15.19 Appropriate heat is one of the most reliable disinfection methods of water systems. The manufacturer should record the time and temperature of the heat disinfection cycle, e.g. one hour above 60°C for purified water (PW) and at continuous circulation conditions at a temperature higher than 70°C for water for injections (WFI). This contact time should be validated.
- 15.20 Ultraviolet (UV) light is bactericidal but should not “sterilize” as water can attenuate the radiation quickly. The design and maintenance of the system is essential. Lamp life-time is usually less than 12 months, and the use should be recorded.
- 15.21 Where disinfection of portable is done by ozone, it should be “removed” before the water is used in the manufacture of pharmaceuticals as it could degrade the active pharmaceutical ingredients
- 15.22 Ozone also reduces the total organic carbon (TOC) level in water. Ozone may be removed by ultraviolet (UV) light at 254 nm by reducing the ozone to oxygen.
- 15.23 When chlorine and other halogen family representatives are used as disinfectants, care should be taken to ensure that their by products are removed.
- 15.24 System construction materials should be inert when using halogen family disinfectants as they cause considerable corrosion even when using high quality stainless steel.
- 15.25 Peroxygen family chemicals such as hydrogen peroxide, peracetic acid and peroxitane, could be used for disinfection of the system and for treating equipment. Like all other substances used they should be supplied through approved vendors with relevant specifications and documentation.

- 15.26 The use of aldehydes is preferably not recommended due to their toxic vapour and persistent residues.
- 15.27 The manufacturer is responsible for the “in-house” quality of potable water. Water from municipal recirculation systems should be treated because of variation in quality, microbial loads and natural seasonal variations. Raw water, even if it meets “potable” standards, should be treated before use in pharmaceutical manufacturing.
- 15.28 Additional potable water treatment before the WPU in-house purification steps in most cases is limited to filtration, softening, and adsorption by an activated carbon bed or bisulphite to remove disinfectants, e.g. chlorine. If the manufacturer owns a well or some other source of natural water, all steps of pre-treatment as well as purification stages at the manufacturing site should be followed to ensure that the water meets pharmacopoeia grade quality requirements.
- 15.29 Dechlorinating of municipal water, or water from storage tanks, with chlorine disinfectant, should be done with either activated carbon (AC) filtration step or bisulphite injection.
- 15.30 The origin and source of an activated carbon supply should be checked. Charcoal from petroleum sources is preferable to vegetable carbon. Vegetable carbon could have high levels of heavy metals and the content of heavy metals should be checked.
- 15.31 The activated carbon (AC) bed should be sanitized daily, or at a minimum, weekly, and preferably with steam.
- 15.32 There should be detailed procedures covering the handling of potable water and the maintenance/servicing of the water supply system at the manufacturing site.
- 15.33 There should be procedures and specifications for the intended use and for carrying out the sampling and testing (testing methods) according to a written programme.
- 15.34 Official testing methods of feed water for WPU or water supplies from wells or municipal taps should confirm that water is “potable”, and that there are no hazards compounds in the water (pesticides, fertilizers such as nitrates, phosphates, herbicides, fuels, faecal contamination, etc) from the environment or water supply maintenance procedures (pump lubricating oils used or chemicals of disinfections procedures). Testing methods should be validated.

Water storage:

Large-scale Storage of Untreated, Raw Water

- 15.35 Large-scale storage of untreated water should be avoided where possible. However, to guarantee continuous manufacturing, a continuous supply of potable water should be available. If the water supply is not regular, a large-scale storage of raw, untreated or potable water supply in bulk is required. (“Large-scale” has no particular definition; the amount of the storage depends on local circumstances, for instance intermittent water supplies and from the character and amount of production).

- 15.36 Cisterns made of concrete or steel tanks are preferred for storage. Plastic or rubber materials should be avoided as these could be sources of unknown leaches and odours from plasticizers such as phthalates.
- 15.37 The storage tank should be suitably constructed and should keep out insects, birds and animals.
- 15.38 Monitoring and physical inspection of storage tanks and quality of water stored should be carried out at regular intervals.
- 15.39 The storage tank should be emptied and cleaned at regular intervals in accordance with written procedures and records maintained.
- 15.40 Disinfecting of the storage tank should be carried out. If chlorine is used, then a chlorine concentration 1-2ppm, should be checked periodically especially if the water is exposed to sunlight.

Small-scale Storage of Purified Water:

- 15.41 If pharmacopoeia grade water is not generated at the “point of use” it should be stored in small-scale tanks.
- 15.42 Post-treatment storage of highly purified water in bulk represents a high risk of recontamination by micro organisms and other contaminants. To prevent microbial contamination or growth water should be kept hot and continuously circulating.
- 15.43 After the final purification step PW or WFI or other grades of WPU should be stored at 70°C or higher and in a closed system with continuous circulation at linear velocity of 1-2m/sec or more.
- 15.44 The design of the system should include smooth surfaces, moving water, absence of dead legs, and non-return check valves.
- 15.45 Normally heat exchangers should be used at each tapping point if the water is stored hot.
- 15.46 Cooling waters should have lower pressure than the purified water in the distribution network to avoid contamination in case of corrosion damages, e.g. pinholes.
- 15.47 Storage tanks should be designed and constructed using good design elements that will ensure the water quality at the pharmacopoeia monograph requirement level.
- 15.48 Side arm level measuring devices should not be used because they can harbour contaminants. This is an example of a “dead leg” where bacteria and algae can readily grow in the stagnant water.
- 15.49 Storage tanks should have a vent to compensate for the dynamics of changing water levels. The air inlet system could be a source of contamination. Hydrophobic microbial retentive membrane filters fitted onto atmospheric vent filters should be

used in the air inlets. Alternatively, an automatic membrane-filtered or heap-filtered air, or compressed gas and venting system may be used.

