



Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles Fourth Edition

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Table of Contents

INTRODUCTION	1
DEFINITIONS	2
CHAPTER ONE: QUALITY MANAGEMENT SYSTEM	11
Quality Assurance	11
Good Manufacturing Practice	12
Quality Control	13
Product Quality Review	14
Quality Risk Management.....	16
CHAPTER TWO: SANITATION AND HYGIENE.....	16
Principle	16
CHAPTER THREE-PREMISES.....	17
Principle	17
General	17
Storage Area	18
Weighing and sampling areas	19
Production Area	24
Quality Control Area	26
Ancillary Area.....	27
CHAPTER FOUR-EQUIPMENT	27
Principle	27
General	27
CHAPTER FIVE-MATERIALS.....	28

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Principles	28
General	28
Starting Materials	29
Packaging Materials	30
Intermediate and Bulk Products	31
Finished Products.....	31
Rejected, Recovered, Reprocessed and Reworked Materials	31
Recalled Products	32
Returned Products	32
Reagents and Culture Media.....	32
Reference Standards.....	33
Waste Materials.....	33
Miscellaneous	34
CHAPTER SIX PERSONNEL.....	34
Principle	34
General	34
Key Personnel	34
Training.....	37
Personnel Hygiene	38
Consultants	39
CHAPTER SEVEN-PRODUCTION.....	39
Principle	39
General	39
Prevention of Cross Contamination in Production.....	41
Starting Materials	44

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Processing Operation-Intermediate and Bulk.....	44
Packaging Operations	44
CHAPTER EIGHT: QUALITY CONTROL.....	46
Principle	46
General	46
Good Quality Control Laboratory Practice	47
Documentation	47
Sampling	48
Testing	49
Stability Study Monitoring	50
CHAPTER NINE-CONTRACT PRODUCTION AND ANALYSIS	52
Principle	52
General	53
The Contract giver.....	53
The contract Acceptor.....	53
The Contract	54
CHAPTER TEN: COMPLAINTS.....	55
CHAPTER ELEVEN: PRODUCT RECALL	55
CHAPTER TWELVE- SELF-INSPECTION, QUALITY AUDITS AND SUPPLIERS' AUDITS AND APPROVAL	56
Principle	56
Items for Self-Inspection	57
Self-inspection team	57
Frequency of self-inspection	57

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Self-inspection report	58
Quality audit	58
Suppliers' audits and approval.....	58
CHAPTER THIRTEEN- VALIDATION AND QUALIFICATION.....	59
Principles	59
Relationship between validation and qualification	59
Approaches to qualification and validation	59
Validation master plan.....	61
Qualification and validation protocols.....	62
Qualification and Validation Reports	63
Qualification	64
User requirement specifications	65
Design qualification	65
Factory acceptance test and site acceptance test	65
Installation qualification	65
Operational qualification	65
Performance qualification	66
Requalification	66
Revalidation	67
Change management	67
Calibration and verification	67
Process Validation.....	68
General	68
Prospective Validation	69
Concurrent Validation.....	70

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Retrospective Validation.....	70
Qualification of Established (in use) Facilities, Systems and Equipment.....	71
Cleaning Validation	71
Change Control	72
CHAPTER FOURTEEN: COMPUTERIZED SYSTEM.....	73
Principle	73
General	73
System	74
Validation	76
Hardware Validation.....	77
Software Validation	77
Analytical Method Validation	78
Principle	78
General	79
Pharmacopoeial method.....	79
Non-pharmacopoeial method.....	79
Method Validation.....	80
Characteristics of analytical validation	80
System Suitability Testing	82
Revalidation	83
CHAPTER FIFTEEN: DOCUMENTATION	83
Principle	83
General	83
Essential Documents Specifications	85
Specifications for starting and packaging materials.....	85

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Specifications for intermediate and bulk products	85
Specifications for Finished Products	85
Batch Formula and Processing Instruction	86
Packaging Instructions	87
Batch Processing Records	87
Batch Packaging Records	88
Procedures and Records	89
Receipt	89
Sampling	90
Testing	90
Other	90
CHAPTER SIXTEEN: WATER FOR PHARMACEUTICAL USE.....	91
Principle	91
General	92
Water Quality Specification	92
Pharmacopoeial specifications	92
Drinking Water.....	93
Bulk Purified Water.....	95
Bulk Water for Injection.....	97
General considerations for water purification systems	98
Water Storage and Distribution	100
General	100
Storage vessel	101
Water Distribution	102
Good practice for water system.....	102

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

System sanitization and bio-burden control	105
Operational considerations including some qualification and validation principles	106
Continuous system monitoring	107
Maintenance of water systems	108
CHAPTER SEVENTEEN: HEATING, VENTILATION AND AIR CONDITIONING SYSTEM (HVAC)	109
Principle	109
Scope	110
Protection	110
Product and Personnel	110
Temperature and Relative Humidity	119
Dust Control	120
Protection from the Environment	122
General	122
Vapor and Fume Removal	123
HVAC System and Component Principle	124
General	124
Design of HVAC systems and components	125
Full fresh air systems and recirculation systems	127
Air filtration, airflow direction and pressure differentials	129
Commissioning, Qualification and maintenance of HVAC system	130
ANNEX I- MANUFACTURE OF STERILE MEDICINAL PRODUCTS	132
PRINCIPLE	132
General	132
Premises	136

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Barrier technologies	141
Disinfection	144
Equipment	145
Utilities	147
Water systems	148
Steam used as a direct sterilizing agent	150
Gases and vacuum systems	150
Heating and cooling and hydraulic systems	151
Personnel	151
Production and specific technologies	154
Terminally Sterilized Products	154
Aseptic Preparation and Processing	155
FORM-FILL_SEAL (FFS)	159
Blow-fill-seal (BFS)	161
Lyophilization	165
Closed systems	166
Single-use systems	167
Sterilization	169
Sterilization by heat	172
Moist heat sterilization	173
Dry heat sterilization	175
Sterilization by Radiation	177
Sterilization with ethylene oxide	177
Sterilization by filtration of products that cannot be sterilized in their final container	178
Finishing of Sterile Products	183

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Environmental Monitoring.....	185
Aseptic process Simulation (APS).....	189
Quality Control.....	194
ANNEX II- MANUFACTURING BIOLOGICAL MEDICINAL PRODUCTS	197
SCOPE.....	197
Principle	197
Personnel.....	198
Premises and Equipment.....	199
Animal Quarter and Care.....	200
Documentation	201
Production Starting Materials	201
Seed Lot and Cell Bank System.....	201
Operating Principles	202
Quality Control	203
ANNEX 3: GOOD MANUFACTURING PRACTICES FOR MEDICINAL GASES.....	204
Introduction	204
Scope	204
1. Quality Management system	206
2. Personnel.....	208
3. Documentation.....	209
4. Complaints.....	211
5. Recalls.....	211
6. Returns	211
7. Self-inspection, quality audits, and supplier audits and approvals	211
8. Premises	213

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

9.	Equipment and utilities	213
10.	Qualification and validation	215
11.	Production	215
12.	Quality control.....	220
13.	Product life cycle and continuous improvement	223
14.	Storage and distribution	223
	Storage.....	223
	Distribution.....	224

ANNEX 4: GUIDELINE ON GOOD MANUFACTURING PRACTICES FOR RADIOPHARMACEUTICAL PRODUCTS..... 226

	Introduction	226
	SCOPE.....	226
1.	Quality management system.....	229
2.	Qualification and validation	230
3.	Product complaints.....	231
4.	Product recall	231
5.	Outsourced activities.....	232
6.	Personnel and training	232
7.	Premises	232
8.	Equipment	234
9.	Starting materials	234
10.	Documentation.....	235
11.	Good practices in production	235
12.	Good practices in quality control.....	236
13.	Labelling	237

REFERENCE 239

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Abbreviations

AC **Air Conditioner**

AHU	Air Handling Unit
API	Active Pharmaceutical Ingredient
BMR	Batch Manufacturing Record
BPR	Batch Packaging Record
cGMP	Current Good Manufacturing Practice
CFU	Colony Forming Units
CIP	Clean In Place
DQ	Design Qualification
EU	Endotoxin Unit
EFDA	Ethiopian Food, Drug Authority
FAT	Factory Acceptance Test
FEFO	First Expire First Out
FIFO	First In First Out
GMP	Good Manufacturing Practice
HEPA	High Efficiency Particulate Air Filter
HPW	Highly Purified Water
HVAC	Heating, ventilation and air conditioning
IBC	Intermediate & Bulk Container
INN	International Non-proprietary Name
IQ	Installation Qualification
LAF	Laminar Air Flow
OOS	Out of Specification
OQ	Operational Qualification
OSD	Oral Solid Dosage
Ph. Eur.	European Pharmacopoeia
Ph. Int.	International Pharmacopoeia
PQ	Process Qualification
PV	Process Validation
PVC	Poly Vinyl Chloride
PW	Purified Water

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

QA	Quality Assurance
QC	Quality Control
rDNA	Recombinant Deoxyribonucleic Acid
R&D	Research and Development
RH	Relative Humidity
RM	Raw Material
RO	Reverse Osmosis
SIP	Sterilization in Place
SOP	Standard Operating Procedures
SS	Stainless Steel
TOC	Total Organic Carbon
UDAF	Unidirectional Air Flow
URS	Users Requirement Specification
UPS	Uninterrupted Power Supply
USP	United States Pharmacopoeia
UV	Ultraviolet
VMP	Validation Master Plan
WFI	Water for Injection
WHO	World Health Organization
WPU	Water for Pharmaceutical Use

INTRODUCTION

This guideline is intended to assist pharmaceutical manufacturers in implementing modern quality systems and risk management approaches to ensure the consistent production of quality pharmaceutical products that are safe, effective, and suitable for their intended use. These requirements are established in line with the mandate granted to the Authority under Proclamation No. 1112/2019, which provides the legal basis for the establishment and regulatory functions of the Ethiopian Food and Drug Authority (EFDA).

GMP ensures that quality is in-built into the system and processes involved in the manufacture of the products and all those operations should be carried out strictly according to cGMP.

This guideline outlines a comprehensive quality system designed to help pharmaceutical manufacturers develop, implement, and maintain robust, modern quality systems aligned with current Good Manufacturing Practice (cGMP) requirements. The guideline is structured into seventeen chapters, complemented by four annexes that provide specific guidance on the manufacturing of sterile products, biological products, medical gases, and radiopharmaceuticals.

This guideline primarily applies to manufacturers of medicinal products (finished pharmaceuticals). In the future, the Ethiopian Food and Drug Authority (EFDA) may issue supplementary cGMP requirements, where appropriate, to address specific product quality considerations that extend beyond the scope of this main guide.

This guideline serves as a baseline requirement for both local and foreign pharmaceutical manufacturers seeking authorization to market their products in Ethiopia. It also functions as a reference and guidance tool for the Ethiopian Food and Drug Authority (EFDA) in conducting GMP inspections and licensing of pharmaceutical establishments.

The specific requirements for establishment licensing are further detailed in the directive for Establishment Licensing, which should be consulted alongside this document.

This guideline outlines the minimum requirements for Good Manufacturing Practice; however, it does not limit the adoption of new technologies or innovative concepts, provided they are appropriately validated and contribute to strengthening the quality assurance system in pharmaceutical manufacturing.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

DEFINITIONS

For the purposes of this guideline, the following terms have the meanings hereby assigned to them. They may have different meaning in other contexts.

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer-term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Active Pharmaceutical Ingredient: 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.

Actual Yield: The quantity that is actually produced at any stage of production of a particular product from a given amount of input material.

Ancillary Areas: All subsidiary or subordinate areas in the plant, aimed to exist for the support of the main manufacturing and control process.

Annual quality Review: An evaluation, conducted at least annually, that assesses the quality standards of each drug product to determine the need for changes and/or assessment of overall compliance of drug product with specifications or manufacturing or control procedures

Air-handling unit: The air-handling unit serves to condition the air and provide the required air movement within a facility.

Airlock: An enclosed space with two or more doors which is interposed between two or more rooms, e.g., of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

Authority: The Ethiopian Food and Drug Authority

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Authorized person: The 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 requirements of marketing authorization.

Batch (or lot): A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it 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): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

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

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

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a traceable standard over an appropriate range of measurements. Limits for acceptance of the results of measuring should be established.

Cell Bank System: A system where by successive batches of a product are manufactured by culture in cells derived from the same master cell bank that is fully characterized for identity and absence of contamination.

Cell Culture: The result from the in-vitro growth of cells isolated from multi-cellular organisms.

Clean area: An area (room) 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.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Climatic zone: The zones into which the world is divided based on the prevailing annual climatic conditions(See WHO TRS953, Appendix 1).

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

Container closure system: The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the FPP. A packaging system is equivalent to a container closure system. Examples of container are; ampoules, glass bottles, etc.

Consignment: The quantity of a 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: A process or device to contain product, dust, or contaminants in one zone, preventing it from escaping to another zone.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.

Contamination control strategy (CCS). : A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Controlled Area: An area constructed and operated in such a way that some attempt is made to control the introduction of potential contaminant (an air supply approximating to grade D may be appropriate) and the consequences of accidental release of living organisms.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Computerized system: A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Corrective Action: Action taken to eliminate the causes of an existing discrepancy or other undesirable situation to prevent recurrence.

Critical: Describes a process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the finished product meets its specification.

Critical Process Parameters: Process parameters that must be controlled within established operating ranges to ensure that the finished product or intermediate will meet specifications for quality and purity.

Critical Process Steps: Process steps that must be controlled within established operating ranges to ensure that the finished product or intermediate will meet specifications for quality and purity.

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

Date of Manufacture: A date fixed for the individual batch, indicating the completion date of manufacture.

Design condition: Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

Discrepancy: Datum or result outside of the expected range; an unfulfilled requirement; may be called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend.

Documentation: All written procedures, instructions and records involved in the manufacture of drug products.

Dosage form: The form of the finished product, for example, tablet, capsule, elixir or suppository.

Filter: Non-shedding porous material capable of removing viable and non-viable particles from gases, air, and/or solution passing in and out of a closed vessel.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Finished product: A finished dosage form that has undergone all stages of manufacture, including packaging into final container and labeling.

Good Manufacturing Practice: That part of quality assurance, which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.

High Efficiency Particulate Air Filter: Retentive matrix designed to remove a defined percentage of particulate matter of a defined size.

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

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

Manufacture: All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

Manufacturer: A company that carries out operations such as production, packaging, repackaging, labeling and re-labeling of pharmaceuticals.

Marketing Authorization: An official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy and quality.

Master Cell Bank: A culture of fully characterized cells filled into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability.

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

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

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Master Seed Lot: A culture of a microorganism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability.

Media fill: Method of evaluating an aseptic process using a microbial growth medium (Media fills are synonymous to simulated product fills, broth trials, broth fills etc.).

Non-conformity: A deficiency in a characteristic, product specification, process parameter, record, or procedure that renders the quality of a product unacceptable, indeterminate, or not according to specified requirements.

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

Packaging Material: Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any other 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 indirect contact with the product.

Pharmaceutical product: Any material or product intended for human use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control and this includes medicines, traditional medicine, medical device, cosmetics etc. The term 'Pharmaceutical product' is synonymous for 'medicinal products'.

Pressure cascade: A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

Procedure: Descriptions of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal product.

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

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.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Qualification: 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.

Quality Assurance: Proactive and retrospective activities which provide confidence that requirements are fulfilled.

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

Raw Materials: All substances whether active or inactive that are employed in the processing of drugs although not all these substances necessarily remain in the bulk product.

Reconciliation: A comparison between the theoretical quantity and the actual quantity.

Recovery: The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reprocessing: 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.

Retesting: conduct of repeating an analytical procedure on a different portion of the same sample.

Retest date: The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Retest Period: The period during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/ biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

Reworking: 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: Method to assess and characterize the critical parameters in the functionality of an equipment or process.

Sampling Plan: Description of the location, number of units and/or quantity of material that should be collected for testing and associated acceptance criteria.

Self-Contained Area: 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.

Shelf Life: The time during which a drug product and/or drug substance is expected to remain within the approved shelf life specification, if it is stored under the conditions defined on the container label.

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

Specification: Lists 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: 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).

Sterility Test: Test performed to determine if viable microorganisms are present.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Total Organic Carbon: Is the amount of carbon bound in an organic compound and is often used as a non-specific indicator of water quality or cleanliness of pharmaceutical manufacturing equipment; where the source can be bacterial growth and metabolic activity of living organisms or chemicals.

Turbulent flow: Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

Unidirectional airflow: Unidirectional airflow is a rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent flow) (Modern standards no longer refer to laminar flow but have adopted the term unidirectional airflow).

Validation: 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.

Validation Master Plan: VMP is a high-level document, which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

Working Seed Lot: A culture of microorganism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for the master seed lots.

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

CHAPTER ONE: QUALITY MANAGEMENT SYSTEM

1.1. **Principle:** Only the holder of a manufacturing authorization must manufacture pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization and do not place the user at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of top management and requires the participation and commitment of staff working in different departments of the company. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management. 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. There are additional legal responsibilities for the holder of the manufacturing authorization and for the authorized person(s). The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and Quality Risk Management are inter-related. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of pharmaceutical products.

Quality Assurance

1.2. Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

1.3. The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

- a) Medicinal products are designed and developed in a way that takes account of their requirements of Good Manufacturing Practice;
- b) Production and control operations are clearly specified and Good Manufacturing Practice adopted;
- c) Managerial responsibilities are clearly specified;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- d) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- e) All necessary controls on intermediate products, and any other in process controls and validations are carried out;
- f) The finished product is correctly processed and checked, according to the defined procedures;
- g) Medicinal products are not sold or supplied before an authorized person has certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of medicinal products;
- h) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;
- i) There is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the quality assurance system.

Good Manufacturing Practice

1.4. Good Manufacturing Practice is that part of Quality Assurance which ensures that Medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.

1.5. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

1.6. All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications and/or marketing authorization;

1.7. Critical steps of manufacturing processes and significant changes to the process are validated;

1.8. All necessary facilities for GMP are provided including:

- (a) appropriately qualified and trained personnel;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- (b) adequate premises and space;
 - (c) suitable equipment and services;
 - (d) correct materials, containers and labels;
- 1.9. Approved procedures and instructions; Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- 1.10. Operators are trained to carry out procedures correctly;
- 1.11. Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;
- 1.12. Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- 1.13. The distribution (wholesaling) of the products should minimize any risk to their quality;
- 1.14. A system is available to recall any batch of product, from sale or supply;
- 1.15. Complaints about marketed products are examined; the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent re-occurrence.

Quality Control

- 1.16. Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.
- 1.17. The basic requirements of Quality Control are that:
- 1.18. Adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate,

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

- 1.19. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;
- 1.20. Test methods are validated;
- 1.21. Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out.
- 1.22. Any deviations are fully recorded and investigated;
- 1.23. The finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorization, are of the purity required, and are enclosed within their proper containers and correctly labelled;
- 1.24. Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
- 1.25. No batch of product is released for sale or supply prior to certification by an authorized person that it is in accordance with the requirements of the relevant authorizations;
- 1.26. 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

- 1.27. Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 1.27.1. A review of starting materials including packaging materials used in the product, especially those from new sources.
- 1.27.2. A review of critical in-process controls and finished product results.
- 1.27.3. A review of all batches that failed to meet established specification(s) and their investigation.
- 1.27.4. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
- 1.27.5. A review of all changes carried out to the processes or analytical methods.
- 1.27.6. A review of Marketing Authorization variations submitted/granted/refused, including those for third country (export only) dossiers.
- 1.27.7. A review of the results of the stability-monitoring program and any adverse trends.
- 1.27.8. A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- 1.27.9. A review of adequacy of any other previous product process or equipment corrective actions.
- 1.27.10. Review of post-marketing commitments and pharmacovigilance, where applicable.
- 1.27.11. The qualification status of relevant critical equipment and utilities, e.g. HVAC, water, compressed gases, etc.
- 1.27.12. A review of Technical Agreements to ensure that they are up to date.
- 1.27.13. The manufacturer and marketing authorization holder should evaluate the results of this review and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection.
- 1.27.14. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. 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.

- 1.27.15. The data generated from the batch or product should be trended and analyzed using appropriate statistical techniques such as control chart and capability indices. The upper and lower control limits should be established through trending. Improvement plans and actions should be initiated and taken if the process is found to be out of control or has low capability indices. Process capability indices are used to measure how well the data fits into the specification limits. The capability index, Cp/CPk values be targeted at 1.33 or above.

Quality Risk Management

- 1.28. Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the product. It can be applied both proactively and retrospectively. The quality risk management system should ensure that:
- The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient and users;
 - The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.
- 1.29. The general quality risk management process and integration in to the product quality can be referred in ICH Q9.

CHAPTER TWO: SANITATION AND HYGIENE

Principle

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

comprehensive program of sanitation and hygiene. (For Personal hygiene see chapter 6, and for sanitation see chapter 3, “Premises”).

CHAPTER THREE-PREMISES

Principle

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

General

- 3.1. 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.
- 3.2. Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, or packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.
- 3.3. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.
- 3.4. Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.
- 3.5. Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- 3.6. 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.
- 3.7. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 3.8. Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.
- 3.9. Premises should be designed and equipped to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.
- 3.10. Premises should be designed to ensure the logical flow of materials and personnel.
- 3.11. Steps should be taken in order to prevent the entry of unauthorized people.

Storage Area

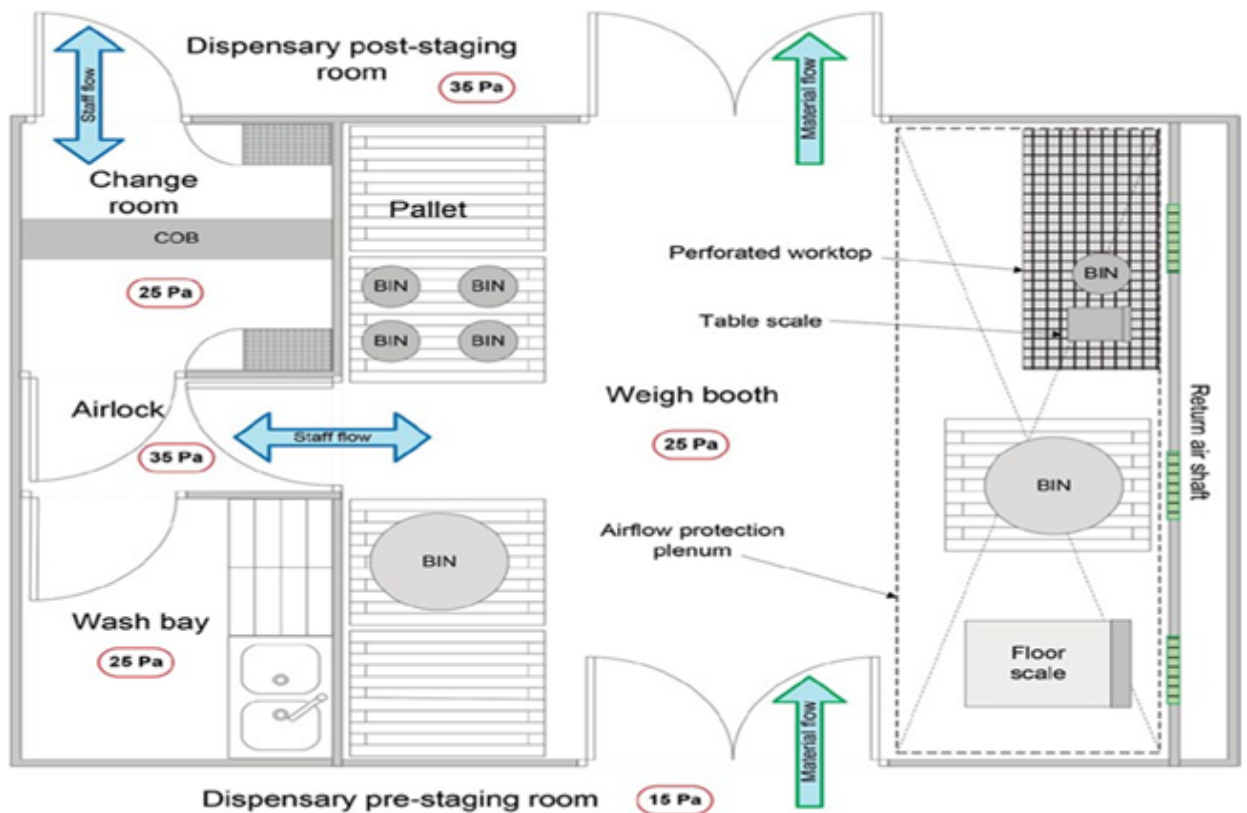
- 3.12. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.
- 3.13. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
- 3.14. Receiving and dispatch bays should protect materials and products from the weather. Receptions areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.
- 3.15. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
- 3.16. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
- 3.17. Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
- 3.18. Highly active (controlled) materials or products should be stored in safe and secure areas.

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

Weighing and sampling areas

3.20. A room for weighing (e.g. dispensing of materials) should be of appropriate design. It is often advantageous to have several rooms associated with weighing activity. These may include a pre-weighing staging area, personnel airlock, material airlock, weighing area with a containment booth, post-weighing staging area; washing area and provision for waste removal (for example, see Figs A3.1 and A3.2).