- 15.50 Good design elements should include vent filters that can be sterilized and integrity tested, a burst (rupture) disk with a rupture alarm device, a spray ball in-line disinfecting (e.g. by periodic heating, ozonization or UV), air breaks to drain, and an in-line 0,2 micrometer filter to “polish” the water.
- 15.51 All construction material of storage tanks and distribution configuration, including pumps, pipelines and joints, should be of high quality stainless steel.
- 15.52 Inner surfaces should be electropolished.
- 15.53 Sanitary fittings and connections should be without crevices. In cases where pipes need to be joined, orbital welding should be used.
- 15.54 There should be documented records for the welding seams, electropolished surfaces and stainless steel quality specification, 316L compliance.

Water System Design:

- 15.55 One of the main principles of water system design is to avoid biological contamination of the water system.
- 15.56 The design of water system and the choice of water treatment methods depend on the grade of output water required by pharmacopoeias for pharmaceuticals under production, and contamination character and level of input potable or raw water. For WFI production, heat treatment distillation should be used.
- 15.57 The basic design, treatment technologies and GMP requirements for the water treatment system should ensure sufficiently pure water for pharmaceutical use to meet its specification.
- 15.58 Reverse osmosis (RO) or deionization (DI) are the most frequently used methods for preparing purified water that meets pharmacopoeia requirements for pharmaceutical manufacturing. RO and DI treated water should be used as feed for further purification by ultra filtration (UF) or distillation. (Note: only distillation is accepted and may be used for water injection production).
- 15.59 Fully automatic orbital welding techniques will ensure a high quality weld and are recommended.
- 15.60 Sporadic contamination of WPU with microorganisms, pyrogens and endotoxins should be avoided by using pipework, valves, fittings, connections and valves that are easy to clean.
- 15.61 The system elements should be designed so as to prevent sites for microbial growth. The gasket should be designed to provide perfect alignment of pipes, no crevices that will allow bacterial attachment, short outlet tee piece, and short outlet with minimum dead leg.

- 15.62 A dead leg should not be greater than twice the diameter of the pipe for WFI or not greater than six times the pipe diameter for other water system (PW).
- 15.63 Ball and cone valves are not recommended and should normally not be used in the water treatment system downstream of reverse osmosis (RO) and deionization (DI) outlets.
- 15.64 Valves without any dead leg are available and should be used in high purity water systems.
- 15.65 Pumps with a sanitary or hygienic design and construction should be applied for the final water treatment steps. Sanitary pumps should have a mechanical seal around the shaft.
- 15.66 Special clamps should make pump joints to pipes and suitable "O" ringfitting should be used.
- 15.67 In case of long runs of pipe to outlets without circulation, the pharmaceutical manufacturer should have a procedure in place that allows the pipework to be completely drained and left dry daily. These pipeline outlets should be included in the control procedure, sampling and testing frequency for microbial counts should be indicated.
- 15.68 Heat exchangers (HE) should have double shell or double tubing as pinholes could allow heating or cooling liquid to contaminate the purified water. Single plate heat exchangers should be under continuous monitoring of pressure differentials across the plates.
- 15.69 Side arm level measuring devices on the WPU storage tanks/vessels are not recommended.
- 15.70 Engineering staff should be fully aware of the microbiological implications of certain connections and valves. Therefore, there should be close liaison between the microbiology department and the engineering section to ensure that each different type of fitting is closely examined for potential entrapment area and growth sites.
- 15.71 Existing water systems that have microbiological problems should be improved by e.g. replacing unsuitable valves and connections where relevant.
- 15.72 Hazard analysis of critical control points concept should be considered for the system.
- 15.73 The water system design should allow for sampling ports at each critical point: feed (potable) water input to the treatment system, after multi-media filters, after softeners, after main purification step, storage tank, and the circulation pipework.
- 15.74 The sampling ports themselves should be designed to prevent microbial contamination of the water system during sampling and also to prevent contamination of the sample itself. Sampling methods should ensure correct determination of microbial status.

- 15.75 The water system should be validated (qualification). Supportive documentation should include: a flow diagram and isometric schematic drawing showing all instrumentation, valves, and pipework; a brief description of each component of the system and its function, specifications for filters, DI units, RO/D/UF units, UV light, heat exchangers, pumps, etc. ; sanitization procedures; a preventative maintenance programme (changing of filters, life-cycle of filters, number of times filters are allowed to be sterilized, etc) and training programme for use of the system.