Fig. A3.1: Example of a weighing area



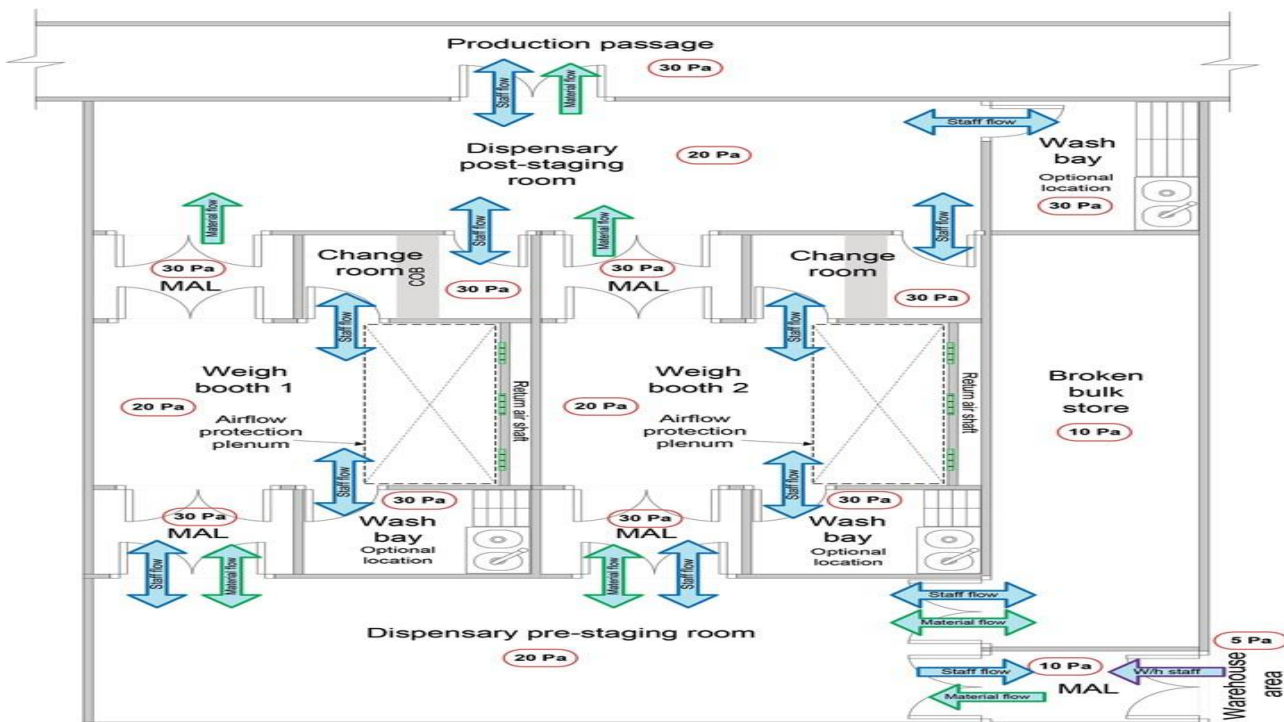


Fig. A3.2: Examples of weighing areas continued

*Note that the adjacent room pressures impact on determining the dispensary pressures.
COB: cross- over bench; MAL: material airlock; W/h: warehouse.*

3.21. Similar aspects may be considered when designing a sampling area, as materials and primary components may be exposed to the environment during sampling (for examples, see Figs A3.3 and A3.4). Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for further processing of the product.

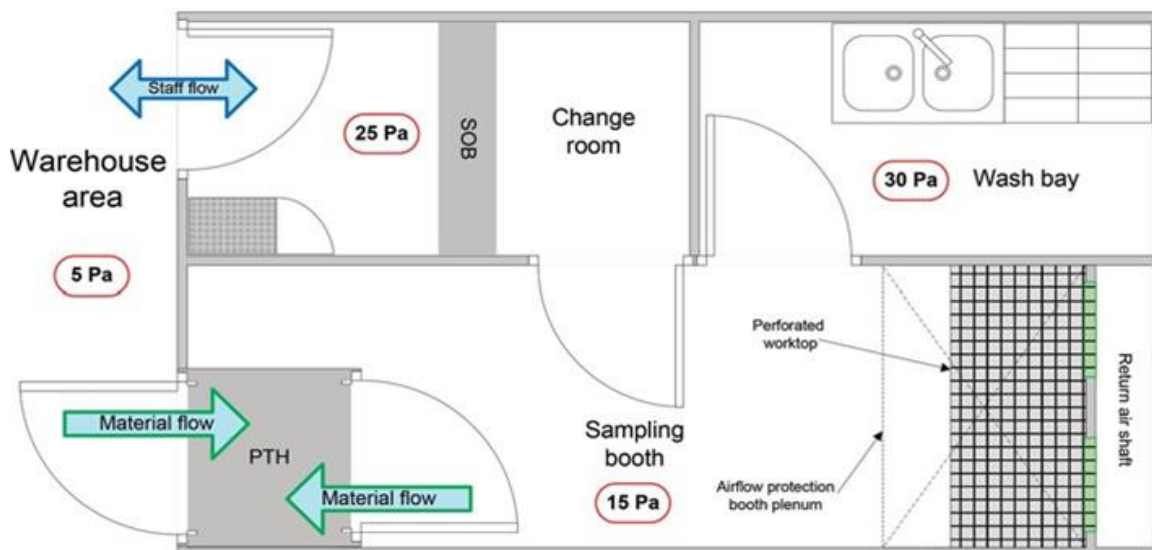
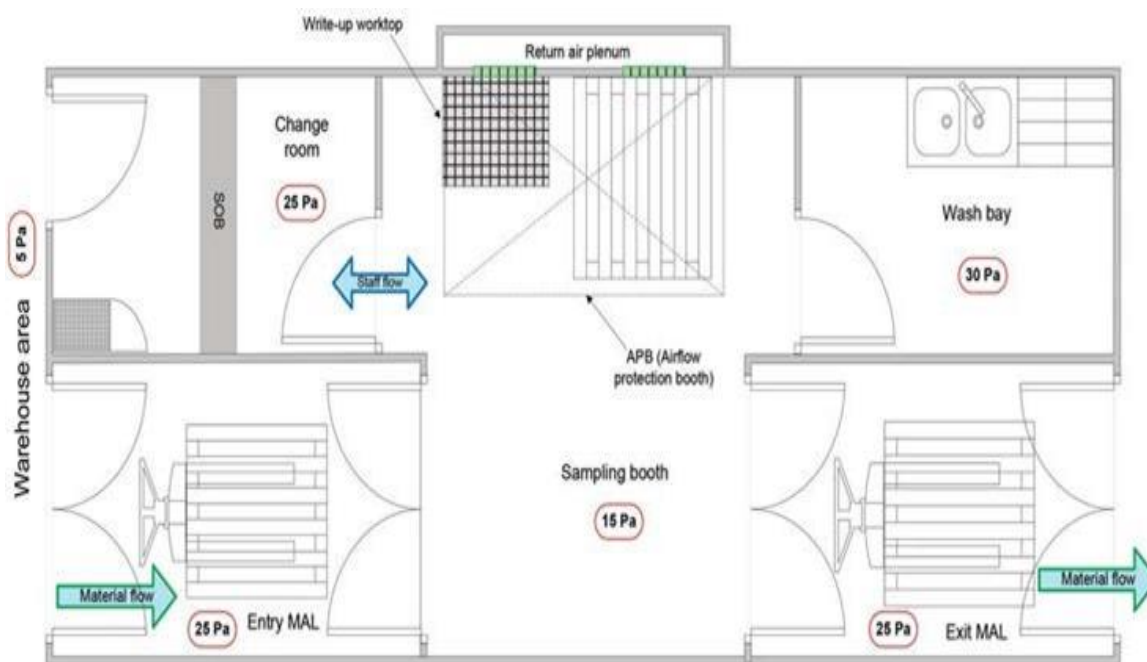


Fig. A3.3 Example of a sampling area



PTH: Pass-through hatch.

Fig. A3.4 Example of a sampling area

MAL: material airlock.

3.22. A clean corridor concept is usually recommended for non-sterile oral solid dosage form production areas, where there is then a higher pressure in the corridor compared to airlocks or production rooms. This is to facilitate containment of dust and contaminants that may have been generated in production rooms (see the principles mentioned in the

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

text on weighing/ dispensing and sampling areas) (for an example, see Fig. A3.5) to further support containment, consideration may also be given to having material airlocks (MALs) and personnel airlocks (PALs), where needed, for entry and exit of processing areas (for an example, see Fig. A3.6). appropriately, designed airlocks can assist in ensuring containment. Additional controls, such as pressure differentials between areas, an appropriate number of air changes in an area, and sufficient filtration of air, should be in place. The use of airlocks assists in ensuring containment; however, other means may be considered to achieve this objective, such as closed systems and pressure gradients between adjacent areas.

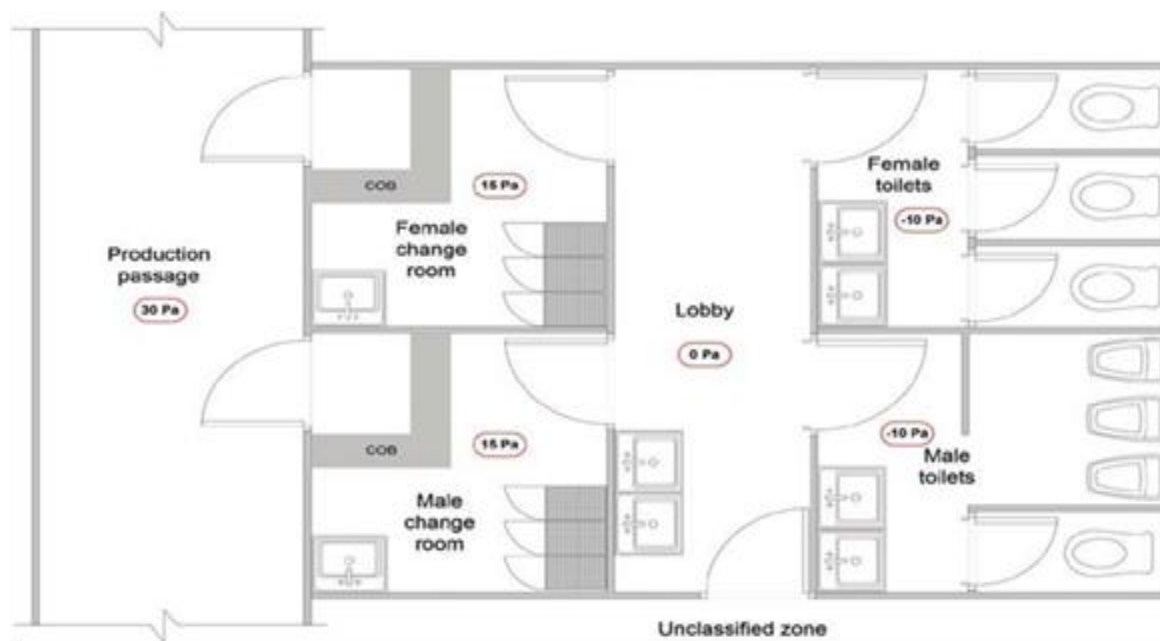


Fig. A3.5: Example of a change room and some production areas

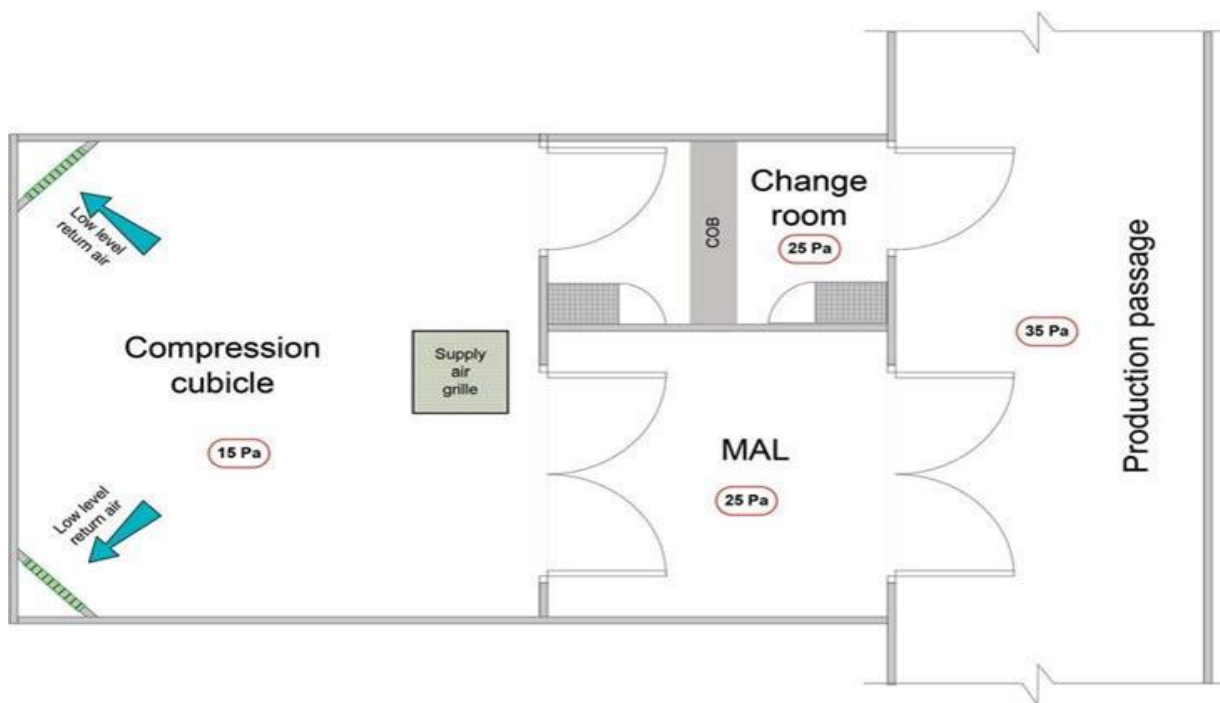


Fig. A3.6: Example of a compression cubicle with material (MAL) and personnel (PAL) airlocks (also used as an area to change garments)

3.23. Washing areas should be designed and used in such a manner that equipment and components will not be re-contaminated after cleaning. The system supplying and extracting air from the area(s) should be suitably designed to ensure that this objective is achieved. Principles that may be considered include (but are not limited to) filtration of air, pressure differentials between areas, air changes per hour and airflow directions (for an example, see Fig. A3.7)

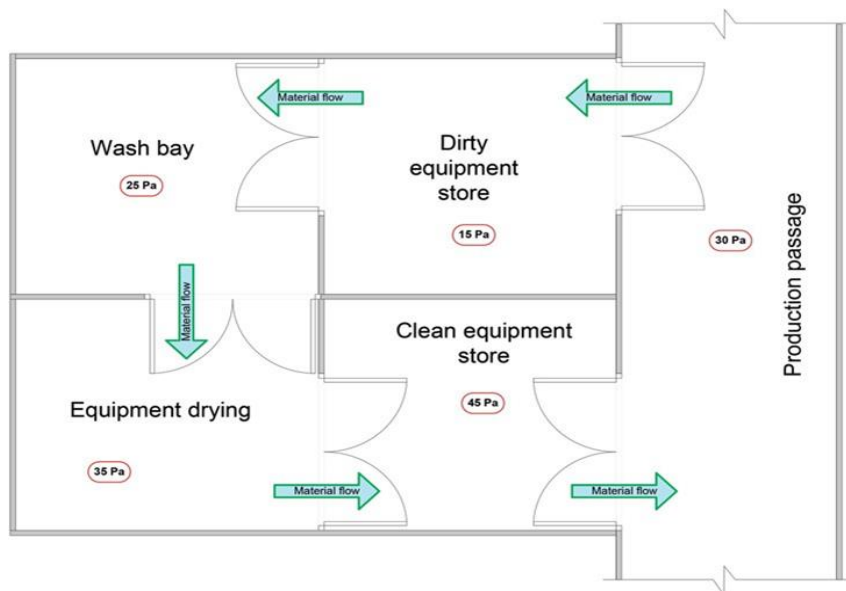


Fig. A3.7: Example of a washing area

Production Area

3.24. In order to minimize the risk of a serious medical hazard due to cross contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g. penicillin) or biological preparations (e.g. from live micro-organisms).

3.25. The production of certain additional products, such as certain antibiotics, certain hormonal steroid drugs, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made

3.26. Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products. Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

- i. The risk cannot be adequately controlled by operational and/or technical measures,

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- ii. Scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitizing materials such as beta lactams) or
- iii. Relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

3.27. Dedication of facilities, equipment, and HVAC systems for hormonal steroid drugs shall be risk-based assessing potency, PDE, and dosage form. High potency hormonal steroids (e.g., sex hormones) require dedicated, physically segregated facilities with HEPA filtered, isolated HVAC system.

3.28. Moderate and low potency hormonal steroidal products may be manufactured in multiproduct facilities, provided:

- (a) A risk assessment justifies acceptable cross-contamination risks
- (b) Validated cleaning procedures meeting PDE limits
- (c) A CCS is implemented

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

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

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

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

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 3.33. Drains should be of adequate size and have trapped gullies. Open channels should be avoided where possible, but, if necessary, they should be shallow to facilitate cleaning and disinfection.
- 3.34. Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.
- 3.35. Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- 3.36. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.
- 3.37. Premises for the packaging of medicinal products should be specifically designed and laid out to avoid mix-ups or cross-contamination.
- 3.38. Production areas should be well lit, particularly where visual on-line controls are carried out.
- 3.39. In-process controls may be carried out within the production area provided they do not carry any risk for production.

Quality Control Area

- 3.40. Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biological, microbiological and radioisotopes, which should also be separated from each other.
- 3.41. Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross contamination. There should be adequate suitable storage space for samples and records.
- 3.42. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.
- 3.43. Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Area

- 3.44. Rest and refreshment rooms should be separated from other areas.
- 3.45. Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.
- 3.46. Separate maintenance workshops should as far as possible from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- 3.47. Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

CHAPTER FOUR-EQUIPMENT

Principle

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

General

- 4.1. Manufacturing equipment should be designed, located and maintained to suit its intended purpose.
- 4.2. Repair and maintenance operations should not present any hazard to the quality of the products.
- 4.3. Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
- 4.4. Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
- 4.5. Equipment should be installed in such a way as to prevent any risk of error or of contamination.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 4.6. Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.
- 4.7. Balances and measuring equipment of an appropriate range and precision should be available.
- 4.8. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
- 4.9. Fixed pipe work should be clearly labeled to indicate the contents and, where applicable, the direction of flow.
- 4.10. Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that details the alarm and action limits for microbiological contamination and the measures to be taken.
- 4.11. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

CHAPTER FIVE-MATERIALS

Principles

The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging). Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labeling materials.

General

- 5.1. No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.
- 5.2. All incoming materials and finished products should be quarantined immediately after receipt or processing and inspection, until they are released for use or distribution.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 5.3. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly manner to permit batch segregation and stock rotation by First Expiry First Out and/or First In First Out rule.
- 5.4. Appropriate stock management system and procedures should be established with the use of bin cards and stock cards or any fully validated electronic record system.
- 5.5. Materials should not be kept directly in contact with floors, nearer to walls and ceilings in order to allow appropriate space for cleaning and inspection.
- 5.6. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting Materials

- 5.7. The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.
- 5.8. Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.
- 5.9. 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.
- 5.10. All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.
- 5.11. 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.
- 5.12. If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 5.13. Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:
- (a) the designated name of the product and the internal code reference where applicable;
 - (b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
 - (c) the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled);
 - (d) where appropriate, an expiry date or a date beyond which retesting is necessary.
 - (e) When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.
- 5.14. There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Each incoming API containers should be sampled at least for identification unless otherwise appropriately justified (See Quality Control Chapter).
- 5.15. Only starting materials released by the quality control department and within their shelf-life and/or retest period should be used for production.
- 5.16. 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 labelled containers.
- 5.17. Each dispensed material and its weight or volume should be independently checked and recorded.
- 5.18. Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such (See also Production).

Packaging Materials

- 5.19. The purchase, handling and control of primary and printed packaging materials should be as for starting materials.
- 5.20. Particular attention should be paid to printed packaging materials. They should be stored in secure conditions to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

stored and transported in separate closed containers to avoid mix-ups. Only designated personnel following an approved and documented procedure should issue packaging materials for use.

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

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

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

Intermediate and Bulk Products

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

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

Finished Products

5.26. 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.

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

Rejected, Recovered, Reprocessed and Reworked Materials

5.28. Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They either should 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.

5.29. 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.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

5.30. 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.

5.31. 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

5.32. 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 Products

5.33. 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 relabeling, 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

5.34. There should be records for the receipt and preparation of reagents and culture media.

5.35. Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. 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.

5.36. 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 inoculums used in positive controls should be appropriate to the sensitivity required.

Reference Standards

- 5.37. Whenever official reference standards exist, these should preferably be used.
- 5.38. Official reference standards should be used only for the purpose described in the appropriate monograph.
- 5.39. 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.
- 5.40. Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.
- 5.41. Reference standards should be properly labelled with at least the following information:
- (a) name of the material;
 - (b) batch or lot number and control number;
 - (c) date of preparation;
 - (d) shelf-life;
 - (e) potency;
 - (f) storage conditions.
- 5.42. All in-house reference standards should be standardized against an official reference standard, initially and at regular intervals thereafter.
- 5.43. All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste Materials

- 5.44. 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 and enclosed cupboards.
- 5.45. Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Miscellaneous

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

CHAPTER SIX PERSONNEL

Principle

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of quality products relies upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks, which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

General

- 6.1. The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
- 6.2. The manufacturer must have an organization chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

Key Personnel

- 6.3. Key Personnel includes the head of Production, the head of Quality Control, and the head of engineering and if at least one of these persons is not responsible for the release of products the authorized person(s) designated for the purpose (Quality Assurance Head). Full-time personnel should occupy normally key posts. The heads of Production and Quality Control must be independent from each other.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

6.4. The head of the Production Department generally has the following responsibilities:

- (a) ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- (b) approve the instructions relating to production operations and to ensure their strict implementation;
- (c) ensure that the production records are evaluated and signed by an authorized person;
- (d) check the maintenance of his department, premises and equipment;
- (e) ensure that the appropriate validations are done;
- (f) ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

6.5. The head of the quality control Department generally has the following responsibilities:

- (a) approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;
- (b) evaluate batch records;
- (c) ensure that all necessary testing is carried out;
- (d) approve specifications, sampling instructions, test methods and other Quality Control procedures;
- (e) approve and monitor any contract analysts;
- (f) check the maintenance of his department, premises and equipment;
- (g) ensure that the appropriate validations are done;
- (h) ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

6.6. The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:

- (a) The authorization of written procedures and other documents, including amendments;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- (b) the monitoring and control of the manufacturing environment;
- (c) plant hygiene;
- (d) process validation;
- (e) training;
- (f) the approval and monitoring of suppliers of materials;
- (g) the approval and monitoring of contract manufacturers;
- (h) the designation and monitoring of storage conditions for materials and products;
- (i) the retention of records;
- (j) the monitoring of compliance with the requirements of GMP;
- (k) the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

6.7. The quality assurance head (authorized and/or designated person (s)) shall have the following general responsibilities:

- (a) Ensuring compliance with technical or regulatory requirement and other national legislation and international standards as applicable;
- (b) Implementation and when needed establishment of the quality system of the company.
- (c) Participation in the development of the company's quality manual.
- (d) Approval of a batch for release of products for sales.
- (e) Conformation that the marketing authorization and the manufacturing authorization requirements for the product have been met;
- (f) Conformation that installed manufacturing premises, equipment and testing procedures have been validated and/or qualified;
- (g) Setting QA compliance objectives and ensuring that targets are achieved;
- (h) Ensures that the principles and guidelines of cGMP, as laid down in these guidelines and other applicable international standards have been followed;
- (i) Retention of records;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- (j) Supervises and ensures that appropriate audits and self-inspection are carried out by experienced and trained staff in a team;
- (k) Any planned changes or deviations in manufacturing or quality control have been notified in accordance with defined written system before any implementation and product release;
- (l) Review and approval of Master Manufacturing and Packaging Record;
- (m) Review of all QC testing results, production documents, results of in-process control and overall compliance to the specification for the finished product prior to release.
- (n) Review and approval of Qualification & Validation Protocols and reports;
- (o) Liaise with the production and quality control heads and staffs that QA system is functioning properly;
- (p) Identifying relevant quality-related training needs and delivering training.
- (q) Ensures that annual product quality review is done as planned

Training

- 6.8. The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.
- 6.9. Beside the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.
- 6.10. 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.

- 6.11. Visitors or untrained personnel should, preferably, not be taken into the production and Quality Control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.
- 6.12. The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personnel Hygiene

- 6.13. Detailed hygiene programs should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programs should be promoted by management and widely discussed during training sessions.
- 6.14. All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.
- 6.15. Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.
- 6.16. Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.
- 6.17. Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.
- 6.18. Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

6.19. Personnel should be instructed to use the hand-washing facilities.

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

Consultants

6.21. Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

6.22. Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

CHAPTER SEVEN-PRODUCTION

Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorizations.

General

7.1. Production should be performed and supervised by competent people.

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

7.3. All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

7.4. Damage to containers and any other problem which might adversely affect the quality

7.5. Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

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

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 7.7. 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.
- 7.8. Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 7.9. Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- 7.10. At every stage of processing, products and materials should be protected from microbial and other contamination.
- 7.11. When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.
- 7.12. At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.
- 7.13. 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 (for example, quarantined, accepted, rejected, clean, etc.).
- 7.14. 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.
- 7.15. Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent authorized person, with the involvement of the Quality Control Department when appropriate.
- 7.16. Access to production premises should be restricted to authorized personnel.
- 7.17. Production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

Prevention of Cross Contamination in Production

- 7.18. Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but, where justified, could be allowed where the measures to prevent cross-contamination with medicinal products described below be applied. The production and/or storage of technical poisons, such as pesticides (except where these are used for manufacture of medicinal products) and herbicides, should not be allowed in areas used for the manufacture and / or storage of medicinal products.
- 7.19. Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapors, aerosols, genetic material or organisms from active substances, other starting materials, and products in process, from residues on equipment, and from operators' clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Products in which cross-contamination is likely to be most significant are those administered by injection and those given over a long time. However, contamination of all products poses a risk to patient safety dependent on the nature and extent of contamination.
- 7.20. Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3 and 4. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross contamination.
- 7.21. A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multiproduct facility, where justified.

7.22. The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organizational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:

Technical Measures

- i. Dedicated manufacturing facility (premises and equipment)
- ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;
- iii. Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning;
- iv. Use of “closed systems” for processing and material/product transfer between equipment;
- v. Use of physical barrier systems, including isolators, as containment measures;
- vi. Controlled removal of dust close to source of the contaminant e.g. through localized extraction;
- vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;
- viii. Use of single use disposable technologies;
- ix. Use of equipment designed for ease of cleaning;
- x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;
- xi. Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- xii. Use of automatic clean in place systems of validated effectiveness;
- xiii. For common general, wash areas, separation of equipment washing, drying and storage areas.

Organizational Measures

- xiv. Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;
 - i. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;
 - ii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;
 - iii. Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;
 - iv. Specific measures for waste handling, contaminated rinsing water and soiled gowning;
 - v. Recording of spills, accidental events or deviations from procedures;
 - vi. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;
 - vii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;
 - viii. Use of common general wash areas on a campaign basis;
 - ix. Supervision of working behavior to ensure training effectiveness and compliance with the relevant procedural controls.

7.23. Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.

Starting Materials

- 7.24. The purchase and handling of starting materials during processing and/or production should meet the requirements GMP for Materials described in this guideline.
- 7.25. Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used for production.
- 7.26. Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 7.27. Each dispensed material and its weight or volume should be independently checked and recorded.
- 7.28. Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing Operation-Intermediate and Bulk

- 7.29. Before any processing operation is started, step should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
- 7.30. Intermediate and bulk products should be kept under appropriate conditions.
- 7.31. Critical processes should be validated.
- 7.32. Any necessary in-process controls and environmental controls should be carried out and recorded.
- 7.33. Any significant deviation from the expected yield should be recorded and investigated with appropriate correctives measures.

Packaging Operations

- 7.34. When setting up a program for the packaging operations, 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.
- 7.35. 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

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

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

7.37. All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

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

7.39. Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

7.40. The correct performance of any printing operation (for example code numbers, expiry dates) to be 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 re-checked at regular intervals.

7.41. Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

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

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

7.44. On-line control of the product during packaging should include at least checking the following:

- a) general appearance of the packages;
- b) whether the packages are complete;
- c) whether the correct products and packaging materials are used;
- d) whether any over-printing is correct;

e) correct functioning of line monitors.

7.45. Samples taken away from the packaging line should not be returned.

7.46. Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

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

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

CHAPTER EIGHT: QUALITY CONTROL

Principle

Quality Control is concerned with sampling, specifications and testing as well as 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

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

8.2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

8.3. Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

8.4. Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

Good Quality Control Laboratory Practice

8.5. Control Laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.

8.6. The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed under Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

8.7. Laboratory documentation should follow the principles given under Documentation chapter. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

- (a) specifications;
- (b) sampling procedures
- (c) testing procedures and records (including analytical worksheets and/or laboratory notebooks)
- (d) analytical reports and/or certificates;
- (e) data from environmental monitoring, where required;
- (f) validation records of test methods, where applicable
- (g) Procedures for and records of the calibration of instruments and maintenance of equipment.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 8.8. Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.
- 8.9. For some kinds of data (e.g. analytical tests results, yields, environmental controls, etc.) it is recommended that records in a manner permitting trend evaluation be kept.
- 8.10. In addition to the information, which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

Sampling

- 8.11. The sample taking should be done in accordance with approved written procedures that describe:
- (a) the method of sampling;
 - (b) the equipment to be used (scoops, spatula, dip tubes, different sampling spears, sample thieves, etc);
 - (c) the amount of the sample to be taken;
 - (d) the type and condition of the sample container to be used;
 - (e) the identification of containers sampled;
 - (f) any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
 - (g) the storage conditions;
 - (h) instructions for the cleaning and storage of sampling equipment.
- 8.12. Reference samples for retention should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).
- 8.13. Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.
- 8.14. Reference samples retained from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after the

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit full re-examination. Reference sample for the purpose of retention does not include samples collected for stability monitoring.

Testing

8.15. Analytical methods should be validated. All testing operations described in the marketing authorization should be carried out according to the approved validated test methods.

8.16. The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

8.17. The tests performed should be recorded and the records should include at least the following data:

- (a) Name of the material or product and, where applicable, dosage form;
- (b) Batch number and, where appropriate, the manufacturer and/or supplier;
- (c) References to the relevant specifications and testing procedures;
- (d) Test results, including observations and calculations, and reference to any certificates of analysis;
- (e) Dates of testing;
- (f) Name and signature of the persons who performed the testing;
- (g) Name and signature of the persons who verified the testing and the calculations, where appropriate;
- (h) A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

8.18. All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

8.19. Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.

8.20. Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of reagents

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

(where applicable) and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

8.21. Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

8.22. Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

Stability Study Monitoring

8.23. Quality control should evaluate the stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products in line with the marketing authorization of the product.

8.24. Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to intended marketing storage conditions (See also guideline for Registration).

8.25. A written program for stability determination should be developed and implemented to include elements such as:

- (a) complete description of the drug involved in the study;
- (b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
- (c) provision for the inclusion of a sufficient number in line with the registration guideline;
- (d) the testing schedule for each drug ;
- (e) provision for special storage conditions;
- (f) provision for adequate sample retention;
- (g) a summary of all the data generated, including the evaluation and the conclusions of the study.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 8.26. Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.
- 8.27. After marketing, the stability of the product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e.g. changes in levels of impurities, or dissolution profile) associated with the formulation in the marketed package.
- 8.28. The purpose of the on-going stability program is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.
- 8.29. This mainly applies to the products in the package in which it is sold, but consideration should also be given to the inclusion in the program of bulk product. For example, when the bulk product is stored for a long period (more than 30 days) before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods (more than 30 days). Stability studies on reconstituted product are performed during product development as part of compatibility study with diluents.
- 8.30. The on-going stability program should be described in a written protocol following the general rules of documentation and results formalized as a report. The equipment used for the on-going stability program (stability chambers among others) should be qualified and maintained following the general rules of Qualification and Validation.
- 8.31. Normally, the protocol for the on-going stability program should be the same as that of the initial long-term stability study as submitted in the marketing authorization dossier however different protocols for on-going stability study can be considered acceptable provided that this is justified and documented in the protocol.
- 8.32. The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

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

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

8.35. Studies should be available at the site of manufacture for review during inspection and/or upon request for the purpose of marketing authorization.

8.36. Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the Authority immediately. The possible impact on batches on the market should be considered and the manufacturer should immediately consult the Authority whenever such scenarios are encountered.

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

CHAPTER NINE-CONTRACT PRODUCTION AND ANALYSIS

Principle

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings, which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor, which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person releasing each batch of product for sale exercises his full responsibility.

General

- 9.1. There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.
- 9.2. 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.

The Contract giver

- 9.3. The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and Guidelines of GMP as interpreted in this Guide are followed.
- 9.4. 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 or the work, which might pose a hazard to his premises, equipment, personnel, other materials or other products.
- 9.5. The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by an authorized person.

The contract Acceptor

- 9.6. The Contract Acceptor must have adequate premises and 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 is the holder of a manufacturing authorization.
- 9.7. The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.
- 9.8. The Contract Acceptor should not pass to a third party any of the work entrusted to him 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

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

should ensure that the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

9.9. The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the Contract Giver.

The Contract

9.10. A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the marketing authorization and agreed by both parties.

9.11. The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorization.

9.12. The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, 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.

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

9.14. The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

9.15. In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the Authority.

CHAPTER TEN: COMPLAINTS

- 10.1. **Principle:** All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.
- 10.2. There should be designated person responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him.
- 10.3. 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.
- 10.4. 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.
- 10.5. If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.
- 10.6. All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 10.7. Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 10.8. Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
- 10.9. The Authority should be informed if a manufacturer is considering recall and other action following possibly faulty manufacture, product deterioration and detection of counterfeiting or any other serious quality problems with a product.

CHAPTER ELEVEN: PRODUCT RECALL

- 11.1. **Principle.** There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.
- 11.2. There should be designated person responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization.

- 11.3. There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.
- 11.4. Recall operations should be capable of being initiated promptly and at any time within 24hr.
- 11.5. The Authority should be informed promptly if products are intended to be recalled because they are, or are suspected of, being defective.
- 11.6. The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working
- 11.7. hours, batches and amounts delivered), including those for exported products and medical samples distributed for health professional as part of promotional activity.
- 11.8. Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 11.9. The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.
- 11.10. The effectiveness of the arrangements for recalls should be evaluated regularly.

CHAPTER TWELVE- SELF-INSPECTION, QUALITY AUDITS AND SUPPLIERS' AUDITS AND APPROVAL

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 program should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up program.

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:

- a) personnel;
- b) premises including personnel facilities;
- c) maintenance of buildings and equipment;
- d) storage of starting materials and finished products;
- e) equipment;
- f) production and in-process controls;
- g) QC;
- h) documentation;
- i) sanitation and hygiene;
- j) validation and revalidation programmes;
- k) calibration of instruments or measurement systems;
- l) recall procedures;
- m) complaints management;
- n) labels control;
- o) 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 who are 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 with 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:
- (a) self-inspection results;
 - (b) evaluation and conclusions;
 - (c) recommended corrective actions.
 - (d) 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 (see chapter 8, “Contract production and analysis”).

Suppliers’ audits and approval

- 12.7. The person responsible for QC should have responsibility, together with other relevant departments, for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.
- 12.8. Before suppliers are approved and included in the approved suppliers’ list or specifications, they should be evaluated. The evaluation should take into account a supplier’s history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier’s ability to conform to GMP standards.

CHAPTER THIRTEEN- VALIDATION AND QUALIFICATION

Principles

It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

Relationship between validation and qualification

- 13.1. In general, qualification and validation follow similar underlying principles. The term “qualification” is normally used, for example, for equipment and utilities, and “validation”, for example, for systems, methods and processes.
- 13.2. Qualification normally precedes validation.

Approaches to qualification and validation

- 13.3. Manufacturers should organize and plan qualification and validation in a manner that will ensure product quality, safety and efficacy throughout its life cycle.
- 13.4. Statistical evaluation should be applied, where appropriate, and provide scientific evidence that, for example, the process, system or other related aspect is appropriately qualified or validated.
- 13.5. Qualification and validation should be done in accordance with predetermined protocols, and the results appropriately documented, in reports.
- 13.6. There should be an appropriate and effective quality management system supporting the organization, planning, execution and management of qualification and validation.
- 13.7. Senior management should ensure that there are sufficient resources to perform validation in a timely manner. Management and persons responsible for quality assurance should be actively involved in the process and authorization of protocols and reports.
- 13.8. Personnel with appropriate education and experience should be responsible for qualification and validation.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 13.9. There should be a specific program or schedule to support planning and execution of qualification and validation activities.
- 13.10. Qualification and validation should be performed in a structured way according to the documented protocols and procedures.
- 13.11. Qualification and validation (as appropriate), should be performed:
- for new premises, equipment and utilities;
 - for new systems, methods, processes and procedures;
 - when changes are made, depending on the outcome of risk assessment;
 - where necessary or indicated, based on the outcome of periodic review (and may include requalification and revalidation).
- 13.12. The scope and extent of qualification and validation should be based on knowledge, experience and the outcome of principles of quality risk management.
- 13.13. Where necessary, worst-case situations or specific challenge tests should be considered for inclusion in the qualification and validation.
- 13.14. Documents associated with qualification and validation may include:
- validation master plan;
 - standard operating procedures (SOPs);
 - specifications;
 - protocols and reports;
 - risk assessment outcomes;
 - process flowcharts;
 - operator manuals;
 - training records;
 - calibration procedures and records;
 - sampling plans;
 - testing plans and methods;
 - statistical methods and results;
 - history of qualification and validation;
 - plan for ensuring maintaining a validated state including review of validation status.

Validation master plan

13.15. A manufacturer should have a validation master plan that reflects the key elements of validation. It should be concise and clear and at least contain reference to/have a short description of the following:

- title page and authorization (approval signatures and dates);
- table of contents;
- abbreviations and glossary;
- validation policy;
- philosophy, intention and approach to validation;
- roles and responsibilities of relevant personnel;
- resources to ensure that qualification and validation are done;
- outsourced services (selection, qualification, management through the life-cycle);
- scope of qualification and validation;
- documentation required in qualification and validation, such as procedures, certificates, protocols and reports;
- premises qualification, such as room verification where appropriate;
- qualification of utilities;
- equipment and instrument qualification;
- process validation;
- cleaning validation;
- personnel qualification (such as analyst qualification);
- analytical method validation;
- computerized system validation;
- establishment of acceptance criteria;
- life-cycle management, including retirement policy;
- requalification and revalidation;
- relationship with other quality management elements;
- validation matrix (such as a table indicating the history and status of qualification and validation on-site);
- retention of qualification and validation documentation;
- deviation management;

- change control;
- risk management principles;
- training;
- references.

13.16. The validation master plan should be reviewed at regular intervals and kept up to date, according to current GMP.

Qualification and validation protocols

13.17. There should be qualification and validation protocols describing the qualification and validation to be performed.

13.18. As a minimum, the protocols should be appropriate for the qualification or validation to be executed, and may include the following significant background information:

- a unique document number and version number;
- the objective and scope;
- the site;
- the responsible personnel;
- reference to applicable standard operating procedures;
- equipment or instruments to be used;
- reference to standards, as appropriate;
- the stage of validation or qualification;
- the processes and/or parameters;
- sampling, testing and monitoring requirements;
- stress testing, where appropriate;
- calibration requirements;
- predetermined acceptance criteria for drawing conclusions;
- change control, deviations;
- attachments and reference to attachments, including source data (where relevant);
- Archiving and retention.

13.19. There should be a description of the procedure for review, evaluation and interpretation of results, including the application of statistical methods, where appropriate.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 13.20. The protocol should be approved by responsible persons, including the quality unit, prior to use. Any changes to a protocol should be approved prior to implementation of the change.
- 13.21. The protocol should be executed by trained personnel. Records of the training and assessment should be retained.

Qualification and Validation Reports

- 13.22. There should be written reports on the qualification and validation performed.
- 13.23. Reports should reflect the protocols and procedures followed and include at least the title and objective of the study; reference to the protocol; reference to the appropriate risk assessment; details of materials, equipment, programs and cycles used; procedures and test methods; data; changes and deviations; out-of-specification and non-conformance results, with appropriate traceability; and a conclusion.
- 13.24. Results should be recorded and be in compliance with good data and record management practices.
- 13.25. Results should be reviewed, analyzed and compared against the predetermined acceptance criteria, interpreted and statistically analyzed, where appropriate.
- 13.26. Results should meet the acceptance criteria. Out-of-specification and out-of-limit results should be documented and investigated according to appropriate procedures. If these are accepted, this should be justified. Where necessary, further studies should be considered.
- 13.27. The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful, and should make recommendations for future monitoring and setting of alert and action limits, where applicable.
- 13.28. The departments responsible for the qualification and validation work should approve the completed report.
- 13.29. When appropriate, the quality assurance department should approve the report. The criteria for approval should be in accordance with the company's quality assurance system.

Qualification

- 13.30. There are different approaches in qualification. The manufacturer should select an appropriate approach for the conduct thereof.
- 13.31. All relevant SOPs for operation, maintenance and calibration should be prepared during qualification.
- 13.32. Training should be provided to operators, and training records should be maintained.
- 13.33. Normally, qualification should be completed before process validation is performed.
- 13.34. The process of qualification should be a logical, systematic process and follow a logical flow from the premises, followed by utilities, equipment, to procedures and processes.
- 13.35. Stages of qualification should normally start with the preparation of user requirement specifications (URS). Depending on the function and operation of the utility, equipment or system, this is followed by, as appropriate, different stages in qualification such as design qualification (DQ), a factory acceptance test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).
- 13.36. One stage of qualification should be successfully completed before the next stage is initiated. For example, OQ normally follows IQ but, depending on the complexity of the equipment, it may be performed as a combined installation/operation qualification (IOQ). Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.
- 13.37. In some cases, only IQ and OQ may be required, as the correct operation of the equipment, utility or system could be considered a sufficient indicator of its performance.
- 13.38. Major equipment and critical utilities and systems, however, may require URS, DQ, IQ, OQ and PQ.
- 13.39. Computerized systems, including equipment with software component(s), should be appropriately qualified and validated.

User requirement specifications

- 13.40. Manufacturers should prepare a document that describes the requirements for the item (such as system(s) for a utility; or equipment) to be sourced. The requirements may include specifications and should ensure that possible GMP risks are addressed; include technical requirements; and reference associated documentation.
- 13.41. The URS should be used when selecting the required item from an approved supplier, and to verify suitability throughout the subsequent stages of qualification.

Design qualification

- 13.42. DQ should provide documented evidence that the design specifications were met and are in accordance with the URS.

Factory acceptance test and site acceptance test

- 13.43. Where appropriate, FAT and SAT should be performed to verify the suitability of the system at site, prior to the subsequent stages of qualification. This should be appropriately documented.

Installation qualification

- 13.44. IQ should provide documented evidence that the installation was complete and satisfactory, including supporting utilities, where appropriate.
- 13.45. The design specifications, including purchase specifications, drawings, manuals, lists of spare parts and vendor details, should be verified during IQ, as should the configuration specifications for the intended operational environment.
- 13.46. Components installed should be verified, and documented evidence should be provided that components meet specifications, are traceable and are of the appropriate construction material.
- 13.47. Applicable control and measuring devices, identified through impact or risk assessment, should be calibrated.

Operational qualification

- 13.48. OQ should provide documented evidence that utilities, systems or equipment operate in accordance with operational specifications.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 13.49. Tests should be designed to demonstrate satisfactory operation over the normal operating range, as well as at the limits of its operating conditions. Worst-case conditions may be included in the testing.
- 13.50. Operation controls, alarms, switches, displays and other operational components should be tested.
- 13.51. Measurements made in accordance with a statistical approach should be fully described.

Performance qualification

- 13.52. Normally, PQ should be conducted prior to release of the utilities, systems or equipment. PQ should be performed under conditions simulating the intended use, to provide documented evidence that these can consistently perform in accordance with the specifications under routine use.

Requalification

- 13.53. Utilities, systems and equipment should be maintained in a qualified state. Any changes made to these should be managed through the change- control procedure. The extent of qualification or requalification as a result of such a change should be determined based on principles of risk management.
- 13.54. Requalification should be done based on the identified need and risk management principles. Factors such as the frequency of use, breakdowns, results of operation, criticality, preventive maintenance, repairs, calibration, and verification may be considered.
- 13.55. Requalification should also be considered after cumulative/multiple changes.
- 13.56. The scope and extent of requalification should be determined when components or parts are replaced.
- 13.57. Where a system or utility or equipment has not been used for an extended period of time, requalification may have to be considered.
- 13.58. Where appropriate, periodic requalification may be performed.

Revalidation

- 13.59. Systems should be in place to ensure that procedures, processes and methods remain in a validated state, for example, through periodic review or verification (e.g. in cleaning validation and analytical method validation)
- 13.60. Revalidation should be done based on the identified need and principles of risk management.
- 13.61. Any changes made to, for example, procedures, processes and methods, should be managed through the change-control procedure. The extent of validation or revalidation as a result of such a change should be determined based on principles of risk management.
- 13.62. Where appropriate, periodic revalidation may be performed.

Change management

- 13.63. Changes should be controlled in accordance with the appropriate quality management system.
- 13.64. When a change is initiated, consideration should be given to previous changes and the impact of the cumulative effect of the changes. The scope and extent of qualification and validation should be determined based on risk management principles.
- 13.65. Deviation management
- 13.66. Any deviation during qualification and validation should be appropriately managed (e.g. investigated, evaluated, the impact assessed, and documented) through an appropriate quality management system.
- 13.67. Corrective actions should be considered.

Calibration and verification

- 13.68. Calibration and verification of equipment, instruments and other devices, as applicable, should be initiated during installation qualification, to ensure that the system operates according to the described specifications and because the calibration status could have been affected during transport and installation.
- 13.69. Thereafter, it should be performed at regular intervals in accordance with a calibration program and SOPs.
- 13.70. Personnel who carry out calibration and preventive maintenance should have appropriate qualification and training.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 13.71. A calibration program should be available and should provide information such as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.
- 13.72. There should be traceability to standards (e.g. national, regional or international standards) used in the calibration. A valid certificate of calibration should be maintained, which is dated and includes reference to and traceability to, for example, standards used, acceptance limits, uncertainty where applicable, range, calibration due date.
- 13.73. Calibrated equipment, instruments and other devices should be labelled, coded or otherwise identified, to indicate the status of calibration and the date on which recalibration is due.
- 13.74. When the equipment, instruments and other devices have not been used for a certain period, their function and calibration status should be verified and shown to be satisfactory before use.
- 13.75. Equipment, instruments and other devices should be calibrated before or on the due date for calibration, to ensure that they are used in a calibrated state.
- 13.76. Where instruments and devices are identified as critical or non-critical, or impacting and non-impacting for the purpose of calibration, documented evidence of the decision-making process should be available. This should include impact and/or risk assessment.

Process Validation

General

- 13.77. 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.
- 13.78. 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).

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 13.79. 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.
- 13.80. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

Prospective Validation

- 13.81. Prospective validation should include, but not be limited to the following:
- (a) short description of the process;
 - (b) summary of the critical processing steps to be investigated;
 - (c) list of the equipment/facilities to be used (including measuring /monitoring / recording equipment) together with its calibration status
 - (d) finished product specifications for release;
 - (e) list of analytical methods, as appropriate;
 - (f) proposed in-process controls with acceptance criteria;
 - (g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
 - (h) sampling plan; that considers –where ,when, how, how many and how much(sample size)
 - (i) methods for recording and evaluating results
 - (j) functions and responsibilities;
 - (k) proposed timetable.
- 13.82. 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.
- 13.83. Batches made for process validation should be the same size as the intended industrial scale batches.
- 13.84. 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

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Practice, including the satisfactory outcome of the validation exercise, and (where applicable) the marketing authorization.

Concurrent Validation

- 13.85. In exceptional circumstances, it may be acceptable not to complete a validation program before routine production starts.
- 13.86. The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.
- 13.87. Documentation requirements for concurrent validation are the same as specified for prospective validation.
- 13.88. The results of process validation should be documented in the validation report. As a minimum, the report should include:
- A description of the process: batch/packaging document, including details of critical steps;
 - A detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not included, reference should be made to the sources used and where it can be found;
 - any work done in addition to that specified in the protocol, or any deviations from the protocol should be formally noted along with an explanation;
 - A review and comparison of the results with those expected; and
 - Formal acceptance or rejection of the work by the team or persons designated as being responsible for the validation, after completion of any corrective action or repeated work.

Retrospective Validation

- 13.89. Retrospective validation is only acceptable for well-established processes (i.e. marketing of the product for not less than 5year, not less than 10 batches per year and/or NLT 25 batches over the past three years) and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment and sterile products.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 13.90. 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.
- 13.91. 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.
- 13.92. 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.
- 13.93. For retrospective validation, generally, data from ten to 25 consecutive batches should be examined to assess process consistency, but fewer batches not less than 10 may be examined if justified.

Qualification of Established (in use) Facilities, Systems and Equipment

- 13.94. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment that have been “in use” for a period of time, and which had not been subjected to installation and or operational qualification. These should include calibration, cleaning, and preventative maintenance, operating procedures, operator training procedures and records.

Cleaning Validation

- 13.95. 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.
- 13.96. 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.
- 13.97. 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

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.

- 13.98. 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.
- 13.99. Cleaning validation limit should be established based on Health-Based Exposure
- 13.100. Limits (HBELs) considering pharmacological and toxicological data. However, historically established cleaning limits may be used when these are more stringent than HBELs (For recommendations, refer to WHO TRS 1033 - Annex 2, which outlines important considerations for including Health-Based Exposure Limits (HBELs) in cleaning validation).
- 13.101. 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.
- 13.102. “Test until clean” is not considered an appropriate alternative to cleaning validation.
- 13.103. 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

- 13.104. 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.
- 13.105. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, requalification and re-validation should be determined.

CHAPTER FOURTEEN: COMPUTERIZED SYSTEM

Principle

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

General

- 14.1. It is essential that there is the closest co-operation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility, which utilizes computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of computerized system.
- 14.2. The use of a computer system includes different stages. These are planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.
- 14.3. The purpose of validation of a computer system is to ensure an acceptable degree of evidence (documented, raw data), confidence (dependability and thorough, rigorous achievement of predetermined specifications), intended use, accuracy, consistency and reliability.
- 14.4. Both the system specifications and functional specifications should be validated.
- 14.5. Periodic (or continuous) evaluation should be performed after the initial validation.
- 14.6. There should be written procedures for performance monitoring, change control, program and data security, calibration and maintenance, personnel training, emergency recovery and periodic re-evaluation.
- 14.7. Aspects of computerized operations that should be considered during validation include:
 - (a) networks

- (b) manual back-ups
- (c) input/output checks
- (d) process documentation
- (e) monitoring
- (f) alarms
- (g) Shut down recovery.