Treatment of Water:

- 15.76 Pre-treatment of raw water should be separated from the “in-house” water treatment system.
- 15.77 A manufacturer owning a water source of large-scale storage and supply should have as a minimum screens and sand filters before undertaking further purification steps.
- 15.77.1 Access of these areas should be controlled.
- 15.77.2 Wells should be inside a special building with access restricted to authorized personnel.
- 15.77.3 The “in-house” process of pre-treatment of drinking water should involve several steps, including physical removal of impurities of chemical treatment.
- 15.77.4 Proper procedures for the regeneration of the unit and/or system should be applied and systems should be properly monitored and sanitized. Control measures should include re-circulation of water during the period of low water use, periodic sanitization of the resin and brine system, use of microbial control devices (e.g. UV, chlorine), appropriate regeneration frequency, effluent monitoring (hardness) and downstream filtration of remove resin fines.
- 15.77.5 The lighting level should allow easy checking of instruments, recording of data and maintenance of equipment.
- 15.77.6 The softened water deionizer should be a twin bed or mixed bed deionizer and water should be kept in continuous circulation.
- 15.77.7 Disinfection of the circulating water should be carried out by In-line ultraviolet irradiation and/or ozonation. The use of heat is not recommended for disinfecting.
- 15.77.8 Ion exchange columns should be regenerated at least once a week, regardless of the conductivity readings, using hydrochloric acid and sodium hydroxide, respectively. Specifications for all materials, resins and regeneration chemicals, used in ion exchange processes and maintenance protocols should be available.

- 15.77.9 The reverse osmosis purification method is used for the purification of water that has to meet pharmacopoeia specifications. RO purified water is preferred for feeding stills as it prevents scaling and ensures high quality preparation of WFI as well as water for the final rinse. RO units employ a semi-permeable membrane and a substantial pressure differential to drive water through the membrane to achieve chemical, microbial and endotoxin level improvement. Control should consist of suitable pre-treatment of the water stream, appropriate membrane material selection, integrity challenges, membrane design, periodical sanitization, monitoring of differential pressures, conductivity, microbial levels, and TOC content.
- RO units can be used alone or in combination with other purification methods, e.g. De-ionization (DI) and Electro-Dialysis (EDI) units for operational and quality enhancements.
- 15.77.10 Water for final rinse of containers should be of the same quality as the water required for pharmaceutical preparation and contact with the final product in the manufacturing process.
- 15.77.11 Water for injection should be pyrogen-free and meet the requirements of *The International Pharmacopoeia* for purified water.
- 15.77.12 WFI should be prepared by distillation and the storage time should be less than 24 hours unless stored at higher than 70°C. Endotoxin levels should be less than 0.25 EU/ml.
- 15.77.13 Clean steam for “sterilize-in-place” equipment or final cleaning, sterilization, procedures of “product contact surfaces” should have the same chemical quality as purified water without pyrogens and endotoxins, and without volatile additives like amines or hydrazines.

Sampling and Testing:

- 15.78 Water systems should be monitored at a frequency that is sufficient to ensure that the system is in control and continues to produce water of acceptable quality. Samples should be taken from representative locations within the processing and distribution system. Established sampling frequencies should be based on water system validation data and should cover all critical areas. The sampling plan should take into consideration the desired attributes of the water being sampled.
- 15.79 Unless samples are tested within a few hours, the sample should be chilled to less than 8°C, but not frozen. During transportation to a remote laboratory, samples should be packed specially with ice packs or dry ice to ensure the samples stay cool. Inclusion of a temperature monitor (maximum/minimum thermometer or data logger) is recommended.
- 15.80 The condition and temperature of the sample should be recorded on arrival at the laboratory.

- 15.81 A corresponding sample registration and tracking system in the laboratory is recommended.
- 15.82 The sampling points should be well designed and hygienic. The practice of flushing them should follow good practices.
- 15.83 Sample points for subsystem, deionizers and RO should be as close to the downstream side as possible to reflect the quality of the water being fed to the next subsystem.
- 15.84 “Target, alert and action” limits in different sampling locations should be included in the specification by a manufacturer and an action plan should be developed if results other than the specification are detected.
- 15.85 The sample container should be inert, securely closable, preferably single-use, sterile, inert plastic containers such as bags.
- 15.86 Plastics that are not inert should not be used as plastic leach can affect the total oxidizable carbon test.
- 15.87 The container with a sample should be properly labelled. The label should bear the date, time of sampling as well the sampling location, sampler’s name and signature.
- 15.88 The manufacturer should have specifications for all types of water used in the factory: for cleaning, washing, rinsing, and for use in product. The chemical, physical and biological specifications from pharmacopoeias should be based on the notion that potable water meeting WHO standards is used in the input, as feed water for further treatment.

ANNEX 1

GOOD MANUFACTURING PRACTICES FOR STERILE VETERINARY MEDICINAL PRODUCTS

Principle:

This annex emphasizes specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate and pyrogen contamination.

1.0 General:

- 1.1 The production of sterile preparations 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 standard of cleanliness and supplied with air that has passed through filters of the required efficiency.
- 1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in

separate areas within a clean area. These areas are classified into four grades (see section 3.1).

- 1.3 Manufacturing operations are divided here into two categories: first, those where the product is terminally sterilized and second, those which are conducted aseptically at some or all stages.

2.0 Sanitation

- 2.1 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written programme. Monitoring should be regularly undertaken in order to detect the emergence of resistant strains of microorganisms. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection.