System

- 14.8. Attention should be paid to installation of equipment in suitable conditions where extraneous factors cannot interfere with the system. The following aspects should be considered during installation of computer system: location, power supply, temperature, and magnetic disturbances. Fluctuations in the electrical supply can influence computer systems and power supply failure can result in loss of memory and data.
- 14.9. A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures, the information to be produced, the limits of any variable and the operating program and test program.
- 14.10. The software is a critical component of a computerized system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of Quality Assurance.
- 14.11. The system should include, where appropriate, built-in checks of the correct entry and processing of data.
- 14.12. Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results. If a manual system is being replaced, the two should be run in parallel for a time, as part of this testing and validation.
- 14.13. Data should only be entered or amended by persons authorized to do so. Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. There should be a defined

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- procedure for the issue, cancellation, and alteration of authorization to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorized persons.
- 14.14. When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.
- 14.15. The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alteration to an entry of critical data should be authorized and recorded with the reason for the change. Consideration should be given to the system creating a complete record of all entries and amendments.
- 14.16. Alterations to a system or to a computer program should only be made in accordance with a defined procedure, which should include provision for validating, checking, approving and implementing the change. Such an alteration should only be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded. Every significant modification should be validated.
- 14.17. For quality auditing purposes, it should be possible to obtain meaningful printed copies of electronically stored data.
- 14.18. Data should be secured by physical or electronic means against willful or accidental damage. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.
- 14.19. Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.
- 14.20. There should be available adequate alternative arrangements for systems which need to be operated in the event of a breakdown. The time required to bring the alternative

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- arrangements into use should be related to the possible urgency of the need to use them. For example, information required to effect a recall must be available at short notice.
- 14.21. The procedures to be followed if the system fails or breaks down should be defined and validated. Any failures and remedial action taken should be recorded.
- 14.22. A procedure should be established to record and analyze errors and to enable corrective action to be taken.
- 14.23. When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency.
- 14.24. When the release of batches for sale or supply is carried out using a computerized system, the system should recognize that only an Authorized Person can release the batches and it should clearly identify and record the person releasing the batches.

Validation

- 14.25. The extent of validation necessary will depend on a number of factors including the use to which the system is to be applied, whether it is prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and changing.
- 14.26. The computer-related systems and vendors should be defined and the vendor and product should be evaluated. The system should be designed and constructed, taking into consideration the types, testing and quality assurance of the software.
- 14.27. After installation of the system, it should be qualified. The extent of the qualification should depend on the complexity of the system. The system should be evaluated and performance qualification, change control, maintenance and calibration, security, contingency planning, SOPs, training, performance monitoring and periodic re-evaluation should be addressed.

Hardware Validation

- 14.28. As part of the validation process appropriate tests and challenges to the hardware should be performed.
- 14.29. Static, dust, power-feed voltage fluctuations and electromagnetic interference could influence the system. The extent of hardware validation should depend on the complexity of the system. Hardware is considered to be equipment, and the focus should be on location, maintenance and calibration of hardware, as well as on validation/qualification.
- 14.30. The validation/qualification of the hardware should prove:
- (a) that the capacity of the hardware matches its assigned function (e.g. different language);
 - (b) that it operates within the operational limits (e.g. memory, connector ports, input ports);
 - (c) that it performs acceptably under worst-case conditions (e.g. long hours, temperature extremes); and
 - (d) reproducibility/consistency (e.g. by performing at least three runs under different conditions).
- 14.31. The computer hardware validation should be done in accordance with written qualification protocols and the results should be recorded in the qualification report. Revalidation should be performed when significant changes are made. Much of the hardware validation may be performed by the computer vendor. However, the ultimate responsibility for the suitability of equipment used remains with the manufacturer.
- 14.32. Hardware validation data and protocols should be kept by the company. When validation information is produced by an outside firm, e.g. computer vendor, the records maintained by the company need not include all of the voluminous test data; however, such records should be sufficiently complete (including general results and protocols) to allow the company to assess the adequacy of the validation. A mere certification of suitability from the vendor, for example, will be inadequate.

Software Validation

- 14.33. Software is the term used to describe the complete set of programs used by a computer, and which should be listed in a menu. Records are considered as software;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- focus is placed on accuracy, security, access, retention of records, review, double checks, documentation and accuracy of reproduction.
- 14.34. The company should identify the following key computer programs: language, name, function (purpose of the program), input (determine inputs), output (determine outputs), fixed set point (process variable that cannot be changed by the operator), variable set point (entered by the operator), edits (reject input/output that does not conform to limits and minimize errors, e.g. four- or five-character number entry), input manipulation (and equations) and program overrides (e.g. to stop a mixer before time).
- 14.35. Software validation should provide assurance that computer programs (especially those that control manufacturing and processing) will consistently perform as they are supposed to, within pre-established limits.
- 14.36. When planning the validation of computer software system, the following points should be considered.
- (a) Function: does the program match the assigned operational function (e.g. generate batch documentation, different batches of material used in a batch listed)?
 - (b) Worst case: perform validation under different conditions (e.g. speed, data volume, frequency).
 - (c) Repeats: sufficient number of times (replicate data entries).
 - (d) Documentation: protocols and reports.
 - (e) Revalidation: needed when significant changes are made.

Analytical Method Validation

Principle

Manufacturers should choose analytical validation protocol and procedures most suitable for testing of the product. The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose. Analytical methods, whether or not they indicate stability, should be validated. The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.

General

- 14.37. There should be specifications for both, materials and products. The tests to be performed should be described in the documentation on standard test methods.
- 14.38. Specifications and standard test methods in pharmacopoeias (“pharmacopoeial methods”), or suitably developed specifications or test methods (“non-pharmacopoeial methods”) as approved in the marketing authorization by the authority may be used.
- 14.39. Well-characterized reference materials, with documented purity, should be used in the validation study.
- 14.40. The most common analytical procedures include identification tests, assay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing, determination of particle size and residual solvents.
- 14.41. The results of analytical procedures should be reliable, accurate and reproducible.
- 14.42. Verification or revalidation should be performed when relevant, for example, when there are changes in the process for synthesis of the drug substance; changes in the composition of the finished product; changes in the analytical procedure; when analytical methods are transferred from one laboratory to another; or when major pieces of equipment instruments change.
- 14.43. The verification or degree of revalidation depends on the nature of the change(s). There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses (“analyst proficiency”).

Pharmacopoeial method

- 14.44. When pharmacopoeia methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (method verification).
- 14.45. Pharmacopoeia methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the substance under consideration (no placebo interference).

Non-pharmacopoeial method

- 14.46. Non-pharmacopoeial methods should be appropriately fully validated.

Method Validation

- 14.47. Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.
- 14.48. Justification should be provided when non-pharmacopoeial methods are used if pharmacopoeial methods are available. Justification should include data such as comparisons with the pharmacopoeial or other methods.
- 14.49. Standard test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, reference standards, the formulae for the calculation of results and system suitability tests.

Characteristics of analytical validation

- 14.50. The analytical characteristics that should be considered during validation of analytical methods are; specificity, linearity, range, accuracy, precision, detection limit, quantitation limit, robustness.
- 14.51. **Accuracy** is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure. Note: it is acceptable to use a “spiked” placebo where a known quantity or concentration of a reference material is used.
- 14.52. **Precision** is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping) and expressed as the relative standard deviation (RSD).

- 14.53. **Repeatability** should be assessed using a minimum of nine determinations covering the specified range for the procedure e.g. three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.
- 14.54. **Intermediate precision** expresses within-laboratory variations (usually on different days, different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.
- 14.55. **Reproducibility expresses** precision between laboratories.
- 14.56. **Robustness (or ruggedness)** is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase, and should show the reliability of an analysis when deliberate variations are made in method parameters. Factors that can have an effect on robustness when performing chromatographic analysis include:
- stability of test and standard samples and solutions;
 - reagents (e.g. different suppliers);
 - different columns (e.g. different lots and/or suppliers);
 - extraction time;
 - variations of pH of a mobile phase;
 - variations in mobile phase composition;
 - temperature; and
 - flow rate
- 14.57. **Linearity** indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used.
- 14.58. **Range** is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable for the product. The specified range is normally derived from linearity studies.

14.59. **Specificity (selectivity)** is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and assay.

14.60. **Detection limit (limit of detection)** is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:

- visual evaluation;
- signal to noise ratio;
- standard deviation of the response and the slope;
- standard deviation of the blank; and
- calibration curve

14.61. **Quantitation limit (limit of quantitation)** is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:

- visual evaluation;
- signal to noise ratio;
- standard deviation of the response and the slope;
- standard deviation of the blank; and calibration curve.

System Suitability Testing

14.62. System suitability testing is an integral part of many analytical procedures and method validation. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure being evaluated, for instance, a resolution test for an HPLC procedure.

Revalidation

14.63. 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 FIFTEEN: DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

General

- 15.1. Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.
- 15.2. Manufacturing Formulae, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.
- 15.3. Procedures give directions for performing certain operations e.g. cleaning, clothing, environmental control, sampling, testing, and equipment operations.
- 15.4. Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent for the quality of the final product.
- 15.5. Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorization dossiers.
- 15.6. Documents should be approved, signed and dated by appropriate and authorised persons.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 15.7. Documents should have unambiguous contents; 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.
- 15.8. Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.
- 15.9. Documents should not be hand-written; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.
- 15.10. Any alteration made to the entry on 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.
- 15.11. The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.
- 15.12. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed 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 result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention.

Essential Documents Specifications

15.13. There should be appropriately authorized and dated specifications for starting and packaging materials, and finished products; where appropriate, they should be also available for intermediate or bulk products.

Specifications for starting and packaging materials

15.14. Specifications for starting and primary or printed packaging materials should include:

- description of the materials, including: the designated name and the
- Internal code reference;
- the reference, if any, to a pharmacopoeia monograph;
- the approved suppliers and, if possible, the original producer of the products;
- a specimen of printed materials;
- directions for sampling and testing or reference to procedures;
- qualitative and quantitative requirements with acceptance limits;
- storage conditions and precautions;
- the maximum period of storage before re-examination.

Specifications for intermediate and bulk products

15.15. 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

15.16. Specifications for finished products should include:

- a) the designated name of the product, reference number, version, date of authorization, date of revision;
- b) the formula or a reference to the manufacturing and/or master formula;
- c) description of the pharmaceutical form and package details;
- d) directions for sampling and testing or a reference to procedures;
- e) the qualitative and quantitative requirements, with the acceptance limits;
- f) the storage conditions and any special handling precautions, where applicable;

- g) the shelf-life.

Batch Formula and Processing Instruction

15.17. Formally authorized Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document and named master formula.

The Manufacturing Formula should include:

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

The Processing Instructions should include:

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

Packaging Instructions

15.18. There should be formally authorized Packaging Instructions for each product for pack size and type. These should normally include, or have a reference to, the following:

- (a) name of the product;
- (b) description of its pharmaceutical form, and strength where applicable;
- (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;
- (f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- (h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

15.19. A Batch Processing Record should be kept for each product batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions (Master Formula). The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

15.20. Before any processing begins, there should be recorded checks that the equipment and workstation are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

15.21. 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 in agreement by the person responsible for the processing operations:

- (a) the name of the product;
- (b) dates and times of commencement, of significant intermediate stages and of completion of production;
- (c) name of the person responsible for each stage of production;
- (d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- (e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- (f) any relevant processing operation or event and major equipment used;
- (g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- (h) the amount of product yield obtained at different and pertinent stages of manufacture;
- (i) notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions.

Batch Packaging Records

15.22. A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry 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.

15.23. Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

required for the planned packaging operations, and that equipment is clean and suitable for use.

15.24. The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

- (a) the name of the product;
- (b) the date(s) and times of the packaging operations;
- (c) the name of the responsible person carrying out the packaging operation;
- (d) the initials of the operators of the different significant steps;
- (e) records of checks for identity and conformity with the Packaging Instructions including the results of in-process controls;
- (f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
- (g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- (h) notes on any special problems or unusual events including details with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions;
- (i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Procedures and Records

Receipt

15.25. There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material. The records of the receipts should include:

- (a) the name of the material on the delivery note and the containers;
- (b) the "in-house" name and/or code of material (if different from a);
- (c) date of receipt;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- (d) supplier's name and, if possible, manufacturer's name;
- (e) manufacturer's batch or reference number;
- (f) total quantity, and number of containers received;
- (g) the batch number assigned after receipt;
- (h) any relevant comment (e.g. state of the containers).

15.26. There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

15.27. There should be written procedures for sampling, which include the person(s) authorized to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

Testing

15.28. 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.

Other

15.29. 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 the authorized person(s) designated for the purpose.

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

15.31. There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:

- validation;
- equipment assembly and calibration;
- maintenance, cleaning and sanitization;
- personnel matters including training, clothing, hygiene;
- environmental monitoring;
- pest control;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- complaints;
- recalls;
- returns.

15.32. Clear operating procedures should be available for major items of manufacturing and test equipment.

15.33. Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

15.34. Log books should also record in chronological order the use of major or critical equipment and the areas where the products have been processes.

CHAPTER SIXTEEN: WATER FOR PHARMACEUTICAL USE

Principle

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

Different grades of water quality are required depending on the route of administration of the pharmaceutical products. Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Unlike other product and process ingredients, water is usually drawn from a system on demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is, therefore, essential. Additionally, certain microbiological tests may require periods of incubation and, therefore, the results are likely to lag behind the water use. It is very important to minimize microbial contamination by routine sanitization and taking appropriate measures to prevent microbial proliferation.

General

- 16.1. Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified, validated, operated and maintained to ensure the consistent and reliable production of water of appropriate quality.
- 16.2. The capacity of these systems should be enough to meet both the minimum and peak demand. These systems should be able to operate continuously for significant periods of time in order to avoid the inefficiencies and equipment stresses that occur when equipment cycles turn on and off too frequently.
- 16.3. Qualification may include stages such as preparing User Requirement Specifications (URS), Factory Acceptance Tests (FAT), Site Acceptance Tests (SAT), as well as installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The release and use of the system should be approved by the quality unit, e.g. quality assurance (QA) at an appropriate stage of qualification and validation (see section twelve below).
- 16.4. Water sources and treated water should be monitored regularly for chemical, microbiological and, where appropriate, endotoxin contamination. The performance of water treatment, storage and distribution systems should also be monitored. Records of the results monitored, trend analysis and any actions taken should be maintained.

Water Quality Specification

Pharmacopoeial specifications

- 16.5. Pharmacopoeias include specifications for water used in bulk and in dosage forms. Where this document refers to specifications, such as those in pharmacopoeias, the relevant, current publications should be used. Pharmacopoeial requirements or guidance for WPU are described recognized international pharmacopoeias and limits for various impurities, or classes of impurities, are either specified or recommended. Requirements or guidance are given in pharmacopoeias on the microbiological and chemical quality of water.

Drinking Water

- 16.6. Drinking water may be derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and seas. The condition of the source water should be considered when choosing a treatment to produce drinking- water.
- 16.7. Drinking water should comply with Ethiopian drinking water specifications standard for physical, chemical and bacteriological requirements.
- 16.8. Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.
- 16.9. Drinking-water may be derived from a public water supply system. This includes an off-site source, such as a municipality. Appropriate drinking-water quality should be ensured by the supplier. Tests should be conducted to guarantee that the drinking-water delivered is of drinking quality. This testing is typically performed on water when taken from the water source. Where required, quality may be achieved through processing on-site.
- 16.10. Where drinking-water is purchased in bulk and transported to the user by water tankers, controls should be put into place to mitigate any associated risks. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.
- 16.11. It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the purified water (PW) treatment system meets the appropriate drinking-water requirements. In these situations, the point at which drinking-water quality is achieved should be identified and a water sample taken and tested at defined intervals thereafter.
- 16.12. If drinking-water is used directly in certain stages of pharmaceutical manufacture, such as in the production of APIs or in the feed water for the production of higher qualities of WPU, then testing should be carried out periodically by the water user's site; for example, at the point of use, to confirm that the quality meets the standards required for drinking-water. The selection of tests to be performed, and the frequency of testing, should be based on a risk assessment.

16.13. Where drinking-water is produced through the treatment of raw water by a system on-site, the system configuration and water-treatment steps used should be described.

16.14. Examples of typical processes employed to produce drinking-water may include:

- desalination;
- filtration;
- softening;
- disinfection or sanitization, such as by ozone or sodium hypochlorite (chlorine);
- iron (ferrous) removal;
- precipitation; and
- the reduction of concentration of specific inorganic and/or organic materials.

16.15. Controls should be implemented to minimize the microbiological contamination of sand filters, carbon beds and water softeners. The techniques selected should be appropriate and may include back flushing, chemical and/or thermal sanitization and frequent regeneration.

16.16. The quality of drinking-water should be monitored routinely to account for environmental, seasonal or supply changes which may have an impact on the source water quality.

16.17. Where drinking-water is stored and distributed by the user, the storage and distribution systems should minimize the degradation of the water quality prior to use. After any such storage, testing should be carried out routinely and in accordance with a defined procedure. The storage and distribution of drinking-water should be done in a manner to ensure a turnover or recirculation of the water, if possible.

16.18. The equipment and systems used to produce and store drinking-water should be able to be drained or flushed, and sanitized.

16.19. Storage tanks should be closed with appropriately protected vents and should allow for visual inspection.

16.20. Distribution pipework should be able to be drained or flushed, and sanitized.

16.21. If possible, the results from testing drinking water should be subjected to statistical analysis in order to identify trends and changes. If the drinking-water quality changes significantly, but is still within specification, the direct use of this water as a WPU, or as the feed water to downstream treatment stages, should be reviewed for any potential risks. The appropriate action should be taken and documented.

16.22. Changes to an in-house system or to its operation should be made in accordance with change control procedures.

16.23. Additional testing should be considered if there is any change in the raw water source, treatment techniques or system configuration.

Bulk Purified Water

16.24. Bulk purified water (BPW) should meet the relevant pharmacopoeial specifications for chemical and microbiological purity. The appropriate and applicable test procedures should be followed.

16.25. BPW should be prepared from drinking water as a minimum-quality feed water.

16.26. Any appropriate, qualified purification technique, or sequence of techniques, may be used to prepare BPW. BPW could be prepared by, for example, ion exchange, reverse osmosis (RO), RO/electro-deionization (EDI), ultrafiltration, or any combination of these techniques.

16.27. The following are examples of aspects that should be considered when configuring a water purification system or defining URS:

- the quality of feed water and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required;
- the number and location of sampling points
- design of sampling points in such a way so as to avoid potential contamination;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- unit process steps provided and documented with the appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity and total organic carbon;
 - material of construction
 - sanitization strategy
 - main components;
 - interlocks, controls and alarms; and
 - appropriate software, electronic data management, system security and audit trail.
- 16.28. Ambient-temperature systems such as ion exchange and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. Sanitization at defined intervals (e.g. based on the data collected from the system validation and system behavior), as well as other controls, should be defined to prevent and minimize microbiological contamination.
- 16.29. Methods for sanitizing each stage of purification should be appropriate and validated. The removal of any agents used for sanitization should be proven.
- 16.30. The following controls, for example, should be considered in order to minimize microbial contamination:
- the maintenance of water flow at all times in the storage and distribution system to prevent water from stagnating;
 - control of temperature in the system, for example, by heat exchangers or room cooling in order to reduce the risk of microbial growth;
 - the provision of ultraviolet disinfection at appropriate locations in the system;
 - the use of water-treatment system components that can periodically be thermally sanitized above 70 °C for a defined period of time, or

chemically sanitized using, for example, ozone, hydrogen peroxide and/or per acetic acid; and

- a combination of thermal and chemical sanitization, if required.

16.31. BPW should have appropriate alert and action limits for chemical and microbiological purity determined from a knowledge of the system and data trending. BPW should be protected from recontamination and microbial proliferation.

Bulk Water for Injection

16.32. BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxins). BWFI is the highest quality of pharmacopoeial WPU.

16.33. BWFI is not a final dosage form. It is an intermediate bulk product suitable to be used as an ingredient during formulation.

16.34. As a robust technique should be used for the production of BWFI, the following are examples of what should be considered when configuring a water purification system or defining URS:

- the quality of feed water and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required, where appropriate;
- based on the selection of components, material of construction and type of system, the appropriate URS, qualification and validation;
- the optimum generator size or generators with variable control to avoid over-frequent start/stop cycling;
- blow-down and dump functions;
- cool-down venting to avoid contamination ingress;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;
- appropriate instrumentation to measure parameters as required;

- sanitization strategy;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

- 16.35. BWFI may be prepared, for example, by distillation as the final purification step. Alternatively, BWFI may be produced by means other than distillation. Techniques such as deionization, electro deionization, nano-filtration, ultrafiltration, water-softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a single or double pass RO system. For full details, see Production of water for injection by means other than distillation as published in the WHO Technical Report Series, No. 1025, Annex 3, 2020.
- 16.36. BWFI should have appropriate microbial and chemical alert and action limits and should also be protected from recontamination and microbial proliferation.

General considerations for water purification systems

- 16.37. Pharmaceutical manufacturers should apply the current principles of quality risk management in selecting and using the appropriate water purification systems. An appropriate method for the production of WPU should be used. Risks and controls should be identified for each stage of the production, storage, distribution, use and monitoring of WPU.
- 16.38. Risks identified should be evaluated in order to determine the scope and extent of validation and qualification of the system, including the computerized systems used for the production, control and monitoring of WPU.
- 16.39. Risk management should be an ongoing part of the quality management process for WPU. A mechanism to review or monitor events associated with the production, storage, distribution and use of WPU should be implemented.
- 16.40. Procedures for managing changes and deviations should be followed. Where applicable, the appropriate risk and impact assessments should be carried out in such a way that changes and deviations are managed.
- 16.41. The chosen water purification system, method or sequence of purification steps must be appropriate in order to ensure the production of water of the intended grade. Based

on the outcome of the risk assessment, the following should at least be considered when selecting the water treatment system and method:

- the quality of the available feed water and the variation over time (seasonal changes);
- the availability of suitable support facilities for the system (e.g. electricity, heating, steam, chilled water and compressed air);
- the extent of pre-treatment required
- the sequence of purification steps required;
- the design and location of sampling points;
- the sanitization strategy;
- the availability of water-treatment equipment on the market;
- the reliability and robustness of the water-treatment equipment in operation;
- the yield or efficiency of the purification system;
- the ability to adequately support and maintain the water purification equipment;
- the continuity of operational usage considering hours/days/years and planned downtime;
- the total life-cycle of the system (including capital, operation and maintenance);
- the final water quality specification; and
- the minimum, average and maximum quantity of water required by the user.

16.42. The specifications for water purification equipment, storage and distribution systems should take into account at least the following:

- the location of the plant room;
- the extremes in temperature that the system will encounter;
- the risk of contamination, for example, from materials of construction (contact materials) and the environment;

- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;
- corrosion resistance;
- freedom from leakage;
- system configuration to avoid or minimize proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and/or chemical);
- the sanitization strategy;
- system capacity and output requirements; and
- the provision of all necessary instruments, test and sampling points in order to allow for all the relevant critical quality parameters of the complete system to be monitored.

16.43. The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

- the ability to collect samples;
- the space available for the installation and environment around the system;
- structural loadings on buildings;
- the provision of adequate access for maintenance and monitoring; and
- the ability to safely handle regeneration and sanitization chemicals.

Water Storage and Distribution

General

16.44. Where drinking water is stored and distributed, the appropriate controls should be determined and implemented in order to mitigate risks. This applies to all stages in the supply, storage and distribution of drinking water.

16.45. The water storage and distribution systems for PW and BWFI should be appropriately designed, installed, qualified, operated and maintained in order to ensure the storage and distribution of water is of consistent quality to the user points.

Storage vessel

16.46. Storage vessels should be appropriate for their intended use.

16.47. As a minimum, the following should be considered:

- the design and shape to ensure drainage of water from the vessel, when required;
- construction materials
- capacity, including buffer capacity, between the steady state, water generation rate and the potentially variable simultaneous demand from user points, short-term reserve capacity in the event of failure of the water-treatment system or the inability to produce water (e.g. due to a regeneration cycle);
- prevention of stagnant water in the vessel (e.g. the headspace where water droplets can accumulate) and the need for the use of a spray ball or distributor devices to wet the inner surfaces of the vessel;
- the fitting of bacteria-retentive, hydrophobic vent filters which are tested for their integrity at appropriate intervals;
- the fitting of sanitary design pressure safety valves or bursting discs provided with external rupture indicators to ensure that loss of system integrity is detected;
- the design and sanitization, as required, of level indicators;
- the design and location of valves, sampling points and monitoring devices and sensors; and
- the need for heat exchangers or jacketed vessels. Where these are used, double tube sheet or double plate heat exchangers should be considered.

Water Distribution

- 16.48. The water distribution system should be designed as a loop, with continuous circulation of BPW and BWFI. Where this is not the case, the appropriate justification for using a non-recirculating one-way system should be provided as well as robust measures implemented to monitor these.
- 16.49. As a minimum, the following should be considered:
- controls to minimize proliferation of contaminants;
 - material of construction, joints and impact as a result of sanitization; and
 - the design and location of devices, sensors and instruments such as flow meters, conductivity sensors, TOC analyzers and temperature sensors.
- 16.50. Filtration should not be used in distribution loops or at take-off user points.
- 16.51. Where heat exchangers are used, they should be arranged in continually circulating loops or sub-loops in order to avoid unacceptable static water in the system.
- 16.52. When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.
- 16.53. Circulation pumps should be of a sanitary design with the appropriate seals to prevent contamination of the system.
- 16.54. Where stand-by pumps are provided, they should be configured or managed to avoid zones where stagnant water is trapped within the system.
- 16.55. Consideration should be given to preventing contamination in systems where parallel pumps are used. There should be no stagnant water remaining in a pump when the pumps is not being used.
- 16.56. Components should be identified and labelled. The direction of flow should be indicated.

Good practice for water system

- 16.57. The components of water systems, including but not limited to pipework, valves and fittings, seals, diaphragms and instruments, should be appropriate and remain suitable during the full range of operational conditions such as temperature and pressure of the

system at rest, in operation and during sanitization. The construction materials should be of adequate quality.

16.58. As a minimum, the following design and construction practices should be considered.

For drinking water storage, supply and distribution systems on-site

- Materials of construction should be selected based on the following requirements:
- ability to operate at the temperatures/pressures required;
- lack of impact on the final water quality;
- resistant to sanitizing chemicals;
- threaded and flanged joints are permitted; and
- sample valves should preferably be of sanitary design.

Note that the system may have a design life at the end of which it should be replaced or adequately modified.

For purified water and bulk water for injection systems

Note: Construction standards are generally aligned with potable water standards up to the process stage (e.g. RO).

- Materials of construction should be appropriate. It should be non-leaching, non-adsorbing, non-absorbing and resistant to corrosion. Stainless-steel grade 316L or polyvinylidene chloride (PVDC) is generally recommended. The choice of material should take into account the intended sanitization method.
- Stainless steel systems should be orbitally welded, with manual welds where necessary. Inter-weldability between materials should be demonstrated with the maintenance of weld quality through a defined process. Documentation for such a system should be kept and should include, as a minimum, the qualification of the welder, set-up for welding (e.g. machine), work session test pieces (coupons or weld samples), proof of quality of gas used, welding machine calibration record, weld identification and heat numbers, and logs of all welds. Records, photographs or videos of inspection of a defined proportion of welds (e.g. 100% of manual welds, 10% of orbital welds).

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- Joints should be made using sanitary connections, for example, hygienic clamp joints. Threaded joints should not be permitted. Polyvinylidene fluoride or polyvinylidene difluoride (PVDF) systems should be fusion joined and visually inspected.
- Passivation should be considered for stainless steel systems, for example, for non-electropolished surfaces (after initial installation and after significant modification) in accordance with a documented procedure defining the solution to be used, its concentration, the temperature and contact time.
- Internal finish should be smooth.
- Flanges, unions and valves should be of a hygienic or sanitary design. Valves should be diaphragm type forged or machined body, with points of use constructed so that they can drain. Sample valves should be sanitary type with the surface roughness of 1.0 micrometer RA or lower for PW and WFI systems and are typically installed between process stages and on the distribution loop return. The appropriate checks should be carried out in order to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly.
- The system should be installed to promote drainability with a recommended minimum slope of 1/100.
- Where appropriate, pressure or hydro-tests for leaks, spray-ball functionality test and flow turbulence should be considered.
- Provision should be made for in-line measurement for total organic carbon (TOC), conductivity, pressure, flow and temperature.
- Documents should provide evidence of system components and qualification. These include as applicable drawings, original or certified copies of certificates of conformity for materials of construction, records of on-site tests performed, weld/joining records, calibration certificates, system pressure test records and records of passivation.

System sanitization and bio-burden control

- 16.59. Water-treatment, storage and distribution systems should be subjected to controls that will reduce the risk of contamination and the proliferation of microbiological organisms.
- 16.60. Controls may include using chemical and/or thermal sanitization procedures as appropriate for production, storage and distribution systems. The procedure and conditions used (such as times and temperatures, as well as the frequency), should be defined and proven to be effective for sanitizing all relevant parts of the system. The techniques employed should be considered during the design stage of the system as the procedure and technique may impact on the components and materials of construction.
- 16.61. Systems that operate and are maintained at elevated temperatures (e.g. $> 70\text{ }^{\circ}\text{C}$) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed, or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress of contaminants including microorganisms.
- 16.62. Where the chemical sanitization of the water systems is part of the bio contamination control program, a validated procedure should be followed in order to ensure that the sanitizing process selected is effective and that the sanitizing agent has been effectively removed.
- 16.63. Records of sanitization should be maintained.
- 16.64. Other control techniques to be considered may include:
- The maintenance of a continuous circulation of water maintaining turbulent flow evidenced by, for example, a Reynolds number of > 4000 .
 - Ensuring hygienic design, including the use of zero dead leg diaphragm valves where possible, and minimizing dead legs elsewhere. Areas of possible dead legs should be measured and calculated.
 - Installing pipework in a manner to allow for full drainage, if required. A guidance figure for the slope is not less than 1/100.

- Considering the use of ultraviolet lamps in the system where needed with independent monitoring.
- Maintaining the system at an elevated temperature (e.g. > 70 °C), if required.

Operational considerations including some qualification and validation principles

- 16.65. Water systems should be appropriately qualified and validated. The scope and extent of qualification should be determined based on risk assessment.
- 16.66. When commissioning work is done, this should be documented. Commissioning is not a replacement for qualification.
- 16.67. In order to demonstrate the reliability and robustness of a system and its performance, a three-phase approach should be used for validation, covering at least one year of operation over different seasons. Tests on the source water (drinking water) should be included within the validation program and continued as part of the routine monitoring, and these results should meet specifications.

Note: A typical phase 1 to 3 approach for a new system is described below. When changes are made to existing systems, the phase(s) and length of each phase, as well as sampling points and frequency of sampling should be based on documented risk assessment.

Phase 1

Phase I should cover a period of at least two weeks.

Procedures and schedules should cover at least the following activities and testing approaches:

- chemical and microbiological testing in accordance with a defined plan;
- sample, test and monitoring of the incoming feed water to verify its quality;
- sample, test and monitoring after each step in the purification process;
- sample, test and monitoring at each point of use and at other defined sample points including the end of the distribution loop; verification of operating ranges;
- operating, cleaning, and maintenance;
- sanitizing procedures and operating ranges;
- demonstrate the consistent production and delivery of product water of the required quality and quantity;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- establishing provisional alert and action levels; and
- Test-failure procedure.

The system should be monitored intensively for its performance. Water should not be used for product manufacturing during this phase.

Phase 2

Phase 2 should cover at least a further test period of two weeks after the satisfactory completion of Phase 1. The system should be monitored while deploying all the standard operating procedures (SOPs). The sampling program should be generally the same as in Phase 1. The use of the water for product manufacturing purposes during this phase may be acceptable, provided that Phase 1 and ongoing Phase 2 data demonstrate the appropriate water quality and the practice is approved by QA.

The approach should also:

- demonstrate consistent system operation within established ranges; and
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3

Phase 3 should follow phase 2 ensuring that the duration of Phase I, 2 and 3 cover at least 12 months. The sample locations, sampling frequencies and tests may be reduced according to a routine plan which should be based on the established procedures and data from Phase 1 and Phase 2. Data should be trended, for example, quarterly and a system review should be undertaken after the completion of Phase 3 as part of the evaluation of system performance capability. The appropriate action should be taken where such a need is identified. Water can be used during this phase. The data and information obtained during Phase 3 should demonstrate the reliable performance of the system over this period of time covering the different seasons.

Continuous system monitoring

16.68. The system should be subject to continuous monitoring.

16.69. A monitoring plan should be followed where samples are collected in accordance with a written procedure.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 16.70. A combination of online and offline instruments, linked to appropriately qualified alarm systems, should be used. Parameters such as flow, pressure, and temperature should be monitored with online instruments – as well as conductivity and TOC, where possible. Periodic offline testing to confirm the results from online testing is recommended. Other parameters may be monitored through offline testing.
- 16.71. Offline testing (including physical, chemical and microbiological attributes) should be done in accordance with a predetermined program.
- 16.72. Samples should be taken from points of use and dedicated sample points where required. All water samples should be taken using the same methodology as detailed in production procedures, for example, using a hose and with a suitable flushing and drainage procedure in place.
- 16.73. Tests should be carried out to ensure that the relevant pharmacopoeia specification (and approved company specification, where applicable) has been met. This may include the microbiological quality of water, as appropriate.
- 16.74. The results for identified quality attributes should be subjected to statistical analysis at defined intervals, for example, monthly, quarterly and annually, in order to identify trends. The results should be within defined control limits, such as 3 sigma.
- 16.75. Alert and action levels should be established based on historically reported data.
- 16.76. Adverse trends and out-of-limit results should be investigated for the root cause, followed by the appropriate corrective and preventive actions. Where microbial contamination of BWFI occurs, the microorganism should be identified.

Maintenance of water systems

- 16.77. WPU systems should be maintained in accordance with an approved and documented maintenance program. Records should be kept. The maintenance program should take into account at least the following:
- defined frequency for system elements e.g. filters, instruments, gauges;
 - the calibration program;
 - SOPs for specific tasks;
 - the control and storage of approved spare parts;

- preventive maintenance and maintenance plan and instructions, including cleaning after maintenance;
- a review and approval of systems for use upon completion of work;
- a record and review of problems and faults during maintenance

CHAPTER SEVENTEEN: HEATING, VENTILATION AND AIR CONDITIONING SYSTEM (HVAC)

Principle

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. The good manufacturing practice (GMP) requirements for the prevention of contamination and cross-contamination are an essential design consideration of an HVAC system. A well-designed HVAC system also provides for protection of the environment and the operators as well as comfortable working conditions.

This chapter mainly focus on recommendations for HVAC systems used in facilities for the manufacture of non-sterile dosage forms, which include tablets, capsules, powders, liquids, creams and ointments. The general HVAC system design principles contained in these guidelines may, however, also be applied to other dosage forms.

HVAC system design influences architectural building design and layout, for example, with regard to airlock positions, doorways and lobbies. These in turn have an effect on room pressure, pressure differentials, pressure cascades, contamination and cross-contamination control. Therefore, the design of the HVAC system should be considered at the initial design stage of a pharmaceutical manufacturing plant. Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment and instruments.

A comprehensive science- and risk-based approach should be followed throughout the life cycle of an HVAC system, including its design, qualification and maintenance. Risk assessment is, however, not a substitute for GMP

Scope

This chapter focus primarily on GMP for the design, qualification, management and maintenance of HVAC systems in facilities for the manufacture of non-sterile dosage forms.

These guidelines do not cover requirements for manufacturing sites for the production of sterile pharmaceutical products. These guidelines do not cover the specific requirements relating to facilities handling hazardous products.

Protection

Product and Personnel

17.1. Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils and equipment are exposed to the environment, should be classified as “clean areas”.

17.2. The achievement of a particular clean area classification depends on a number of criteria that should be addressed at the design and qualification stages. A suitable balance between the different criteria will be required in order to create an efficient clean area. Some of the basic areas to be considered are; building finishes and structure, air filtration, air change rate or flushing rate, room pressure, location of air terminals and directional airflow, temperature, humidity, material flow, personnel flow, equipment movement, process being carried out, outside air conditions, occupancy and type of product.

17.3. Air filtration and air change rates should ensure that the defined clean area classification is attained. The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters. Primarily the air change rate should be set to a level that will achieve the required clean area classification. Air change rates normally vary between 6 and 20 air changes per hour and are normally determined by the following considerations:

- a) level of protection required
- b) the quality and filtration of the supply air
- c) particulates generated by the manufacturing process
- d) particulates generated by the operators
- e) configuration of the room and air supply and extract locations

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- f) sufficient air to achieve containment effect
- g) sufficient air to cope with the room heat load
- h) sufficient air to maintain the required room pressure

17.4. In classifying the environment, the manufacturer should state whether this is achieved under ‘as-built’, ‘at-rest’ or ‘operational’ condition:

17.4.1. Room classification tests in the “as-built” condition should be carried out on the bare room, in the absence of any equipment or personnel.

17.4.2. Room classification tests in the “at-rest” condition should be carried out with the equipment operating where relevant, but without any operators. Because of the amounts of dust usually generated in a solid dosage facility, most clean area classifications are rated for the “at-rest” condition.

17.4.3. Room classification tests in the “operational” condition should be carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally, a room that is tested for an “operational” condition should be able to be cleaned up to the “at-rest” clean area classification after a short clean-up time. The clean-up time should be determined through validation and is generally of the order of 20 minutes.

17.5. Materials and products should be protected from contamination and cross-contamination during all stages of manufacture. Airborne contaminants should be controlled through effective ventilation. External contaminants should be removed by effective filtration of the supply air. Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow.

17.6. Airborne particulates and the degree of filtration should be considered critical parameters with reference to the level of product protection required. The level of protection and air cleanliness for different areas should be determined according to the product being manufactured, the process being used and the product’s susceptibility to degradation. Examples of level of protection are indicated in the following table:

Level	Condition	Example of area

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Level 1	General	Area with normal housekeeping and maintenance, e.g. warehousing, secondary packing
Level 2	Protected	Area in which steps are taken to protect the exposed pharmaceutical starting material or product from contamination or degradation, e.g. manufacturing, primary packing, dispensing
Level 3	Controlled	Area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product

17.7. The degree to which air is filtered plays an important role in the prevention of contamination and the control of cross-contamination. The type of filters required for different applications depends on the quality of the ambient air and the return air (where applicable) and on the air change rates. The following table gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters:

Level of Protection	Recommended Filters
Level 1	Primary filters only (e.g. EN779 G4 filters)
Level 2 and 3	Production facility operating on 100% outside air: primary plus secondary filters (e.g. EN779 G4 plus F8 filters)
Level 2 and 3	Production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g. EN779 G4 plus F8 plus EN1822 H13 filters)

Note: The filter classifications referred to above relate to the EN1822 and EN779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes H10 to U16).

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 17.8. Filter classes should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (Different test methods result in a different value for the same filter).
- 17.9. In selecting filters, the manufacturer should have to consider other factors, such as particularly contaminated ambient conditions. Good pre-filtration extends the life of the more expensive filters downstream.
- 17.10. Materials for components of an HVAC system should be selected with care so that they do not become the source of contamination. Any component with the potential for liberating particulate or microbial contamination into the air stream should be located upstream of the final filters.
- 17.11. 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.
- 17.12. Directional airflow within production or packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation.
- 17.13. HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread. Supply air diffusers of the high induction type (e.g. those typically used for office-type air-conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect. Air should be exhausted from a low level in rooms to help provide a flushing effect.
- 17.14. Unidirectional airflow (UDAF) should be used to provide product protection by supplying a clean air supply over the product, minimizing the ingress of contaminants from surrounding areas. Where appropriate, the unidirectional airflow should also provide protection to the operator from contamination by the product. Sampling of materials such as starting materials, primary packaging materials and products, should

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

be carried out in the same environmental conditions that are required for the further processing of the product.

- 17.15. In a weighing booth situation, the aim of the design using UDAF should be to provide dust containment. A dispensary or weighing booth should be provided with unidirectional airflow for protection of the product and operator. The dust generated at the weighing station should be extracted through the perforated worktop, thus protecting the operator from dust inhalation and at the same time protecting the product from contamination by the operator by means of the vertical unidirectional airflow stream.
- 17.16. The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent inaccuracies during weighing, provided that sufficient airflow is maintained to provide containment.
- 17.17. 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. There should be no obstructions in the path of a unidirectional flow air stream that may cause the operator to be exposed to dust.
- 17.18. The manufacturer should select either vertical or horizontal unidirectional flow or an appropriate airflow pattern to provide the best protection for the particular application.
- 17.19. Air infiltration of unfiltered air into a pharmaceutical plant should not be the source of contamination. Manufacturing facilities should be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure to prevent the escape of harmful products to the outside (such as penicillin and hormones and other hazardous substance), special precautions should be taken. The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structure is well sealed. 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

- 17.20. Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another. Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment. The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.
- 17.21. Containment can normally be achieved by application of the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or the physical barrier concept.
- 17.22. The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used. Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure. The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required. Building structure should be given special attention to accommodate the pressure cascade design. Airtight ceilings and walls, close fitting doors and sealed light fittings should be in place.
- 17.23. The high pressure differential between the clean and less clean zones should be generated by leakage through the gaps of the closed doors to the cubicle. The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems. In considering room pressure differentials, transient variations, such as machine extract systems, should be taken into consideration. The most widely accepted pressure differential for achieving containment between two adjacent zones is 15 Pa, but pressure differentials of between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, the implications of the upper and lower tolerances on containment should be evaluated to ensure the absence of airflow reversal.

- 17.24. The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in no pressure cascade, if the first room is at the maximum tolerance and the second room is at the minimum tolerance.
- 17.25. Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used.
- 17.26. The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis. Manual control systems, where used, should be set up during commissioning and should not change unless other system conditions change.
- 17.27. Airlocks can be important components in setting up and maintaining pressure cascade systems. Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:
- a) **Cascade airlock:** higher pressure on one side of the airlock and lower pressure on the other (for an example, see Fig. A3.11);
 - b) **Sink airlock:** lower pressure inside the airlock and higher pressure on both outer sides (for an example, see Fig. A3.12);
 - c) **Bubble airlock:** higher pressure inside the airlock and lower pressure on both outer sides (for an example, see Fig. A3.13).

Fig. A3.10: Examples of pressure cascades

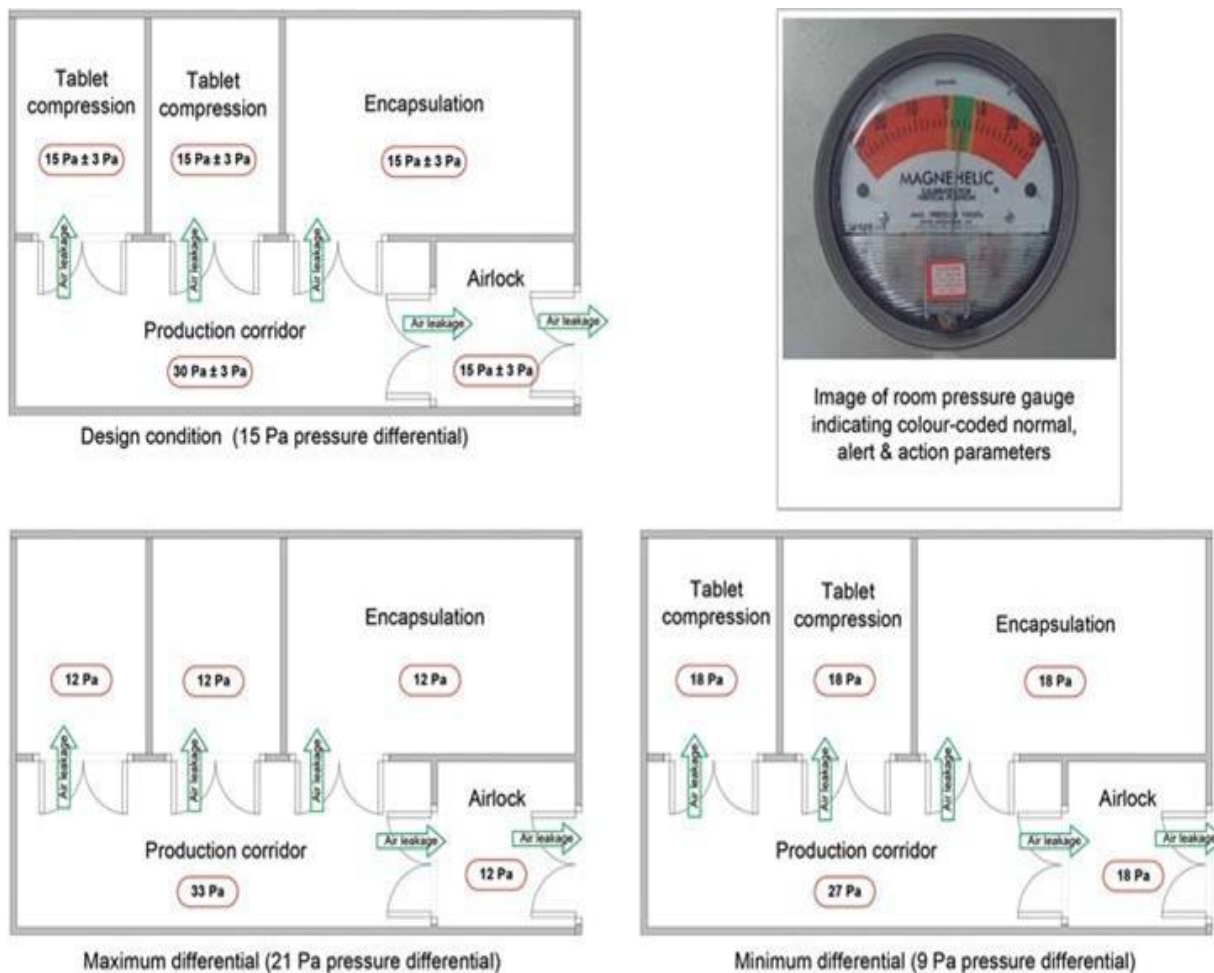


Fig. A3.11

Example of a cascade airlock: in most cases, the internal pressure of the airlock is not critical; the pressure differential between the two outer sides is the important criterion

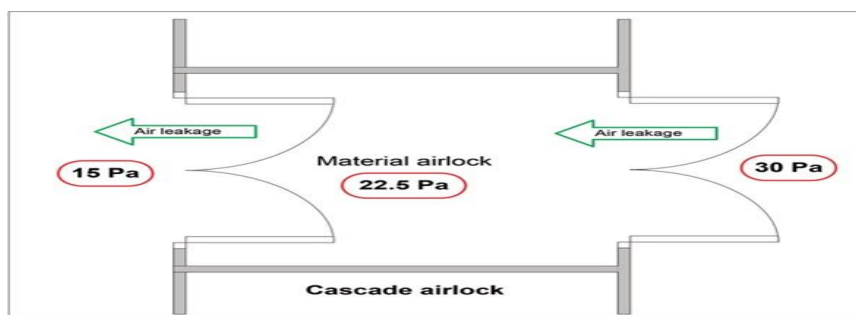


Fig. A3.12 Example of a sink airlock

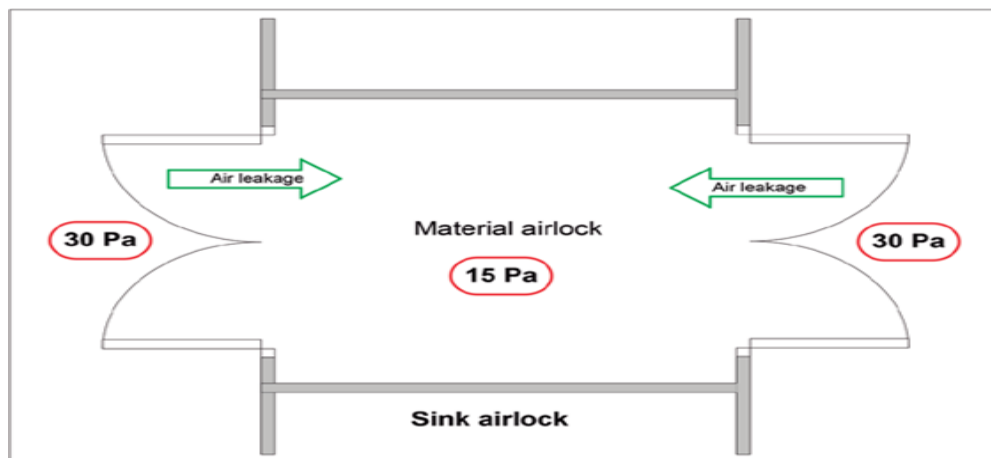
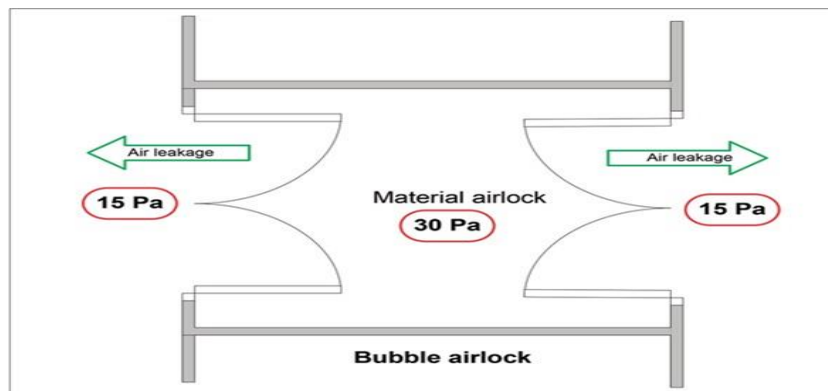


Fig. A3.13

Example of a bubble airlock



Note: The diagrams above and the differential pressures shown here are for illustration purposes only. Pressures indicated in these examples are absolute pressures, whereas the local pressure indication would most likely be the pressure differential from room to room.

17.28. Additional controls should be identified through risk identification and risk assessment. For example, where possible, personnel should not move between different areas during production (such as compression rooms and in process control laboratories), unless there is no risk of contamination of other areas. Personnel often become sources of contamination, as they may carry dust from one area to another. Controls may include airlocks or gowning procedures.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 17.29. 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.
- 17.30. Central dust extraction systems should be interlocked with the appropriate air handling systems, to ensure that they operate simultaneously.
- 17.31. Room pressure imbalance between adjacent cubicles which are linked by common dust extraction ducting should be prevented.
- 17.32. Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting (this would normally occur only if the dust extraction system was inoperative).