Table 1
Limits for microbiological contamination

Grade	Air sample (CFU/m ³)	Settle plates (Diameter 90mm) (CFU/4 hours)	Contact plates (Diameter 55mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	<3	<3	<3	<3
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

^aThese are average values. The grades are defined in section 3.1.

^bThe airborne particulate classification for the four grades is given in Table 2.

^cIndividual settle plates may be exposed for less than 4 hours.

- 2.2 Disinfectants and detergents should be monitored for microbiological contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in grade A and B areas (see section 4.1) should be sterilized before use.
- 2.3 In order to control the microbiological cleanliness of the various grades in operation, the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent and methods such as settle plates, and volumetric air and surface sampling (e.g. swabs and contact plates) should be used. The zones should not be contaminated through the sampling methods used in the operations. The results of monitoring should be considered when batch documentation for release of the finished product is reviewed. Both surfaces and personnel should be monitored after critical operations.
- 2.4 Levels (limits) of detection of microbiological contamination should be established for alert and action purposes, and for monitoring the trends in air quality in the facility. Limits expressed in colony forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 1. The sampling methods and numerical

values included in the table are not intended to represent specifications, but are for information only.

3.0 *Manufacture of sterile preparations*

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

Table 2

Airborne particulate classification for manufacture of sterile pharmaceutical preparations

Grade	At rest		In operation	
	Maximum number of particles permitted/m ³		Maximum number of particles permitted/m ³	
	0.5-5.0µm	>5.0 µm	0.5-5.0µm	>5.0 µm
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Not defined	Not defined

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.

For the manufacture of sterile pharmaceutical preparations, four grades are distinguished here, as follows:

- *Grade A:*
The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are provided by a laminar-airflow workstation. Laminar-airflow systems should provide a homogeneous air speed of approximately 0.45m/s ± 20% (guidance value) at the working position.
- *Grade B:*
In aseptic preparation and filling, the background environment for the grade A zone.
- *Grades C and D:*
Clean areas for carrying out less critical stages in the manufacture of sterile products. The airborne particulate classification for the four grades is given in Table2.

- 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.
- In order to reach the B, C and D air grades, the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it. At least 20 air changes per hour are usually required for a room with a good airflow pattern and appropriate high-efficiency particulate air (HEPA) filters.

Table 3

Comparison of Different Airborne Particulate Classification System for Clean Areas^a

WHO (GMP)	United States (209E)	United States (customary)	ISO/TC (209)	EEC (GMP)
Grade A	M 3.5	Class 100	ISO 5	Grade A
Grade B	M 3.5	Class 100	ISO 5	Grade B
Grade C	M 5.5	Class 10000	ISO 7	Grade C
Grade D	M 6.5	Class 100000	ISO 8	Grade D

EEC: European Economic Commission; ISO/TC: International Organization for Standardization Technical Committee

^aSource: reference 1-4

- Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. is not given here. Reference should be made to other guidelines published in compendia such as the European, Japanese or United States pharmacopoeias, or in documents issued by the European Committee for Standardization and the International Organization for Standardization (ISO).

The different airborne particulate classification systems for clean areas are shown in Table3.

- 3.2 The particulate conditions given in Table 2 for the “at rest” state should be achieved in the absence of the operating personnel after a short “clean-up” period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 2 for grade A “in operation” 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, owing to the generation of particles or droplets from the product itself.
- 3.3 In order to control the particulate cleanliness of the various clean areas during operation, they should be monitored.

- 3.4 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, the appropriate corrective actions should be taken, as prescribed in the operating procedures.
- 3.5 The area grades as specified in sections 3.1 must be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. sterile media fills).

The determination of an appropriate process area environment and a time limit should be based on the microbiological contamination (bioburden) found.

Terminally Sterilized Products

- 3.6 Components and most products should be prepared in at least a grade D environment in order to give low microbial and particulate counts, suitable for filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily not processed mainly in closed vessels), the preparation should generally be done in a grade C environment.
- 3.7 The filling of products for terminal sterilization should generally be done in at least a grade C environment.
- 3.8 Where the product is at unusual risk of contamination from the environment (e.g. 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.
- 3.9 The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.
- 3.10 Terminally sterilised veterinary medicinal products may be manufactured in a clean area of a lower grade but at least in a grade D environment

Aseptic Preparation

- 3.11 Components after washing should be handled in at least a grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be done in a grade A environment with a grade B background.
- 3.12 The preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not sterile filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.
- 3.13 The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be done in a grade A environment with a grade B background.

- 3.14 The transfer of partially closed containers, as used in freeze-drying, should, before stoppering is completed, be done either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.
- 3.15 The 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 subsequently filtered.

4.0 Processing

- 4.1 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.
- 4.2 Preparations containing live microorganisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers, after validated inactivation and validated cleaning procedures, in the same premises as other sterile pharmaceutical products.
- 4.3 The validation of aseptic processing should include simulating the process using a nutrient medium. The form of the nutrient medium used should generally be equivalent to the dosage form of the product. The process-simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. Consideration should be given to simulation of the worst expected condition. The process-simulation test should be repeated at defined intervals and after any significant modification to the equipment and process. The number of containers used for a medium fill should be sufficient to ensure a valid evaluation. For small batches, the number of containers for the medium fill should be at least equal to the size of the product batch.
- 4.4 Care should be taken to ensure that any validation does not compromise the processes.
- 4.5 Water sources, water-treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken.
- 4.6 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum, and the movement of personnel should be controlled and methodical, so as 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.
- 4.7 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.
- 4.8 Components, bulk-product containers and equipment should be handled after the final cleaning process in such a way that they are not re-contaminated. The stage of

processing of components, bulk- product containers and equipment should be properly identified.