Temperature and Relative Humidity

- 17.33. Temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products, and to provide a comfortable environment for the operator where necessary. Maximum and minimum room temperatures and relative humidity should be established.
- 17.34. Temperature conditions should be adjusted to suit the needs of the operators while wearing their protective clothing. The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close.
- 17.35. Cubicles, or suites, in which products requiring low humidity are processed, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher humidity by means of suitable airlocks.
- 17.36. Precautions should be taken to prevent moisture migration that increases the load on the HVAC system. Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.
- 17.37. Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers. Appropriate cooling media for dehumidification such as low temperature chilled water/glycol mixture or refrigerant should be used.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 17.38. Humidifiers should be avoided if possible as they may become a source of contamination (e.g. microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product-contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.
- 17.39. Where steam humidifiers are used, chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system.
- 17.40. Humidification systems should be well drained. No condensate should accumulate in air-handling systems.
- 17.41. Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used because of the potential risk of microbial contamination.
- 17.42. Duct material near the humidifier should not add contaminants to air that would not be filtered downstream.
- 17.43. Air filters should not be installed immediately downstream of humidifiers.
- 17.44. Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components.
- 17.45. When specifying relative humidity, the associated temperature should also be specified.
- 17.46. Chemical driers using silica gel or lithium chloride are acceptable, if they do not become sources of contamination.

Dust Control

- 17.47. Wherever possible, the dust or vapor contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed. Point-of-use extraction should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.
- 17.48. Dust extraction ducting should be designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting. The required transfer

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

velocity should be determined: it is dependent on the density of the dust (the denser the dust, the higher the transfer velocity should be, e.g. 15–20 m/s).

- 17.49. Airflow direction should be carefully chosen, to ensure that the operator does not contaminate the product, and so that the operator is not put at risk by the product. Dust-related hazards to which the operators may be subjected should be assessed. An analysis of the type of dust and toxicity thereof should be done and the airflow direction determined accordingly.
- 17.50. Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow should be used to assist in removing dust and vapours from the room. Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers and extracted from the room at low level to help give a flushing effect in the room.
- 17.51. The HVAC system for areas associated with weighing room should ensure that the areas have at least the same area classification as other production areas where materials and products are exposed to the environment, logical flow of material and personnel, and an appropriate number of AHUs, as well as appropriate pressure differentials, containment, dust control, and rate of air exchange. For example, the dust generated at the weighing location should be extracted through a perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the material and product from contamination by the operator by means of the vertical airflow stream. The airflow velocity should be such that it does not disrupt the sensitivity of balances
- 17.52. The low-level extraction should assist in drawing air downwards and away from the operator's face. The extract grilles should be positioned strategically to draw air away from the operator, but at the same time to prevent the operator from contaminating the product.
- 17.53. When planning the system for the extraction of vapors, the density of the vapor should be taken into account. If the vapor is lighter than air, the extract grilles should be at a high level, or possibly at both high and low levels.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 17.54. When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.
- 17.55. When working with exposed products such as hormones or highly potent products, operators should wear totally enclosed garments. Operators should also be equipped with an air-breathing system that provides a supply of filtered and conditioned air. The air supply to this type of breathing apparatus should normally be through an air compressor. Filtration, temperature and humidity need to be controlled to ensure operator safety and comfort.

Protection from the Environment

General

- 17.56. The rates at which fresh air is supplied (NLT 20m³/min) to the facility should provide operators with an acceptable level of comfort and safety and to remove odors or fumes. The rate of fresh airflow should also be determined by leakage from the building, for pressure control purposes.
- 17.57. Protection of the environment should be compliant with relevant local and national legislation and standards.
- 17.58. Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and should be provided with adequate filtration to prevent contamination of the ambient air.
- 17.59. Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN779 filter standards.
- 17.60. Where harmful substances such as penicillin, hormones, toxic powders and enzymes are manufactured, the final filters on the dust exhaust system should be HEPA filters with at least an H12 classification according to EN1822 filter standards, as appropriate.
- 17.61. 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.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 17.62. When handling hazardous compounds, safe-change filter housings, also called “bag- in-bag-out” filters, should be used.
- 17.63. All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading. Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.
- 17.64. Exhaust filters should be monitored regularly to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in contamination of the ambient air.
- 17.65. Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they should usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow. Alternative types of dust collectors (such as those operating with a mechanical shaker, requiring that the fan be switched off when the mechanical shaker is activated) should be used in such a manner that there is no risk of cross- contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.
- 17.66. Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required.
- 17.67. When wet scrubbers are used, the dust-slurry should be removed by a suitable drainage system.
- 17.68. The quality of the exhaust air should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.
- 17.69. Where necessary, additional filtration may be provided downstream of the dust collector.

Vapor and Fume Removal

- 17.70. The systems for fume, dust and effluent control should be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross-contamination, e.g. an exhaust-air discharge point located close to the HVAC system fresh air inlet.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 17.71. Fumes should be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers). Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.
- 17.72. Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.
- 17.73. The type and quantity of the vapours to be removed should be known to enable the appropriate filter media, as well as the volume of media required to be determined.

HVAC System and Component Principle

The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters provided the air is not re-circulated.

General

- 17.74. There should be no failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan. Failure can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.
- 17.75. Air should be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated by means of passing hot air through one segment of the wheel).
- 17.76. Possible additional components that may be required should be considered depending on the climatic conditions and locations. These may include items such as:
- a) frost coils on fresh air inlets in very cold climates to preheat the air;
 - b) snow eliminators to prevent snow entering air inlets and blocking airflow;
 - c) dust eliminators on air inlets in arid and dusty locations;
 - d) moisture eliminators in humid areas with high rainfall; and
 - e) fresh air pre-cooling coils for very hot or humid climates.
- 17.77. Appropriate alarm systems should be in place to alert personnel if a critical fan fails.

17.78. Low-level return or exhaust air grilles are usually preferred. However, where this is not possible, a higher air change rate may be needed to achieve a specified clean area classification, e.g. where ceiling return air grilles are used.

Design of HVAC systems and components

17.79. The HVAC system should be appropriately designed, taking into consideration the design of the facility, with various rooms or areas for storage of materials and in-process materials or products, processing, and movement of materials, products and personnel.

17.80. The required cleanliness classification should be achieved, as well as other parameters, such as air filtration, airflow velocity, air volumes, pressure differentials, temperature, relative humidity, viable and non-viable particle counts and containment. Conditions and limits should be specified, based on need. Manufacturers should determine and define limits for these. These should be realistic, appropriate, scientifically justifiable at rest, in operation, and as built at the time of design.

17.81. In determining these, relevant factors and risks should be considered, including but not limited to possible failures of AHUs, seasonal variations, properties and types of materials and products, numbers of personnel and risks of cross-contamination.

17.82. Other aspects, such as the number of AHUs, dust-collecting or dust-extraction systems, the need for recirculation of air, percentage of fresh air (in the case of recirculated air) and the level of filtration of air should be defined by the manufacturer when considering the design of the facility and activities in different areas and rooms.

17.83. Manufacturers should maintain schematic drawings of the HVAC system, AHUs and components. These should reflect the initial design and installation, as well as the current situation. Changes made during the life-cycle of the system should be reflected in change-control records and qualification protocols and reports, as appropriate. The components selected in an HVAC system should be of sufficient capacity to ensure that the design objectives are met (e.g. for heating, cooling, humidification, dehumidification, airflow volumes), considering impacting factors, such as loss of air due to leakage and seasonal variations. Materials for construction of components, and their placement, should be such that these do not become the source of contamination. For example, components should not shed particles and the sequence of components

should be logical; for example, filters should be placed in such a manner that any possible contaminants generated in the system can be retained by filters and not be introduced into the production area.

- 17.84. To prevent contamination of areas, components such as ventilation dampers, filters and other services should be accessible from outside the manufacturing areas (such as service corridors). The overall design should be such that there is no possibility of undesired, unfiltered air or contaminants entering manufacturing areas.

Containment

- 17.85. Manufacturers should ensure that appropriate measures are taken to contain product dust in a manufacturing area, thus preventing or minimizing the risk of contamination of other areas and possible cross-contamination. In some cases, it may be advisable to have airlocks or pass-through hatches between rooms or areas. In addition, sufficient dilution, pressure differentials (recommended minimum values of 5 Pa) and airflow directions can further support containment in an area.

Cleanliness

- 17.86. Areas should be maintained at the defined levels of cleanliness and classifications. The HVAC system can support this through, for example, appropriate levels of filtration of air, dilution and dust removal. Equipment, containers, personnel and other related components should be appropriately located or placed in areas so as not to obstruct airflow and the effectiveness of the HVAC system. Recontamination should be prevented by ensuring that movement of material and personnel is within the same area classification and not back and forth between areas of different classification. Where such back-and-forth movement is unavoidable, appropriate controls should be identified and implemented, to ensure that moving from a higher class to a lower-classified area and back to a higher-classified area will not result in contaminants being brought into the cleaner classified area.

Automated monitoring systems

- 17.87. The performance of the HVAC system achieving and maintaining the desired results for parameters such as temperature, relative humidity, airflow and pressure differential should be carefully controlled and monitored. This is to ensure that there is no

departure from these limits during manufacturing. Monitoring systems should be in place to ensure that the system operates within its design limits. Manual or automated (computerized) systems may be used. Automated monitoring systems may provide possibilities for ongoing monitoring with better assurance of compliance with the defined limits. Where these automated systems are considered good practice (GXP) systems, these should be appropriately validated. The scope and extent of validation of the computerized system should be determined, justifiable and appropriately executed. This includes, but is not limited to, access and privileges to the software, setting of limits, monitoring and acknowledging alarms, audit trails, controls, and reporting.

Switching off air-handling units

17.88. It is recommended that the HVAC system be operational on an ongoing basis. Where a manufacturer decides to use energy-saving modes or switch some selected AHUs off at specified intervals, such as overnight, at weekends or for extended periods of time, care should be taken to ensure that materials and products are not affected. In such cases, the decision, procedures and records should be sufficiently documented and should include risk assessment, standard operating procedures, records and validation. This includes procedures and records for the start-up and shutdown sequence of AHUs.

Full fresh air systems and recirculation systems

17.89. Manufacturers may select to have full fresh air systems (for an example, see Fig. A2.8) or recirculate treated air supplied to production areas (in a full fresh air system, no air is recirculated; in recirculation systems, a defined percentage of the air is recirculated).

17.90. Manufacturers using recirculation systems should determine the percentage of fresh air to be supplied to the relevant manufacturing areas, as required by national and international standards. This volume of air should be verified during qualification.

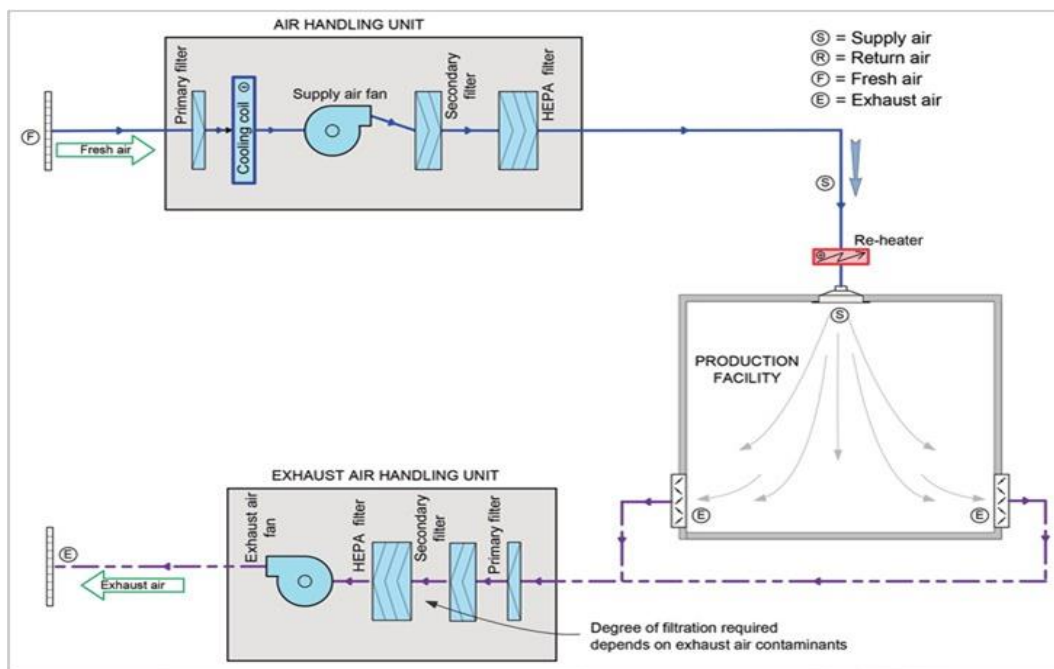
17.91. There should be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

17.92. Depending on the airborne contaminants in the return-air system, it may be acceptable to use re-circulated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN1822 classification of H13.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 17.93. HEPA filters may not be required for OSD where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.
- 17.94. Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.
- 17.95. HEPA filters may be located in the air-handling unit or placed terminally.
- 17.96. Air containing dust from highly toxic processes should never be re-circulated to the HVAC system.
- 17.97. Full (100% fresh) air would normally be used in a facility dealing with toxic products, where recirculation of air with contaminants should be avoided. The required degree of filtration of the exhaust air depends on the exhaust air contaminants and environmental regulations.
- 17.98. In both scenarios, appropriate levels of filtration should be applied, to prevent contamination and cross-contamination. Manufacturers should ensure that when high-efficiency particulate air (HEPA) filters are used, these are appropriately installed, not damaged and thus suitable for the intended use.

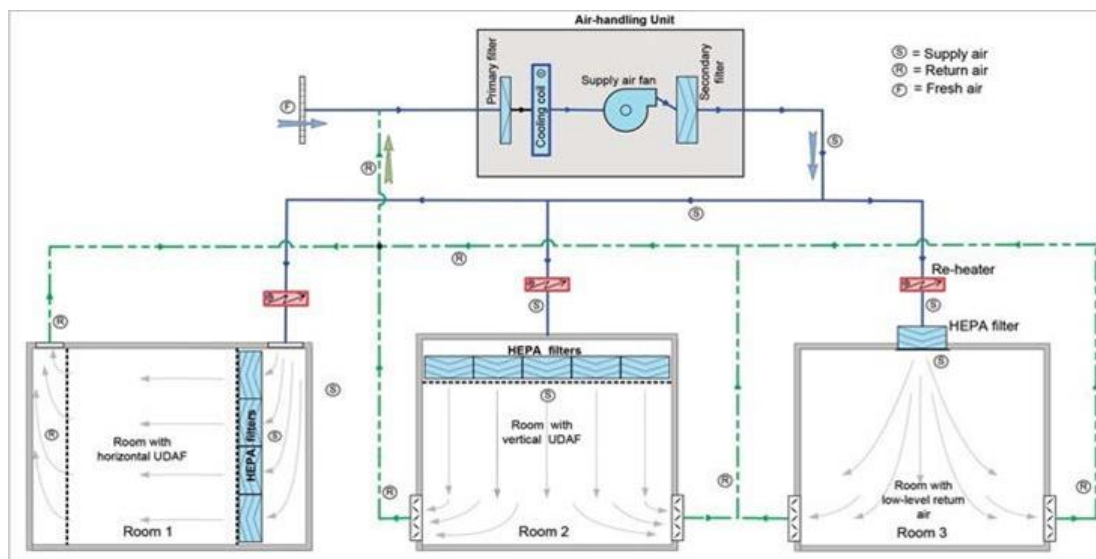
Fig. A3.14 Example of a full fresh air system



Air filtration, airflow direction and pressure differentials

- 17.99. Manufacturers should determine which classes of filters should be used in ensuring that contaminants from outside are not introduced into manufacturing areas and that where recirculation systems are used, filtration of recirculated air is carried out effectively, to ensure that there is no risk of cross-contamination.
- 17.100. Where different products are manufactured in different rooms in the same facility at the same time, appropriate controls should be in place to ensure containment and prevention of contamination and cross-contamination.
- 17.101. When a manufacturer chooses to install HEPA filters to achieve the desired degree of filtration of air, these filters may be placed in the AHU, or may be installed terminally near the supply grille.
- 17.102. The number of air changes or air-exchange rates should be sufficient. A guidance value is between 6 and 20 air changes per hour. Manufacturers should also establish how much time it takes for a room that is out of its classification to return within the specified class. This is often referred to as clean up or recovery time. A guidance period for clean up or recovery is about 15–20 minutes.
- 17.103. Airflow directions should be specified and proven to promote containment and not be adversely affected or obstructed by equipment, utilities, containers or personnel. The location of supply and return or exhaust air grilles should facilitate appropriate air flow directions in an area. Fig. A3.15 is a schematic diagram of an example of an air-handling system serving rooms with horizontal directional flow, vertical directional flow and turbulent flow, for rooms 1, 2 and 3, respectively. In these rooms, the HEPA filters are indicated to have been placed terminally mounted in the rooms and not in the AHU. Whenever HEPA filters are terminally mounted, it can assist with preventing cross-contamination from room to room in the event of a fan failure.

Fig. A3.15: Example of horizontal airflow, vertical flow and turbulent flow



Commissioning, Qualification and maintenance of HVAC system

- 17.104. Commissioning should include the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that it meets all the requirements, as specified in the user requirement specification (URS), and capacities as specified by the designer or developer. The installation records of the system should provide documented evidence of all measured capacities of the system.
- 17.105. The data should include items such as the design and measurement figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).
- 17.106. Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation. Training should be provided to personnel after installation of the system, and should include operation and maintenance. Commissioning should be a precursor to system qualification and process validation.
- 17.107. Based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include: temperature, relative humidity, supply air quantities for all diffusers, return air or exhaust air quantities, room air change rates, room pressures (pressure differentials), room airflow patterns, unidirectional flow velocities, containment system velocities, HEPA filter penetration tests, room particle counts, room clean-up rates, microbiological air and surface counts where appropriate, operation of de-dusting, warning/alarm systems where applicable.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

17.108. Periodic re-qualification of parameters should be done at regular intervals, e.g. annually. Re-qualification should also be done when any change, which could affect system performance, takes place.

17.109. There should be a planned preventive maintenance program, procedures and records for the HVAC system. Records should be kept. Maintenance personnel should receive appropriate training. Maintenance activities should normally be scheduled to take place outside production hours, and any system stoppage should be assessed with a view to the possible need for re-qualification of an area as a result of an interruption of the service.

ANNEX I- MANUFACTURE OF STERILE MEDICINAL PRODUCTS

PRINCIPLE

The manufacture of sterile products covers a wide range of sterile product types (such as active substances, excipients, primary packaging materials and finished dosage forms), packed sizes (single unit and multiple units), processes (from highly automated systems to manual processes) and technologies (for example, biotechnology, small molecule manufacturing, and closed systems). This guideline provides general guidance that should be used in the design and control of premises, equipment, utilities, systems and procedures used for the manufacture of all sterile products. The principles of quality risk management should be applied to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

General

1. The manufacture of sterile products is subject to specific requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. As a minimum, the following areas should be considered:
 - i. Premises, equipment and process should be appropriately designed, qualified and validated and, where applicable, be subjected to ongoing verification according to the relevant sections of the good manufacturing practices (GMP) guide. The use of appropriate technologies (such as restricted access barrier systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential sources of endotoxin/pyrogen, particulate and microbial contamination, such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.
 - ii. Personnel should have adequate qualifications, experience, and training. They should behave in a manner that ensures the protection of sterile product during the manufacturing, packaging and distribution processes.
 - iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

with appropriate process, engineering and microbiological knowledge and experience.

- iv. Raw materials and packaging materials should be adequately controlled and tested for bioburden and endotoxin/pyrogen. These materials should meet their specification and should be suitable for use.
2. Processes, equipment, facilities and manufacturing activities should be managed in accordance with the principles of quality risk management to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale and scientific justification. Quality risk management principles should cover the appropriate design of the facility, equipment and processes, as well as well designed procedures, and the application of monitoring systems that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.
3. A Contamination control strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational) and monitoring measures employed to manage risks to medicinal product quality. The combined strategy of the CCS should provide robust assurance of contamination prevention. The CCS should be reviewed periodically and, where appropriate, updated to drive continual improvement. Its effectiveness should be reviewed as part of the periodic management review process. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.
4. Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources should include a series of interrelated events and measures. These should be assessed and controlled and their effectiveness monitored individually and collectively.
5. The manufacturer should take all necessary steps and precautions to ensure the sterility of the products manufactured. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product testing.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

6. Cleanroom classification is part of the cleanroom qualification and is a method of confirming the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the particle concentration. Classification activities should be scheduled and performed in order to avoid any impact on process or product quality. For example, initial classification should be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation (APS).
7. For classification of the cleanroom, the minimum number of sampling locations and their positioning can be found in ISO 14644 Part 1. For the aseptic processing area and the background environment (the grade A and B areas, respectively) additional sample locations should be considered, and all critical processing areas, such as the point of fill and container closure feeder bowls, should be evaluated. Critical processing locations should be determined by documented risk assessment and knowledge of the process and operations to be performed in the area.
8. For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 μm should be measured. Maximum permitted particle concentration limits are specified in Table 1 below

Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle $\geq 0.5 \mu\text{m}/\text{m}^3$		Maximum limits for total particle $\geq 5 \mu\text{m}/\text{m}^3$	
	At rest	In operation	At rest	In operation
A	3 520	3 520	Not specified ^a	Not specified ^a
B	3 520	352 000	Not specified ^a	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined ^b	29 300	Not predetermined ^b

a Classification including 5 μm particles may be considered where indicated by the CCS or historical trends.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

b For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

- i. Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles $\geq 5.0\mu\text{m}$ in remote sampling systems with long lengths of tubing. Isokinetic sample heads should be used in unidirectional airflow systems.
 - ii. “In operation” classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.
9. Cleanroom classification should be carried out in the at rest and in operation states.
 - i. The definition of the at rest state is the condition whereby the installation of all the utilities is complete, including any functioning HVAC, with the main manufacturing equipment installed as specified but not operating and without personnel present in the room.
 - ii. The definition of the in operation state is the condition whereby the installation of the cleanroom is complete, the HVAC system fully operational, and the equipment is installed and functioning in the manufacturer’s defined operating mode, with the maximum number of personnel present performing or simulating routine operational work. The total particle limits given in Table.1 above for the at rest state should be achieved after a clean-up period upon completion of operations and line clearance or cleaning activities. The clean-up period (guidance value of less than 20 minutes) should be determined during the qualification of the rooms, documented, and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.
10. The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol, including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working

position (for example, where high-risk operations occur and where product or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36–0.54 metres per second (m/s) (guidance value) at the working level, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.

Premises

11. The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through change rooms that act as airlocks. Cleanrooms and change rooms should be maintained at an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.
12. The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix-up and contamination.
13. RABS or isolators may be beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be documented in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.
14. Four grades of cleanrooms or zones are normally used for the manufacture of sterile products.

Grade A. This is the critical zone for high-risk operations (for example, aseptic processing line, filling zone, stopper bowl, open primary packaging, or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localized airflow protection, such as unidirectional airflow work stations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (for example, without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

Grade B. For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Where applicable, air pressure differential between grade B and an adjacent area should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used.

Grades C and D. These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation or filling of terminally, sterilized products (see section 8 for specific details on terminal sterilization activities).

15. In cleanrooms and critical zones, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms.
16. To reduce accumulation of dust and to facilitate cleaning, there should be no recesses that are difficult to clean effectively. Projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed to avoid recesses that cannot be cleaned. Sliding doors may be undesirable for this reason.
17. Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles. These should permit the repeated application of cleaning, disinfecting and sporicidal agents where used.
18. Ceilings should be designed and sealed to prevent contamination from the space above them.
19. Sinks and drains should be prohibited in the grade A and B areas. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower-grade cleanrooms should be fitted with traps or water seals designed to prevent backflow and should be regularly cleaned, disinfected and maintained.
20. The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed, and if they cannot be eliminated appropriate, controls should be implemented.

21. The transfer of materials, equipment and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilized and passed into these areas through double-ended sterilizers (for example, through a double-door autoclave or de-pyrogenation oven or tunnel) sealed into the wall. Where sterilization upon transfer of the items is not possible, a procedure that achieves the same objective of not introducing contamination should be validated and implemented (for example, using an effective transfer disinfection process, rapid transfer systems or ports for isolators, or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (such as materials, waste and environmental samples) should be carried out via a separate unidirectional process. If this is not possible, time-based separation of movement (incoming or exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.
22. Airlocks should be designed and used to provide physical separation and to minimize microbial and particle contamination of the different areas, and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel or material) by procedure should be considered. Airlocks should be effectively flushed with filtered air to ensure that the grade of the cleanroom is maintained. The final airlock should, in the at rest state, be of the same cleanliness grade (viable and total particle) as the cleanroom into which it leads. The use of separate change rooms for entering and leaving the grade B area is desirable. Where this is not practical, time-based separation of activities (inward or outward) by procedure should be considered. Where the CCS indicates that the risk of contamination is high, separate change rooms for entering and leaving production areas should be used. Airlocks should be designed as follows:
 - i. Personnel airlocks: areas of increasing cleanliness used for entry of personnel (for example, from the grade D area to the grade C area to the grade B area). In

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

general, handwashing facilities should be provided only in the first change room and should not be present in change rooms directly accessing the grade B area.

- ii. Material airlocks: used for materials and equipment transfer.
 - Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process should be transferred into the grade A or B areas via an airlock or pass-through hatch. Equipment and materials intended for use in the grade A area should be protected when transiting through the grade B area. Any unapproved items that require transfer should be preapproved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.
 - Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with active filtered air supply of appropriate grade in accordance with the CCS.
 - The movement of material or equipment from lower-grade or unclassified areas to higher-grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.
23. For pass-through hatches and airlocks (for material and personnel), the entry and exit doors should not be opened simultaneously. For airlocks leading to the grade A and B areas, an interlocking system should be used. For airlocks leading to grade C and D areas, a visual or audible warning system should be operated as a minimum. Where required to maintain area segregation, a time delay between the closing and opening of interlocked doors should be established and validated.
24. Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure differential of a minimum of 10 pascals (guidance value). Particular attention should be paid to the protection of the critical

zone. The recommendations regarding air supplies and air pressures may need to be modified where it is necessary to contain certain materials (such as pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination (for example, of the cleanrooms and the heating, ventilation and air-conditioning (HVAC) systems) and the treatment of air leaving a clean area may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be an area of the same or higher grade.