- 4.9 The interval between the washing and drying and the sterilization of components, bulk-product containers and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.
- 4.10 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.
- 4.11 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.
- 4.12 The bioburden of products should be monitored before sterilization. There should be a working limit on the contamination of products immediately before sterilization that is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large-volume parenterals, should be passed through a microorganism-retaining filter, if possible immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets should be protected, e.g. by hydrophobic microbiological air filters.
- 4.13 Components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress should be sterilized and, wherever possible, passed into the area through double-ended sterilizers sealed into the wall. Other procedures that prevent the introduction of contamination (e.g. triple wrapping) may be acceptable in some circumstances.
- 4.14 The efficacy of any new processing procedure should be validated, and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

5.0 Sterilization

- 5.1 Whenever possible, products intended to be sterile should preferably be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal sterilization by heating due to the instability of a formulation, a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing.
- 5.2 Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (but not with ultraviolet radiation unless the process is thoroughly validated), by ethylene oxide (or other suitable gaseous sterilizing agents) or by filtration with subsequent aseptic filling of sterile final containers. Each method has its particular advantages and disadvantages. Where possible and practicable, heat sterilization is the method of choice.

- 5.3 The microbiological contamination of starting materials should be minimal, and their bioburden should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.
- 5.4 All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeia or other national standards or when it is used for a preparation that is not a simple aqueous or oily solution.
- 5.5 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing 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.
- 5.6 For effective sterilization, the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved.
- 5.7 Biological indicators should be considered only as an additional method of monitoring the sterilization process. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid any transfer of microbiological contamination from them.
- 5.8 There should be a clear means of differentiating products that have not been sterilized from those that have. Each basket, tray, or other carrier of products or components should be clearly labeled with the name of the material, its batch number, and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the batch is, in fact, sterile.
- 5.9 Sterilization records should be available for each sterilization run. They should be approved as part of the batch-release procedure.

6.0 Terminal Sterilization

6.1 Sterilization by Heat

- 6.1.1 Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/temperature chart with a suitably large scale. The temperature should be recorded by a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. The chart, or a photocopy of it, should form part of the batch record. Chemical or biological indicators may also be used but should not take the place of physical controls.

- 6.1.2 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time must be determined for each type of load to be processed.
- 6.1.3 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized.

6.2 Sterilization by Moist Heat

- 6.2.1 Sterilization by moist heat (heating in an autoclave) is suitable only for water-wettable materials and aqueous formulations. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which should be routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.
- 6.2.2 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.
- 6.2.3 Care should be taken to ensure that the steam used for sterilization is of suitable quality and does not contain additives at a level that could cause contamination of the product or equipment.

6.3 Sterilization by Dry Heat

Sterilization by dry heat may be suitable for non-aqueous liquids or dry powder products. 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. If air is supplied, it should be passed through a microorganism-retaining filter (e.g. an HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins will be required as part of the validation.

6.4 Sterilization by radiation

- 6.4.1 Sterilization by radiation is used mainly for the sterilization of heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.
- 6.4.2 If sterilization by radiation is carried out by an outside contractor, the manufacturer is responsible for ensuring that the requirements of section are met, and that the

sterilization process is validated. The responsibilities of the radiation plant operator (e.g. for using the correct dose) should also be specified.

- 6.4.3 During the sterilization procedure, the radiation dose should be measured. For this purpose, the dosimeters used must be independent of the dose rate and must provide 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 chamber. Where plastic dosimeters are employed, they should be used within the time-limit of their calibration. Dosimeter absorbance should be read shortly after exposure to radiation. Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.
- 6.4.3 Validation procedures should ensure that consideration is given to the effects of variations in the density of the packages.
- 6.4.4 Handling procedures should prevent any misidentification of irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.
- 6.4.5 The total radiation dose should be administered within a predetermined period of time.

6.5 Sterilization by Gases and Fumigants

- 6.5.1 This method of sterilization should only be used for products where there is no suitable alternative.
- 6.5.2 Various gases and fumigants may be used for sterilization (e.g. ethylene oxide, hydrogen peroxide vapour). Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits should be incorporated in the specifications.
- 6.5.3 Direct contact between gas and microorganisms is essential; precautions should therefore be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.
- 6.5.4 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. This requirement should be balanced against the need to minimize the waiting time before sterilization.

- 6.5.5 Each sterilization 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.
- 6.5.6 Biological indicators should be stored and used according to the manufacturer's instructions, and their performance checked by positive controls.
- 6.5.7 For each sterilization 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. The pressure and temperature should be recorded on a chart throughout the cycle. The records should form part of the batch record.
- 6.5.8 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow concentrations of residual gas and reaction products to fall to their prescribed levels. This process should be validated.