25. Airflow visualization studies should demonstrate airflow patterns within cleanrooms and zones proving that there is no ingress from lower-grade to higher-grade areas and that air does not flow from less clean areas (such as the floor) or over operators or equipment, thus transferring contaminants to the higher-grade areas. Where unidirectional airflow is required, visualization studies should be performed to demonstrate compliance (refer to paragraphs 15.107). When filled and closed products are transferred to an adjacent cleanroom of a lower grade via a small exit point, airflow visualization studies should demonstrate that there is no ingress from the lower-grade cleanroom to the grade B area. Where air movement is shown to be a contamination risk to the clean area or critical zone, corrective action, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (for example, simulating operator interventions). Video recordings of the airflow patterns should be carried out by following good practices to demonstrate the above. Recordings should be retained. The outcome of the air visualization studies should be documented and taken into consideration when establishing the facility's environmental monitoring program.
26. Indicators of air pressure differential should be fitted between cleanrooms and between isolators and their background. Set points and the criticality of air pressure differential should be considered within the CCS. Air pressure differentials identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differential (below set limits for those identified as critical). The warning signal should not be overridden without appropriate assessment and a procedure should

be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differentials should be monitored and recorded at regular intervals.

27. Facilities should be designed to permit observation of production activities from outside the grade A and B areas (for example, through the provision of windows or remote cameras with a full view of the area and processes to enable observation and supervision without entry). This requirement should be considered when designing new facilities or during the refurbishment of existing facilities.

Barrier technologies

28. Isolators and RABS, which are different technologies, and the associated processes, should be designed to provide protection through separation of its grade A environment and the surrounding environment. The hazards introduced from entry or removal of items during processing should be minimized and supported by high-capability transfer technologies or validated systems that effectively prevent contamination and are appropriate for the respective technology.
29. The design of the technology and processes used should ensure that appropriate conditions are maintained in the critical zone to protect the exposed product during operations.

i. Isolators:

- a) The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
- b) The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase the risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.

- c) Negative pressure isolators should only be used when containment of the product is considered essential (for example, radiopharmaceutical products) and specialized risk control measures should be applied to ensure the critical zone is not compromised.

ii. RABS:

- a) The design of RABS should ensure grade A conditions with unidirectional airflow and first air protection in the critical zone. A positive airflow from the critical zone to the supporting background environment should be maintained.

30. The background environment for isolators and RABS should ensure that the risk of transfer of contamination is minimized.

i. Isolators:

- a) The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the CCS.
- b) Key considerations when performing the risk assessment for the CCS of an isolator should include the bio decontamination programme, the extent of automation, the impact of glove manipulations that may potentially compromise first air protection of critical process points, the impact of potential loss of barrier or glove integrity, transfer mechanisms used, and activities such as set-up or maintenance that may require the doors to be opened prior to the final biodecontamination of the isolator. Where additional process risks are identified, a higher grade of background should be considered unless appropriately justified in the CCS.
- c) Airflow pattern studies should be performed at the interfaces of open isolators to demonstrate the absence of air ingress.

ii. RABS:

- a) The background environment for RABS used for aseptic processing should correspond to a minimum of grade B, and airflow pattern studies should be

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

performed to demonstrate the absence of air ingress during interventions, including door openings if applicable.

31. The materials used for glove systems (for both isolators and RABS) should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.

- i. Isolators:

- a) For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally, glove integrity testing should be performed at a minimum frequency at the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary, depending on the validated campaign length. Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.
 - b) For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.
 - c) Integrity and leak testing of isolator systems should be performed at defined intervals.

- ii. RABS:

- a) For RABS, gloves used in the grade A area should be sterilized before installation and sterilized or effectively biodecontaminated by a validated method prior to each manufacturing campaign. If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed. Gloves should be visually examined with each use, and integrity testing should be performed at periodic intervals.

32. Decontamination methods (cleaning and biodecontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the biodecontamination step is essential, as any residues

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and biodecontamination agents used do not have any adverse impact on the product produced within the RABS or isolator.

i. Isolators:

- a) The biodecontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (for example, gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure overall contact with the agent. Methods used (cleaning and sporicidal biodecontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.

ii. RABS:

- a) The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to effectively include all areas of the interior surfaces and ensure a suitable environment for aseptic processing.

Disinfection

33. The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written program. For disinfection to be effective, cleaning to remove surface contamination should be performed prior to disinfection. Cleaning programs should effectively remove disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection program and to detect changes in types of microbial flora (for example, organisms resistant to the disinfection regime currently in use).
34. The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.

35. Disinfectants and detergents used in grade A and B areas should be sterile. Disinfectants used in grade C and D areas may also be required to be sterile where determined in the CCS. Where the disinfectants and detergents are diluted or prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination, and they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned (and sterilized, where applicable) containers and should only be stored for the defined period. If the disinfectants and detergents are supplied ready-made, then results from certificates of analysis or conformance can be accepted, subject to successful completion of the appropriate vendor qualification.
36. Where fumigation or vapor disinfection (for example, vapor phase hydrogen peroxide) of cleanrooms and associated surfaces is used, the effectiveness of the fumigation agent and dispersion system should be validated.

Equipment

37. A detailed written description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification documentation and be kept up to date.
38. Equipment monitoring requirements should be defined in user requirements specifications during early stages of development, and confirmed during qualification. Process and equipment alarm events should be acknowledged and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).
39. As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel and generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be performed where appropriate. If sterilization

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

of equipment is required, it should be carried out, wherever possible, after complete reassembly.

40. The validated cleaning procedure should be able to:
 - i. remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used;
 - ii. minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.
41. For aseptic processes, direct and indirect product contact parts should be sterilized. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product but may be exposed to other sterilized surfaces, the sterility of which is critical to the overall product sterility (for example, sterilized items such as stopper bowls and guides, and sterilized components).
42. All equipment, such as sterilizers, air-handling systems (including air filtration systems) and water systems, should be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance or repairs, their return to use should be approved.
43. Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.
44. A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (for example, in a sterilizing tunnel).
45. Particle counters, including sampling tubing, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1 m unless justified, and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

positioned as close as possible to the critical location to ensure that samples are representative.

Utilities

46. The nature and extent of controls applied to utility systems should be Commensurate with the risk to product quality associated with the utility. The impact should be determined through risk assessment and documented as part of the CCS.
47. In general, higher-risk utilities are those that:
 - i. directly contact product (for example, water for washing and rinsing, gases and steam for sterilization);
 - ii. contact materials that will ultimately become part of the product;
 - iii. contact surfaces that come into contact with the product;
 - iv. otherwise directly impact the product.
48. Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner that ensures that the utility system functions as expected.
49. Results for critical parameters and critical quality attributes of high-risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.
50. Records of utility system installation should be maintained throughout the system's life cycle. Such records should include current drawings and schematic diagrams, construction material lists and system specifications.

Typically, important information includes attributes such as:

- i. pipeline flow direction, slope, diameter and length
 - ii. tank and vessel details
 - iii. valves, filters, drains, sampling points and user points.
51. Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.

Water systems

52. Note: Refer to chapter Fifteen of this guidelines the main principles on water systems; and the minimum requirements for the quality of water for injection. Water treatment plant and distribution systems should be designed, constructed, installed, commissioned, qualified, monitored and maintained to prevent microbiological contamination and to ensure a reliable source of water of an appropriate quality. Measures should be taken to minimize the risk of presence of particulates, microbial contamination and proliferation, and endotoxin/pyrogen (for example, by sloping pipes to provide complete drainage and the avoidance of dead legs). Where filters are included in the system, special attention should be given to their monitoring and maintenance. Water produced should comply with the current monograph of the relevant pharmacopoeia.
53. Water systems should be qualified and validated to maintain the appropriate levels of physical, chemical and microbial control, taking the effect of seasonal variation into account.
54. Water flow should remain turbulent through the pipes in water distribution systems to minimize the risk of microbial adhesion and subsequent biofilm formation. The flow rate should be verified during qualification and be routinely monitored.
55. Water for injection (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner that minimizes the risk of microbial growth (for example, by constant circulation at a temperature above 70 °C). WFI should be produced by distillation or other suitable means. These may include reverse osmosis coupled with other appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.
56. Where storage tanks for water for pharmaceutical use and WFI are equipped with hydrophobic bacteria-retentive vent filters, the filters should not be a source of contamination and the integrity of the filter should be tested before installation and after use. Controls should be in place to prevent condensation formation on the filter (for example, heating).

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

57. To minimize the risk of biofilm formation, sterilization, sanitization, disinfection or regeneration, as appropriate, of water systems should be carried out according to a predetermined schedule and as a remedial action following out-of-limit or specification results. Disinfection of a water system with chemicals should be followed by a validated rinsing or flushing procedure. Water should be tested after disinfection or regeneration.
58. Chemical testing results should be approved before the water system is returned to use and microbiological (endotoxin, where appropriate) results verified to be within specification and approved before batches manufactured using water from the system are considered for certification or release.
59. Regular ongoing chemical and microbial monitoring of water systems should be performed to ensure that the water continues to meet compendial expectations. Alert levels should be based on the initial qualification data and thereafter periodically reassessed on data obtained during subsequent requalification, routine monitoring and investigations.
60. The review of ongoing monitoring data should be carried out to identify any adverse trend in system performance. Sampling programs should reflect the requirements of the CCS and should include all outlets and points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. Sample plans should be based on the qualification data, should consider the potential worst case sampling locations and should ensure that at least one representative sample is included every day of the water that is used for manufacturing processes.
61. Alert level excursions should be documented and reviewed, and include an investigation to determine whether the excursion is a single (isolated) event or if results are indicative of an adverse trend or system deterioration. Each action limit excursion should be investigated to determine the probable root causes and any potential impact on the quality of product and manufacturing processes because of the use of the water.

WFI systems should include continuous monitoring systems, for example for total organic carbon and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk.

Steam used as a direct sterilizing agent

62. Feed water to a pure steam (clean steam) generator should be appropriately purified.
63. Pure steam generators should be designed, qualified and operated in a manner that ensures that the quality of steam produced meets defined chemical and endotoxin levels.
64. Steam used as a direct sterilizing agent should be of suitable quality and should not contain additives at a level that could cause contamination of product or equipment. For a generator supplying pure steam used for the direct sterilization of materials or product contact surfaces (such as porous hard-good autoclave loads), steam condensate should meet the current monograph for WFI of the relevant pharmacopoeia (microbial testing is not mandatory for steam condensate). A suitable sampling schedule should be in place to ensure that the sample for analysis is collected on a regular basis. The sample should be representative of the pure steam. Other aspects of the quality of pure steam used for sterilization should be assessed periodically against parameters. These parameters should include the following (unless otherwise justified) non-condensable gases, dryness value (dryness fraction) and superheat.

Gases and vacuum systems

65. Gases that come in direct contact with the product or primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the gas and the design of the gas generation system, and, where applicable, should comply with the current monograph of the relevant pharmacopoeia or the product quality requirement.
66. Gases used in aseptic processes should be filtered through a sterilizing grade filter (with a nominal pore size of a maximum of 0.22 μm) at the point of use. Where the filter is used on a batch basis (for example, for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results reviewed as part of the batch certification and release process. Any transfer pipework or tubing that is located after the final sterilizing grade filter should be sterilized. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.

67. Where backflow from vacuum or pressure systems poses a potential risk to the product, there should be a mechanism to prevent backflow when the vacuum or pressure system is shut off

Heating and cooling and hydraulic systems

68. Major items of equipment associated with hydraulic, heating and cooling systems should, where possible, be located outside the filling room. There should be appropriate controls to contain any spillage or cross contamination associated with the system fluids.
69. Any leaks from these systems that would present a risk to the product should be detectable (for example, using an indication system for leakage).

Personnel

70. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.
71. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.
72. Personnel, including those performing cleaning, maintenance and monitoring and those that access cleanrooms, should receive regular training and undergo gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology and hygiene (with a specific focus on cleanroom practices), contamination control, aseptic techniques and the protection of sterile products (for those operators entering the grade B cleanrooms or intervening into grade A), and the potential safety implications for the patient if the product is not sterile. The level of training should be based on the criticality of the function and area in which the personnel are working.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

73. The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviors. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment using monitoring locations such as gloved fingers, forearms, chest and hood (face mask and forehead). Unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful APS.
74. Unqualified persons should not enter grade B cleanrooms or grade A when in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified persons are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified persons during their activities and should assess the impact of these activities on the cleanliness of the area. Access by these persons should be assessed and recorded in accordance with the PQS.
75. There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on specified aspects, including ongoing assessment or identification of an adverse trend from the personnel monitoring program or implication in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering grade B cleanrooms or performing intervention into grade A, this requalification should include consideration of participation in a successful APS.
76. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.
77. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition, which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

who could be introducing undue microbiological hazard should be decided by a designated qualified person.

78. Wristwatches, make-up and jewelry should not be worn in clean areas.
79. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.
80. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.
81. The description of clothing required for each grade is given below:
 - a) Grade B (including access or interventions into grade A). Appropriate garments that are dedicated for use under a sterilized suit should be worn before gowning appropriately sterilized, non-powdered, rubber or plastic gloves should be worn while donning the sterilized garments. Sterile headgear should enclose all hair (including facial hair) and, where separate from the rest of the gown, should be tucked into the neck of the sterile suit. A sterile facemask and sterile eye coverings (such as goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. The appropriate sterilized footwear (such as over boots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibers and other particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.
 - b) Grade C, Hair, beards and moustaches should be covered. A single- or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected

shoes or overshoes should be worn. They should minimize the shedding of fibres and particles.

- c) Grade D. Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. The appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.
- d) Additional gowning, including gloves and a face mask, may be required in grade C and D areas when performing activities considered to be a contamination risk, as defined by the CCS.

- 82. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.
- 83. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants that can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibers and may increase the risk of shedding of particles.

Production and specific technologies

Terminally Sterilized Products

- 84. Preparation of components and materials should be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/ pyrogen and particle contamination, so that the product is suitable for sterilization. Where the product is at a high or unusual risk of microbial contamination (for example, the product actively supports microbial growth and must be held for long periods before filling, or the product is not processed mostly in closed vessels), then preparation should be carried out in at least a grade C environment. The preparation of ointments, creams, suspensions and emulsions should be carried out in at least a grade C environment before terminal sterilization.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

85. Primary packaging containers and components should be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.
86. The filling of products for terminal sterilization should be carried out in at least a grade C environment.
87. Where the CCS identifies that the product is at an unusual risk of contamination from the environment – for example, when the filling operation is slow or when the containers are wide necked or are necessarily exposed for more than a few seconds before closing then the product should be filled in grade A with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilization.
88. The processing of the bulk solution should include a filtration step with a microorganism-retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers. The maximum permissible time between preparation and filling should be defined.
89. Examples of operations to be carried out in the various grades are given in Table 2

Table 2: Examples of operations and grades for terminally sterilized preparation and processing operations

Grade	Operation
Grade A	<ul style="list-style-type: none">• Filling of products, when unusually at risk
Grade C	<ul style="list-style-type: none">• Preparation of solutions, when unusually at risk• Filling of products
Grade D	<ul style="list-style-type: none">• Preparation of solutions and components for subsequent filling

Aseptic Preparation and Processing

90. The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.

91. Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilization), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibers should be minimized in cleanrooms.
92. Where possible, the use of equipment such as RABS, isolators or other systems should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (for example, dry heat tunnel, automated lyophilizer loading, sterilization in place).
93. Examples of operations to be carried out in the various environmental grades are given in Table 3.

Table 3 Examples of operations and grades for aseptic preparation and processing operations

Grade	Operation
Grade A	<ul style="list-style-type: none">• Aseptic assembly of filling equipment• Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing grade filter; these connections should be sterilized by steam-in-place whenever possible• Aseptic compounding and mixing• Replenishment of sterile bulk product, containers and closures• Removal and cooling of unprotected (e.g. with no packaging) items from sterilizers• Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

	<ul style="list-style-type: none">• Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials• Loading of a lyophilizer
Grade B	<ul style="list-style-type: none">• Background support for grade A (when not in an isolator)• Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A
Grade C	<ul style="list-style-type: none">• Preparation of solutions to be filtered, including sampling and dispensing
Grade D	<ul style="list-style-type: none">• Cleaning of equipment• Handling of components, equipment and accessories after cleaning• Assembly under high-efficiency particulate air (HEPA)-filtered airflow of cleaned components, equipment and accessories prior to sterilization• Assembly of closed and sterilized SUS using intrinsic sterile connection devices

94. For sterile products where the final formulation cannot be filtered, the following should be considered:

- i. All product and component contact equipment should be sterilized prior to use.
- ii. All raw materials or intermediates should be sterilized and aseptically added.
- iii. Bulk solutions or intermediates should be sterilized.

95. The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background.

96. Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in grade A with a grade B background when the product

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

and components are exposed to the environment and the product is not subsequently filtered (via a sterilizing grade filter) or terminally sterilized.

97. Aseptic connections should be performed in grade A with a grade B background unless subsequently sterilized in place or conducted with intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Intrinsic sterile connection devices should be designed to mitigate risk of contamination.
98. Aseptic connections should be appropriately assessed and their effectiveness verified (for requirements regarding intrinsic sterile connection devices).
99. Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized using engineering design solutions such as preassembled and sterilized equipment. Whenever feasible, product contact piping and equipment should be preassembled and sterilized in place.
100. There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production. Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized. The process of designing interventions should include the consideration of any impact on airflows and critical surfaces and products. Operators should use engineering solutions whenever possible to minimize incursion during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and aseptic process simulation and should be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorization of the quality unit. The details of the intervention conducted should be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.
101. Interventions and stoppages should be recorded in the batch record. Each line stoppage or intervention should be sufficiently documented in batch records with the associated time, duration of the event, and operators involved.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

102. The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including:

- i. the holding time between equipment, component, and container cleaning, drying and sterilization;
- ii. the holding time for sterilized equipment, components, and containers before use and during filling or assembly;
- iii. the holding time for a decontaminated environment, such as the RABS or isolator before use;
- iv. the time between the start of the preparation of a product and its sterilization or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process (there should be a maximum permissible time defined for each product that takes into account its composition and the prescribed method of storage);
- v. the holding time for sterilized product prior to filling;
- vi. the aseptic processing time;
- vii. the filling time.

103. Personnel (independent from the aseptic operation) with specific expertise in aseptic processing to verify the correct performance of operations, including operator behavior in the cleanroom, and to address inappropriate practices if detected should monitor aseptic operations (including aseptic process simulation) on a regular basis. Records should be maintained.

FORM-FILL_SEAL (FFS)

104. The conditions for FFS machines used for terminally sterilized product should comply with the environmental requirements of paragraph 27 of this guideline. The conditions for FFS machines used in aseptic manufacture should comply with the environmental requirements of Paragraph 86 of this guideline.

105. Contamination of the packaging films used in the FFS process should be minimized by appropriate controls during component production, supply and handling. Due to the criticality of packaging films, procedures should be implemented to ensure that the films supplied meet defined specifications and are of the appropriate quality, including material thickness and strength, microbial and particulate contamination, integrity and

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

artwork, as relevant. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of packaging films and associated components should be defined and controlled within the PQS and considered in the CCS.

106. Particular attention should be given to understanding and assessing the operation of the equipment, including set-up, filling, sealing and cutting processes, so that critical process parameters are understood, validated, controlled and monitored appropriately.

107. Any product contact gases (such as those used to inflate the container or used as a product overlay) should be appropriately filtered, as close to the point of use as possible. The quality of gases used and the effectiveness of gas filtration systems should be verified periodically in accordance with 60 and 61.

108. The controls identified during qualification of FFS should be in alignment with the CCS. Aspects to be considered include:

- i. determination of the boundaries of the critical zone;
- ii. environmental control and monitoring of both the machine and the background in which it is placed;
- iii. personnel gowning requirements;
- iv. integrity testing of the product filling lines and filtration systems as relevant;
- v. duration of the batch or filling campaign;
- vi. control of packaging films, including any requirements for film decontamination or sterilization;
- vii. cleaning in place and sterilization in place of equipment, as necessary;
- viii. machine operation, settings and alarm management, as relevant.

109. Critical process parameters for FFS should be determined during equipment qualification and should include:

- i. settings for uniform package dimensions and cutting in accordance with validated parameters;
- ii. setting, maintenance and monitoring of validated forming temperatures (including preheating and cooling), forming times and pressures, as relevant;
- iii. setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures, as relevant;

- iv. environmental and product temperature;
 - v. batch-specific testing of package seal strength and uniformity;
 - vi. settings for correct filling volumes, speeds and uniformity;
 - vii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised;
 - viii. methods and parameters for integrity testing of filled containers
110. The appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.
111. Operational procedures should describe how forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.
112. The appropriate maintenance procedures should be established based on risk, and should include maintenance and inspection plans for tooling critical to the effectiveness of unit sealing. Any issues identified that indicate a potential product quality concern should be documented and investigated.

Blow-fill-seal (BFS)

113. BFS equipment used for the manufacture of products that are terminally sterilized should be installed in at least a grade D environment. The conditions at the point of fill should comply with the environmental requirements.
114. BFS used for aseptic processing:
- i. For shuttle type equipment used for aseptic filling, the parison is open to the environment. Therefore, the areas where parison extrusion, blow moulding and sealing take place should meet grade A conditions at the critical zones. The filling environment should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
 - ii. For rotary-type equipment used for aseptic filling, the parison is generally closed to the environment once formed. The filling environment within the parison should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
 - iii. The equipment should be installed in at least a grade C environment, provided that grade A/B clothing is used. The microbiological monitoring of operators

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

wearing grade A/B clothing in a grade C area should be performed in accordance with risk management principles. The limits and monitoring frequencies should be applied with consideration of the activities performed by these operators.

115. Due to the generation of particles from polymer extrusion, cutting during operation, and the restrictive size of critical filling zones of BFS equipment, in operation monitoring of total particle for BFS equipment is not expected. However, data should be available to demonstrate that the design of the equipment ensures that critical zones of the filling process environment would meet grade A conditions in operation.
116. Viable environmental monitoring of BFS processes should be risk based and designed in accordance with section 9 of this guideline. In operation viable monitoring should be undertaken for the full duration of critical processing, including equipment assembly. For rotary-type BFS equipment, it is acknowledged that monitoring of the critical filling zone may not be possible.
117. The environmental control and monitoring program should take into consideration the moving parts and complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process (for example, through the use of airflow visualization studies or other equivalent studies). Environmental monitoring programs should also consider factors such as air filter configuration, air filter integrity, cooling system integrity (refer to paragraph 63), equipment design and qualification.
118. Air or other gases that make contact with critical surfaces of the container during extrusion, formation or sealing of the molded container should undergo appropriate filtration. The quality of gas used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 60 and 61.
119. Particulate and microbial contamination of the polymer granulate should be prevented by the appropriate design, control and maintenance of the polymer granulate storage, sampling and distribution systems.
120. The capability of the extrusion system to provide appropriate sterility assurance for the molded container should be understood and validated. The sampling frequency, the

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

bioburden and, where applicable, endotoxin/ pyrogen levels of the raw polymer should be defined and controlled within the PQS and considered in the CCS.

121. Interventions requiring cessation of filling or extrusion, molding and sealing and, where required, re-sterilization of the filling machine should be clearly defined and described in the filling procedure, and included in the APS.

122. The controls identified during qualification of BFS should be in alignment with the site's CCS. Aspects to be considered include:

- i. determination of the boundaries of the critical zone;
- ii. environmental control and monitoring of both the machine and the background in which it is placed;
- iii. personnel gowning requirements;
- iv. integrity testing of the product filling lines and filtration systems, as relevant;
- v. duration of the batch or filling campaign;
- vi. control of polymer granulate, including distribution systems and critical extrusion temperatures;
- vii. cleaning in place and sterilization in place of equipment, as necessary;
- viii. machine operation, settings and alarm management, as relevant.

123. Critical process parameters for BFS should be determined during equipment qualification and should include:

- i. cleaning in place and sterilization in place of product pipelines and filling needles (mandrels);
- ii. setting, maintenance and monitoring of extrusion parameters, including temperature, speed and extruder throat settings for parison thickness;
- iii. setting, maintenance and monitoring of mold temperatures, including rate of cooling where necessary for product stability;
- iv. preparation and sterilization of ancillary components added to the molded unit, such as bottle caps;
- v. environmental control, cleaning, sterilization and monitoring of the critical extrusion, transfer and filling areas, as relevant
- vi. batch-specific testing of package wall thickness at critical points of the container;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- vii. settings for correct filling volumes, speeds and uniformity;
- viii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality are not compromised;
- ix. methods and parameters for integrity testing of 100% of all filled containers
- x. settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).

124. The appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.

125. Operational procedures should describe how blowing, forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.

126. Where the BFS process includes the addition of components to molded containers (for example, addition of caps to large-volume parenteral bottles), these components should be appropriately decontaminated and added to the process using a clean, controlled process.