7.0 *Aseptic Processing and Sterilization by Filtration*

- 7.1 The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods (see sections 5 and 6).
- 7.2 The operating conditions should be such as to prevent microbial contamination.
- 7.3 In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to: (a) the environment; (b) the personnel; (c) the critical surfaces; (d) the container/closure sterilization and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilizing filter.
- 7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22µm (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.
- 7.5 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized 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.
- 7.6 The fibre-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters must not be used under any circumstances.
- 7.7 The integrity of the filter should be checked by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test, immediately after use (it may also be useful to test the filter in this way before use). 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 from these values should be noted and investigated. The results of these checks should be recorded 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. Consideration should be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high temperature air.

- 7.8 The same filter should not be used for more than 1 working day unless such use has been validated.
- 7.9 The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

8.0 Personnel

- 8.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside such areas as far as possible.
- 8.2 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.
- 8.3 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.
- 8.4 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbiological hazards should be decided by a designated competent person.
- 8.5 Outdoor clothing should not be brought into clean areas, and personnel entering changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure designed to minimize the contamination of clean area clothing or the carry-through of contaminants to clean areas.
- 8.6 Wrist-watches and jewelry should not be worn in clean areas, and cosmetics that can shed particles should not be used.

8.7 The clothing worn and its quality should be appropriate for the process and the grade of the working area (workplace). It should be worn in such a way as to protect the product from contamination. The clothing required for each grade is as follows:

- **Grade D.**

The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.

- **Grade C.**

The hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.

- **Grades A/B.**

Headgear should totally enclose the hair and, where relevant, beard and moustache. A single or two-piece trouser suit, gathered at the wrists and with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A face mask should be worn to prevent the shedding of droplets. Appropriate, sterilized, non-powdered rubber or plastic gloves and sterilized 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 should retain particles shed by the body.

8.8 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B room, clean sterilized or adequately sanitized protective garments should be provided at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary.

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

9.0 Premises

9.1 All premises should, as far as possible, be designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas should be designed so that all operations can be observed from outside.

- 9.2 In clean areas, all exposed surfaces should be smooth, impervious and broken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.
- 9.3 To reduce the 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 carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.
- 9.4 False ceilings should be sealed to prevent contamination from the space above them.
- 9.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.
- 9.6 Sinks and drains should be avoided wherever possible and should be excluded from grade A/B areas where aseptic operations are carried out. Where installed, they should be designed, located and maintained so as to minimize the risks of microbiological contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent back-flow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbiological contaminants.
- 9.7 Changing rooms should be designed as airlocks and used to separate the different stages of changing, thus minimizing particulate and microbiological contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes necessary. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.
- 9.8 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system can be installed to prevent the opening of more than one door at a time.
- 9.9 A filtered air supply should be used to maintain a positive pressure and airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 Pascals (guidance value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e. g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.
- 9.10 It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk.

- 9.11 A warning system should be included to indicate failure in the air supply. An indicator of pressure difference should be fitted between areas where this difference is important, and the pressure difference should be regularly recorded.
- 9.12 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. grade A filling zones, by means of a physical barrier.

10.0 Equipment

- 10.1 A conveyor belt should not pass through a partition between a grade A or B lean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel).
- 10.2 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.
- 10.3 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be re-sterilized after complete reassembly, wherever possible.
- 10.4 When equipment maintenance is carried out within a clean area, clean instruments and tools should be used, and the area should be cleaned and disinfected again, where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.
- 10.5 All equipment, including sterilizers, air-filtration systems, and water-treatment systems, including stills, should be subject to planned maintenance, validation and monitoring; its approved use following maintenance work should be documented.
- 10.6 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. Consideration should be given to including a testing programme in the maintenance of a water system. Water for injection should be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70°C or not more than 4°C.

11.0 Finishing of Sterile Products

- 11.1 Containers should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.
- 11.2 Containers sealed under vacuum should be sampled and the samples tested, after an appropriate predetermined period, to ensure that the vacuum has been maintained.
- 11.3 Filled containers of parenteral products should be inspected individually. 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 eyesight 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. The results should be recorded.

12.0 Quality Control

12.1 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, for example:

- (a) for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;
- (b) for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

12.2 The sterility of the finished product is ensured by validation of the sterilization cycle in the case of terminally sterilized products, and by “media-fills” runs for aseptically processed products. Batch processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeia methods must be used for the validation and performance of the sterility test.

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

ANNEX 2

GOOD MANUFACTURING PRACTICES FOR VETERINARY BIOLOGICAL PRODUCTS

Principle:

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

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

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

The manufacture of biological products shall be undertaken in accordance with the basic principles of good manufacturing practices (GMP). The points covered by these guidelines should therefore be considered supplementary to the general requirements set out in "Good manufacturing practices for veterinary medicinal products" and relate specifically to the production and control of biological products.

The way in which biological products are produced, controlled and administered makes some particular precautions necessary. Unlike conventional pharmaceutical products, which are normally produced and controlled using reproducible chemical and physical techniques, biological products are manufactured by methods involving biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These processes display inherent variability, so that the range and nature of by-products are variable. For this reason, in the manufacture of biological products full adherence to GMP is necessary for all production steps, beginning with those from which the active ingredients are produced.

Control of biological products nearly always involves biological techniques that have a greater variability than physicochemical determinations. In-process controls take on a great importance in the manufacture of biological products because certain deficiencies may not be revealed by testing the finished product.

The present guidelines do not lay down detailed requirements for specific classes of biological products, and attention is therefore directed to other guidance issued by OIE and in particular to the Requirements for Biological Substances, which include requirements for vaccines.

1.0 Personnel

- 1.1 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.
- 1.2 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. diarrhoea, coughs, colds, infected skin 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 conditions 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 from working in the production area.
- 1.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Inspection and control procedures should be conducted from outside of these areas as far as possible.
- 1.4 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.
- 1.5 The staff engaged in the manufacturing process should be separate from the staff responsible for animal care.
- 1.6 To ensure the manufacture of high-quality products, personnel should be trained in good manufacturing and laboratory practices in appropriate fields such as bacteriology, virology, biometry, chemistry, medicine, immunology, biotechnology, pharmacology and veterinary medicine.
- 1.7 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.
- 1.8 All personnel engaged in production, maintenance, testing and animal care (including 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.

2.0 Premises and Equipment

Premises

- 2.1 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.
- 2.2 Live biological agents should be handled in contained areas. The level of containment should depend on the pathogenicity of the micro-organism and whether it has been classified as exotic.
- 2.3 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-sterilised media.
- 2.4 Open circuit operations involving products or components not subsequently sterilised should be carried out within a laminar air flow work station (grade A) in a grade B area.
- 2.5 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.
- 2.6 Containment premises should be easily disinfected and should have the following characteristics:
 - 2.6.1 The absence of direct venting to the outside;
 - 2.6.2 A ventilation with air at negative pressure. Air should be extracted through HEPA filters and not be re-circulated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the re-circulated 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;
 - 2.6.3 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 re-circulated;
 - 2.6.4 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;
- 2.6.5 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;
 - 2.6.6 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.
 - 2.6.7 In many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.
 - 2.7 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 equipped with air extraction facilities 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.
 - 2.8 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.
 - 2.9 Production areas where biological agents particularly resistant to disinfection (e.g. sporeforming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.
 - 2.10 With the exception of blending and subsequent filling operations, one biological agent only should be handled at a time within an area.
 - 2.11 Production areas should be designed to permit disinfection between campaigns, using validated methods.
 - 2.12 Production of biological agents may take place in controlled areas provided it is carried out in totally enclosed and heat sterilised equipment, all connections being also heat sterilised 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 sterilisation 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 crosscontamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.

- 2.13 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. Animal houses where animals used for quality control, involving the use of pathogenic biological agents, are accommodated, should be adequately contained.
- 2.14 Access to manufacturing areas should be restricted to authorised personnel. Clear and concise written procedures should be posted as appropriate.
- 2.15 Documentation relating to the premises should be readily available in a plant master file. 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. The animal species accommodated in the animal houses or otherwise on the site should be identified. The activities carried out in the vicinity of the site should also be indicated. 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.

Equipment

- 2.16 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 and subsequently be regularly maintained and validated.
- 2.17 Where appropriate, the equipment should ensure satisfactory primary containment of the biological agents. Where appropriate, the equipment should be designed and constructed as to allow easy and effective decontamination and/or sterilisation.
- 2.18 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. Inlets and outlets for gases should be protected so as to achieve adequate containment e.g. by the use of sterilizing hydrophobic filters. The introduction or removal of material should take place using a sterilisable closed system, or possibly in an appropriate laminar air flow.
- 2.19 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. 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. All sterilisation procedures should be validated.

- 2.20 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. 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. 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.
- 2.21 Relevant equipment, such as that requiring temperature control, should be fitted with recording and/or alarm systems. To avoid breakdowns, a system of preventive maintenance, together with trend analysis of recorded data, should be implemented.
- 2.22 The loading of freeze dryers requires an appropriate clean/contained area. Unloading freeze dryers contaminate the immediate environment. Therefore, for single-ended freeze dryers, 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 dryers should be sterilised after each cycle unless opened in a clean area. Sterilisation of freeze dryers should be done in accordance with item 3.20. In case of campaign working, they should at least be sterilised after each campaign.

3. *Animal Quarters and Care*

- 3.1 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.

- 3.2 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 current Requirements for Biological Substances No. 7.

4.0 Production

- 4.1 Standard operating procedures shall be available and maintained up to date for all manufacturing operations.
- 4.2 Specifications for starting materials should include details of their source, origin and method of manufacture and of the controls applied, in particular microbiological controls, to ensure their suitability for use. Release of a finished product is conditional on satisfactory results being obtained in the tests on starting materials.
- 4.3 Media and cultures shall be added to fermenters and other vessels under carefully controlled conditions to avoid contamination. Care shall be taken to ensure that vessels are correctly connected when cultures are added.
- 4.4 If possible, media should be sterilized *in situ*. In-line sterilizing filters for routine addition of gases, media, acids, alkalis, defoaming agents, etc. to fermenters should be used where possible.
- 4.5 Careful consideration should be given to the validation of sterilization methods.
- 4.6 When an inactivation process is performed during manufacture, measures should be taken to avoid the risk of cross-contamination between treated and untreated products.
- 4.7 A wide variety of equipment is used for chromatography; in general such equipment should be dedicated to the purification of one product and should be sterilized or sanitized between batches. Problems of decontamination and purification may arise through repeated use of the same equipment at the same or different stages of processing. The life span of columns and the sterilization method shall be defined. Particular care should be given to monitoring microbial loads and endotoxins.

5.0 Master Seed

- 5.1 Facilities must be adequate to provide for all applicable production functions, such as: storage of master seeds, ingredients, and other production materials; preparation of growth media and cell cultures; preparation of glassware and production equipment; inoculation, incubation, and harvest of cultures; storage of in-process materials; inactivation, centrifugation, addition of adjuvant, and formulation of product; filling, desiccation, sealing of containers, labelling and storage of final product; quality control testing of in-process materials and final product; and research and development.
- 5.2 The objective of testing the master seed is to ensure vaccine safety, quality and efficacy. Safety should be tested in an early stage. A master seed should be established for each microorganism used in the production of a product to serve as the source of seed for inoculation of all production cultures.

- 5.3 Working seeds and production seeds may be prepared from the master seed by subculturing; generally the final production cultures should not be more than five (sometimes ten) passages from the master seed. The number of passages should be determined by data and designated in each case. Using a master seed and limiting the number of passages of seed microorganism in this manner assists in maintaining uniformity and consistency in production.
- 5.4 Records of the source of the master seed should be maintained. For genetically modified microorganisms, the source of the gene(s) for the immunogenic antigens and the vector microorganism should be identified. Furthermore, the gene sequences introduced into the seed microorganism genome during construction of the modified seed should be provided. The master seed should consist of a single uniform batch/serial of seed that has been mixed and filled into containers as one batch/serial.
- 5.5 Master seed should be frozen or desiccated and stored at low temperatures such as -40°C or -70°C , or under other conditions found to be optimal for maintaining viability. Each master seed should be tested to ensure its identity, safety and efficacy. Genetically modified seeds should also be tested to ensure stability and safety of the inserted gene sequences. Purity should also be established by testing to ensure freedom from extraneous bacteria, fungi, mycoplasma, and viruses.
- 5.6 When cell cultures are used to prepare a product, a master cell stock (MCS) should be established for each type of cell to be used. Records of the source of the master cell stock should be maintained. For each product, the highest and lowest passage levels of cells that may be used for production should be established and specified in the SOP.
- 5.7 Each MCS should be characterized to ensure its identity, and its genetic stability should be demonstrated when subcultured from the lowest to the highest passage used for production. The karyotype of the MCS should be shown to be stable with a low level of polyploidy. Freedom from oncogenicity or tumorigenicity should be demonstrated by *in-vivo* studies in appropriate species using the highest cell passage that may be used for production. Purity of MCSs should be established by testing to ensure freedom from extraneous bacteria, fungi, mycoplasma, and viruses.

6.0 Lot Processing Records (Protocols) and Distribution Records

- 6.1 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.
- 6.2 A separate processing record should be prepared for each lot of biological product, and should include the following information:
 - 6.2.1 The name and dosage of the product;
 - 6.2.2 The date of manufacture;

- 6.2.3 The lot identification number;
 - 6.2.4 The complete formulation of the lot, including identification of seed or starting materials;
 - 6.2.5 The batch number of each component used in the formulation;
 - 6.2.6 The yield obtained at different stages of manufacture of the lot;
 - 6.2.7 A duly signed record of each step followed, precautions taken and special observations made throughout the manufacture of the lot;
 - 6.2.8 record of all in-process control tests and of the results obtained;
 - 6.2.9 Specimen of the label;
 - 6.2.10 Identification of packaging materials, containers and closures used;
 - 6.2.11 A dated signature of the expert responsible for approving the manufacturing operations;
 - 6.2.12 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;
 - 6.2.13 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.
- 6.3 The records 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.
- 6.4 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.

7.0 Quality Assurance and Quality Control

- 7.1 The quality assurance and /or quality control department should have the following principal duties:
- 7.1.1 To prepare detailed instructions for each test and analysis;
 - 7.1.2 To ensure adequate identification and segregation of test samples to avoid mix-up and cross-contamination;
 - 7.1.3 To ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;

- 7.1.4 To release or reject raw materials and intermediate products, if necessary;
 - 7.1.5 To release or reject packaging and labeling materials and the final containers in which drugs are to be placed;
 - 7.1.6 To release or reject each lot of finished preparation;
 - 7.1.7 To evaluate the adequacy of the conditions under which raw materials, intermediate products, and finished biological preparations were stored;
 - 7.1.8 To evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;
 - 7.1.9 To establish expiry dates on the basis of the validity period related to specified storage conditions;
 - 7.1.10 To establish and, when necessary, revise control procedures and specifications and
 - 7.1.11 To be responsible for the examination of returned preparations to determine whether such preparation should be released, reprocessed or destroyed; adequate records of the distribution of such preparations should be maintained.
- 7.2 A manufacturer'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.
- 7.3 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.
- 7.4 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 manufacturer of the starting material, provided that:
- 7.4.1 There is a history of reliable production,
 - 7.4.2 The manufacturer is regularly audited, and
 - 7.4.3 At least one specific identity test is conducted by the manufacturer of the final product.
- 7.5 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.

- 7.6 Certain operations require the continuous monitoring of data during a production process, for example monitoring and recording of physical parameters during fermentation.
- 7.7 Special consideration needs to be given to the quality control requirements arising from production of biological products by continuous culture.

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