- i. For aseptic processes, the addition of components should be performed under grade A conditions to ensure the sterility of critical surfaces using pre-sterilized components.
- ii. For terminally sterilized products, the validation of terminal sterilization processes should ensure the sterility of all critical product pathways between the component and molded container, including areas that are not wetted during sterilization.
- iii. Testing procedures should be established and validated to ensure the effective sealing of components and molded containers.

127. The appropriate maintenance procedures should be established based on risk, and should include maintenance and inspection plans for items critical to unit sealing, integrity and sterility.

128. The molds used to form containers are considered critical equipment and any changes or modification to molds should result in an assessment of finished product container integrity and, where the assessment indicates, should be supported by validation. Any issues identified that indicate a potential product quality concern should be documented and investigated.

Lyophilization

129. Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilized product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particle contamination between the filling of products for lyophilization and completion of the lyophilization process. All control measures in place should be determined by the site's CCS.

130. The sterilization of the lyophilizer and associated equipment (such as trays and vial support rings) should be validated, and the holding time between the sterilization cycle and use appropriately challenged during APS (refer to paragraph 138). Re-sterilization should be performed following maintenance or cleaning. Sterilized lyophilizers and associated equipment should be protected from contamination after sterilization.

131. Lyophilizers and associated product transfer and loading or unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilization should be determined on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation should be sterilized before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilization should be justified and documented as part of the CCS.

132. The integrity of the lyophilizer should be maintained following sterilization and during lyophilization. The filter used to maintain lyophilizer integrity should be sterilized before each use of the system and its integrity testing results should be part of the batch certification and release. The frequency of vacuum and leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

133. Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.

134. Points to consider for the design of loading (and unloading, where the lyophilized material is still unsealed and exposed) include:

- i. Loading patterns within the lyophilizer are specified and documented.
- ii. The transfer of partially closed containers to a lyophilizer are undertaken under grade A conditions at all times and handled in a manner designed to minimize direct operator intervention. (For example, clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained. Alternatively, where supported by validation, trays closed in a grade A area and not reopened whilst in the grade B area may be used to protect partially stoppered vials (such as appropriately closed boxes).
- iii. Airflow patterns are not to be adversely affected by transport devices and venting of the loading zone.
- iv. Unsealed containers (such as partially stoppered vials) are maintained under grade A conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures.
- v. With regard to opening the lyophilizer chamber after incomplete closure or partial stoppering of product or material, product removed from the lyophilizer should remain under grade A conditions during subsequent handling.
- vi. Utensils used during loading and unloading of the lyophilizer (such as trays, bags, placing devices and tweezers) should be kept sterile.

Closed systems

135. The use of closed systems can reduce the risk of microbial, particle and chemical contamination from the adjacent environment. Closed systems should always be designed to reduce the need for manual manipulation and the associated risks.

136. It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure that sterility is achieved and maintained. The connection of

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

sterile equipment (such as tubing or pipework) to the sterilized product pathway after the final sterilizing grade filter should be designed to be connected aseptically (for example, by intrinsic sterile connection devices).

137. The appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. The appropriate system integrity tests should be considered when there is a risk of compromising product sterility. The supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

138. The background environment in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in grade A. If the system can be shown to remain integral at every usage (for example, via pressure testing and monitoring) then a lower-classified area may be used. Any transfer between classified areas should be thoroughly assessed (refer to paragraph 16). If the closed system is opened (for example, for maintenance of a bulk manufacturing line), then this should be performed in a classified area appropriate to the materials (for example, grade C for terminal sterilization processes or grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilization in the case of aseptic processes).

Single-use systems

139. Single-use systems (SUS) are those technologies used in manufacture of sterile products that are used as an alternative to reusable equipment. They can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors. SUS should be designed to reduce the need for manipulation and complexity of manual interventions.

140. There are some specific risks associated with SUS that should be assessed as part of the CCS. These risks include:

- i. the interaction between the product and product contact surface (such as adsorption, or leachables and extractables);

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- ii. the fragile nature of the system compared with fixed reusable systems;
- iii. the increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made;
- iv. the complexity of the assembly;
- v. the performance of the pre- and post-use integrity testing for sterilizing grade filters
- vi. the risk of holes and leakage;
- vii. the potential for compromising the system at the point of opening the outer packaging;
- viii. the risk of particle contamination.

141. Sterilization processes for SUS should be validated and shown to have no adverse impact on system performance.

142. The assessment of suppliers of disposable systems, including sterilization, is critical to the selection and use of these systems. For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilization of each unit should be checked on receipt.

143. The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.

144. The extractable and leachable profiles of the SUS and any impact on the quality of the product, especially where the system is made from polymer based materials, should be evaluated. An assessment should be carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk from leachable, including those that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.

145. SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single-use components is necessary where these may be exposed to more extreme conditions (such as freezing and thawing processes) during either routine processing or transportation. This should

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

include verification that intrinsic sterile connection devices (both heat sealed and mechanically sealed) remain integral under these conditions.

146. Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the product and its processes. Upon receipt, each piece of an SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (including appearance of exterior carton and product pouches) and label printing and review of attached documents (such as a certificate of conformance and proof of sterilization) should be carried out and documented prior to use.

147. The critical manual handling operations of SUS, such as assembly and connections, should be subject to the appropriate controls and verified during APS.

Sterilization

148. Where possible, the finished product should be terminally sterilized, using a validated and controlled sterilization process, as this provides greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilization, consideration should be given to using post-aseptic processing terminal heat treatment, combined with an aseptic process to give improved sterility assurance.

149. The selection, design and location of the equipment and cycle or programme used for sterilization should be based on scientific principles and data that demonstrate repeatability and reliability of the sterilization process. All parameters should be defined and, where critical, these should be controlled, monitored and recorded.

150. All sterilization processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilized and its sterilization.

151. Before any sterilization process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilizing conditions in all parts of each type of load to be processed, should be validated – notably by physical measurements and, where appropriate, by biological indicators.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

152. For effective sterilization, the whole of the product and surfaces of equipment and components should be subject to the required treatment, and the process should be designed to ensure that this is achieved.
153. Particular attention should be given when the adopted product sterilization method is not described in the current edition of the pharmacopoeia, or when it is used for a product that is not a simple aqueous solution. Where possible, heat sterilization is the method of choice.
154. Validated loading patterns should be established for all sterilization processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.
155. The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.
156. Routine operating parameters should be established and adhered to for all sterilization processes (for example, physical parameters and loading patterns).
157. There should be mechanisms in place to detect a sterilization cycle that does not conform to the validated parameters. Any failed sterilization or sterilization that deviates from the validated process (for example, having longer or shorter phases such as heating cycles) should be investigated.
158. Suitable biological indicators placed at appropriate locations should be considered as an additional method to support the validation of the sterilization process. Biological indicators should be stored and used according to the manufacturer's instructions. Where biological indicators are used to support validation or to monitor a sterilization process (for example, with ethylene oxide), positive controls should be tested for each sterilization cycle. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. Biological indicator results in isolation should not be used to override other critical parameters and process design elements.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

159. The reliability of biological indicators is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that biological indicator quality is not compromised. Prior to use of a new batch or lot of biological indicators, the population, purity and identity of the indicator organism of the batch or lot should be verified. For other critical parameters (such as D-value or Z-value), the batch certificate provided by the qualified supplier can normally be used.
160. There should be a clear means of differentiating products, equipment and components that have not been subjected to the sterilization process from those that have. Equipment, such as baskets or trays used to carry products and other items of equipment or components, should be clearly labelled (or electronically tracked) with the product name and batch number and an indication as to whether or not it has been sterilized. Indicators such as autoclave tape or irradiation indicators – may be used, where appropriate, to indicate whether a batch (or sub-batch material, component or equipment) has passed through a sterilization process. These indicators show only that the sterilization process has occurred; they do not indicate product sterility or achievement of the required sterility assurance level.
161. Sterilization records should be available for each sterilization run. Each cycle should have a unique identifier. Their conformity should be reviewed and approved as part of the batch certification or release procedure.
162. Where required, materials, equipment and components should be sterilized by validated methods appropriate to the specific material. Suitable protection after sterilization should be provided to prevent recontamination. If sterilized items are not used immediately after sterilization, these should be stored using appropriately sealed packaging and the established maximum hold time should be followed. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (for example, by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilization.

163. Where materials, equipment, components and ancillary items are sterilized in sealed packaging and then transferred into grade A, this should be done using appropriate, validated methods (for example, airlocks or pass through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade A and B areas.
164. Where materials, equipment, components and ancillary items are sterilized in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilization method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilization and the maximum shelf life assigned to the sterilized items. The integrity of the sterile protective barrier system for each of the sterilized items should be checked prior to use.
165. For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing but cannot be sterilized, an effective and validated disinfection and transfer process should be in place. These items, once disinfected, should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring program.

Sterilization by heat

166. Each heat sterilization cycle should be recorded either electronically or by hard copy, using equipment with suitable accuracy and precision. The system should have safeguards or redundancy in its control and monitoring instrumentation to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle (for example, by the use of duplex or double probes connected to independent control and monitoring systems).

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

167. The position of the temperature probes used for controlling and recording should be determined during the validation and selected based on system design and in order to correctly record and represent routine cycle conditions. Validation studies should be designed to demonstrate the suitability of system control and recording probe locations, and should include the verification of the function and location of these probes by the use of an independent monitoring probe located at the same position during validation.
168. The whole of the load should reach the required temperature before measurement of the sterilizing time period starts. For sterilization cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring that the load probe temperature is controlled within a defined temperature range prior to cycle commencement.
169. After completion of the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilized material should be sterilized.
170. In those cases where parametric release has been authorized, a robust system should be applied to the product life cycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed.

Moist heat sterilization

171. Moist heat sterilization can be achieved using steam (direct or indirect contact), but also includes other systems such as superheated water systems (cascade or immersion cycles) that could be used for containers that may be damaged by other cycle designs (such as BFS containers or plastic bags).
172. The items to be sterilized, other than products in sealed containers, should be dry and packaged in a protective barrier system that allows removal of air and penetration of steam and prevents recontamination after sterilization. All loaded items should be dry upon removal from the sterilizer. Load dryness should be confirmed by visual inspection as a part of the sterilization process acceptance.
173. For porous cycles (hard goods), time, temperature and pressure should be used to monitor the process and should be recorded. Each sterilized item should be inspected

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

for damage, packaging material integrity and moisture upon removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.

174. For autoclaves capable of performing pre-vacuum sterilization cycles, the temperature should be recorded at the chamber drain throughout the sterilization period. Load probes may also be used where appropriate, but the controlling system should remain related to the load validation. For steam-in-place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilization period.
175. Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature, and the minimum/maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and F0. Critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilization validation and routine cycle acceptance criteria.
176. Leak tests on the sterilizer should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilization, to a pressure lower than the environment surrounding the sterilizer.
177. There should be adequate assurance of air removal prior to and during sterilization when the sterilization process includes air purging (for example, porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or the use of an air detector system. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensate.
178. Distortion and damage of non-rigid containers that are terminally sterilized, such as containers produced by BFS or FFS technologies, should be prevented by appropriate cycle design and control (for instance, setting correct pressure, heating and cooling rates and loading patterns).
179. Where steam-in-place systems are used for sterilization (for example, for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to ensure that all parts of the system are subjected to the required

treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilized. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilized by steam-in-place it should remain integral and, where operations require, be maintained under positive pressure or otherwise equipped with a sterilizing vent filter prior to use.

180. In fluid load cycles where superheated water is used as the heat transfer medium, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.
181. Validation of the sterilization of fluid loads in a superheated water autoclave should include temperature mapping of the entire load and heat penetration and reproducibility studies. All parts of the load should heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring probes should be correlated to the worst-case positions identified during the qualification process.

Dry heat sterilization

182. Dry heat sterilization utilizes high temperatures of air or gas to sterilize a product or article. Dry heat sterilization is of particular use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as endotoxin/pyrogen and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components or equipment are exposed should produce an adequate and reproducible level of lethality and endotoxin/pyrogen inactivation or removal when operated routinely within the established limits. The process may be operated in an oven or in a continuous tunnel process (for example, for sterilization and depyrogenation of glass containers).
183. Dry heat sterilization or depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the grade A sterilizing zone by maintaining appropriate pressure differentials and airflow through the tunnel. Air pressure difference profiles should be established and monitored. Departures from

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

established limits should be investigated, where appropriate. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests (at least every six months) should be performed to demonstrate air filter integrity. Any tunnel parts that come into contact with sterilized components should be appropriately sterilized or disinfected. Critical process parameters that should be considered during validation or routine processing should include:

- i. belt speed and dwell time within the sterilizing zone;
- ii. minimum and maximum temperatures;
- iii. heat penetration of the material or article;
- iv. heat distribution and uniformity;
- v. airflows determined by air pressure differential profiles correlated with the heat distribution and penetration studies.

184. When a thermal process is used as part of the depyrogenation process for any component or product contact equipment or material, validation studies should be performed to demonstrate that the process provides a suitable F_h value and results in a minimum 3 log₁₀ reduction in endotoxin concentration. When this is attained, there is no additional requirement to demonstrate sterilization in these cases.

185. Containers spiked with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed (in respect to composition of the packaging materials, porosity, dimensions and nominal volume). Endotoxin quantification and recovery efficiency should also be demonstrated.

186. Dry heat ovens are typically employed to sterilize or depyrogenate primary packaging components, starting materials or active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower-grade clean areas throughout the sterilization and post-sterilization hold process unless the integrity of the packaging is maintained. All air entering the oven should pass through a HEPA filter. Critical process parameters that should be considered in qualification or routine processing should include:

- i. temperature;

- ii. exposure period of time;
- iii. chamber pressure (for maintenance of overpressure);
- iv. air speed
- v. air quality within the oven;
- vi. heat penetration of material or article (slow-to-heat spots);
- vii. heat distribution and uniformity;
- viii. load pattern and configuration of articles to be sterilized or depyrogenated, including minimum and maximum loads.

Sterilization by Radiation

187. Sterilization by radiation is used mainly for the sterilization of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilization.
188. Validation procedures should ensure that the effects of variation in the density of the product and packages are considered.

Sterilization with ethylene oxide

189. This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing result in the reduction of any residual ethylene oxide gas and reaction products to defined acceptable limits for the given product or material.
190. Direct contact between gas and microbial cells is essential. Precautions should be taken to avoid the presence of organisms likely to be enclosed in material, such as crystals or dried protein. The nature, porosity and quantity of packaging materials can significantly affect the process.
191. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. Where steam is used to condition the load for sterilization, it should be of an appropriate quality. The time required for this should be balanced against the opposing need to minimize the time before sterilization.
192. Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst-case locations during validation.

193. Critical process parameters that should be considered as part of the sterilization process validation and routine monitoring include:

- i. ethylene oxide gas concentration
- ii. pressure
- iii. the amount of ethylene oxide gas used
- iv. relative humidity
- v. Temperature
- vi. exposure time.

194. After sterilization, the load should be aerated to allow ethylene oxide gas or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a sterilizer chamber or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall ethylene oxide sterilization process validation.

Sterilization by filtration of products that cannot be sterilized in their final container

195. If the product cannot be sterilized in its final container, solutions or liquids should be sterilized by filtration through a sterile sterilizing grade filter (with a nominal pore size of a maximum of 0.22 μm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilized container. The selection of the filter used should ensure that it is compatible with the product and is as described in the marketing authorization.

196. Suitable bioburden reduction pre-filters or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilizing filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilization processes, an additional filtration through a sterile sterilizing grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS.

197. The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including prefilters, should be based on the critical quality attributes of the product, justified and documented. The filtration system should minimize the generation of fibers and particles and should not cause or

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

contribute to unacceptable levels of impurities or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely affected by the product to be filtered. Adsorption of product components and extraction or leaching of filter components should be evaluated.

198. The filtration system should be designed to:

- i. allow operation within validated process parameters;
- ii. maintain the sterility of the filtrate;
- iii. minimize the number of aseptic connections required between the final sterilizing grade filter and the final filling of the product;
- iv. allow cleaning procedures to be conducted as necessary;
- v. allow sterilization procedures, including sterilization in place, to be conducted as necessary;
- vi. permit in-place integrity testing of the 0.22 μm final sterilizing grade filter, preferably as a closed system, both prior to and following filtration as necessary; in-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.

199. Sterile filtration of liquids should be validated in accordance with relevant pharmacopoeial requirements. Validation can be grouped by different strengths or variations of a product but should be based on risk (for example, product and conditions). The rationale for grouping should be justified and documented.

200. During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilizing grade filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be selected and should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.

201. Filtration parameters that should be considered and established during validation should include:

- i. The wetting fluid used for filter integrity testing should be based on the filter manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- ii. If the system is flushed or integrity tested in situ with a fluid other than the product, the appropriate actions should be taken to avoid any deleterious effect on product quality.

Filtration process conditions to be considered include:

- i. fluid pre-filtration holding time and effect on bioburden;
- ii. filter conditioning, with fluid if necessary;
- iii. maximum filtration time or total time filter is in contact with the fluid;
- iv. maximum operating pressure;
- v. flow rate;
- vi. maximum filtration volume;
- vii. temperature;
- viii. the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.

202. Routine process controls should be implemented to ensure adherence to validated filtration parameters. The results of critical process parameters should be included in the batch record, including the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. Any significant difference from critical parameters during manufacturing should be documented and investigated.

203. The integrity of the sterilized filter assembly should be verified by integrity testing before use (pre-use post-sterilization integrity test or PUPSIT) to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilization due to process constraints (such as the filtration of very small volumes of solution). In these cases, an alternative approach may be taken provided that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include:

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- i. in-depth knowledge and control of the filter sterilization process to ensure that the potential for damage to the filter is minimized;
- ii. in-depth knowledge and control of the supply chain to include:
 - contract sterilization facilities
 - defined transport mechanisms
 - packaging of the sterilized filter to prevent damage to the filter during transportation and storage;
- iii. in-depth process knowledge, such as:
 - the specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test;
 - Pre-filtration and processing steps, prior to the final sterilizing grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.

204. The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing.

205. The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods, integrity testing should be carried out at installation and prior to replacement. The maximum duration of use should be specified and monitored based on risk (for example, considering the maximum number of uses and heat treatment or sterilization cycles permitted, as applicable).

206. For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.

207. If the sterilizing filtration process has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilizing unit and all filters within the system should satisfactorily pass integrity testing after use.

208. In a redundant filtration system (where a second redundant sterilizing grade filter is present as a backup but the sterilizing process is validated as only requiring one filter), a post-use integrity test of the primary sterilizing grade filter should be performed and, if it is demonstrated to be integral, then a post-use integrity test of the redundant (backup) filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, a post-use integrity test on the secondary (redundant) filter should be performed, in conjunction with an investigation and risk assessment to determine the reason for the primary filter test failure.
209. Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. In cases where a redundant filtration setup is used, it should be taken prior to the first filter. Systems for taking samples should be designed so as not to introduce contamination.
210. Liquid sterilizing grade filters should be discarded after the processing of a single batch and the same filter should not be used continuously for more than one working day unless such use has been validated.
211. Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:
- i. assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid;
 - ii. conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise the performance of the final sterilizing grade filter or filtrate quality;
 - iii. document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration, and maintain records of these controls;
 - iv. implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.

Finishing of Sterile Products

212. Open primary packaging containers should be maintained under grade A conditions with the appropriate background.
213. Filled containers should be closed by appropriately validated methods.
214. Where fusion for example, blow-fill-seal (BFS), form-fill-seal (FFS), or small- or large-volume parenteral bags, glass, close filled containers or plastic ampoules – the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small- volume containers (≤ 100 mL) closed by fusion should be subject to 100% integrity testing using validated methods. For large-volume containers (> 100 mL) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. Visual inspection is not an acceptable integrity test method.
215. Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier qualification, packaging component specifications and process knowledge.
216. Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate predetermined period prior to certification and release and during shelf life.
217. The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively affect the integrity of the container (for example, by decompression or extreme temperatures).
218. Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination, such as locating the equipment at a physically separate station equipped with adequate air extraction, and should be taken.
219. Vial capping of aseptically filled products can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials should be protected by grade A conditions up to the point of

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped. The supporting background environment of grade A air supply should meet at least grade D requirements. Where capping is a manual process, it should be performed under grade A conditions either in an appropriately designed isolator or in grade A with a grade B background.

220. Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately, qualified, automated methods for stopper height detection should be in place.
221. Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize contamination.
222. All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects.
223. When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually.
224. Where automated methods of inspection are used, the process should be validated to detect known defects (which may affect product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start-up and at regular intervals throughout the batch.
225. The results of the inspection should be recorded and defect types and numbers trended. The reject levels for the various defect types should also be trended based on statistical principles. The impact to the product on the market should be assessed as part of the investigation when adverse trends are observed.

Environmental Monitoring

226. Clean rooms and clean air devices should be routinely monitored in operation, the monitoring locations based on a formal risk analysis study, and the results obtained during the classification of rooms and/or clean air devices.
227. For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.
228. The grade A area should be monitored continuously (for particles ≥ 0.5 and ≥ 5 μm) and with a suitable sample flow rate (at least 28 liters per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms, including the consideration of additional microbial monitoring.
229. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.
230. The monitoring of grade A should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination of the sterile equipment surfaces, containers, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.
231. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.

232. In Grade A and B zones, the monitoring of the $\geq 5.0\mu$ particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of $\geq 5.0\mu$ particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation. The particle limits given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes in an unmanned state after completion of operations.

233. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.

234. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard. Examples of operations to be carried out in the various grades are given in the table four below:

Grade	Examples of operations for terminally sterilized products
A	Filling of products, when unusually at risk
C	Preparation of solution, when unusually at risk. Filling of products
D	Preparation of solution and components for subsequent filling

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

235. Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (for example, using swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B air flow patterns. Cleanroom and equipment surfaces should be monitored at the end of an operation,
236. Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (for example, post disinfection, prior to start of manufacturing, upon completion of the batch and after a shutdown period), and in associated rooms that have not been used in order to detect potential incidents of contamination that may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (such as cleaning and disinfection).
237. Continuous viable air monitoring in grade A (for example, air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be detected and captured to alert any risk caused.
238. A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions (at a minimum gloves, but may require monitoring of areas of gown as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where the monitoring of gloves is performed after critical interventions, outer gloves should be replaced prior to continuation of activity. Where the monitoring of gowns is required after critical interventions, each gown should be replaced before further activity in the cleanroom.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

239. Microbial monitoring of personnel in the grade A and B areas should be performed.

Where operations are manual in nature (such as aseptic compounding or filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.

240. Action limits for viable particle contamination are shown in the table five below:

Maximum action limits for viable particle contamination

<i>Grade</i>	<i>Air sample CFU/m³</i>	<i>Settle plates (diam. 90 mm) CFU/4 hours^a</i>	<i>Contact plates (diam. 55 mm) CFU/plate^b</i>	<i>Glove print, incl. 5 fingers on both hands CFU/glove</i>
A	No growth			
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

CFU = colony-forming unit.

a Settle plates should be exposed for the duration of operations and changed as required, or after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

Note 1: *All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.*

Note 2: *Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.*

Note 3: *For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table.6 should apply.*

Note 4: *Sampling methods should not pose a risk of contamination to the manufacturing operations.*

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

Aseptic process Simulation (APS)

242. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilization.

243. Periodic verification of the effectiveness of the controls in place for aseptic processing should include an aseptic process simulation (APS) (also known as media fill) using a sterile nutrient medium or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the PQS and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient medium or surrogate should be made based on the ability of the medium or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination (for example, aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.

244. The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:

- i. The APS should cover all aseptic operations performed subsequent to the sterilization and decontamination cycles of materials utilized in the process to the point where the container is sealed.
- ii. For non-filterable formulations, any additional aseptic steps should be covered.

- iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended.
- iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in the same containers as those used in the process under evaluation.
- v. Separate simulations of individual unit operations (for example, processes involving drying, blending, milling and subdivision of a sterile powder) should be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process.
- vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain, including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst-case operating parameters.
- vii. The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable:
 - the use of air to break vacuum instead of nitrogen or other process gases;
 - replicating the maximum interval between sterilization of the lyophilizer and its use;
 - replicating the maximum period of time between filtration and lyophilization;
 - quantitative aspects of worst-case situations, for example, loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.

245. APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

occur in, and after any significant modification to operational practices, facilities, services or equipment that are assessed to have an impact on the sterility assurance of the product (such as modification to the HVAC system or equipment, changes to process, number of shifts and numbers of personnel, or major facility shutdown). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shutdown, before long periods of inactivity or before decommissioning or relocation of a line.

246. The number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10 000 units should be filled. For small batches (for example, those under 5000 units), the number of containers for APS should at least equal the size of the production batch.

247. Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the medium with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those that have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production standard operating procedures clearly specify that units must be removed under the same circumstances (that is, type of intervention, line location and specific number of units removed). In no case should more units be removed during an APS intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of intervention. To fully understand the process and assess contamination risks during aseptic set-up or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.

248. Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (such as amber glass or

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.

249. Filled APS units should be incubated immediately to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.

250. On completion of incubation:

- i. Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Inspection should be conducted under conditions that facilitate the identification of any microbial contamination.
- ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.

251. The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken.

- i. An investigation should be undertaken to determine the most probable root causes.
- ii. Appropriate corrective measures should be determined and implemented.
- iii. A sufficient number of successful, consecutive repeat APS (normally a minimum of three) should be conducted in order to demonstrate that the process has been returned to a state of control.
- iv. A prompt review should be made of all appropriate records relating to aseptic production since the last successful APS:
 - The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome.
 - v. All products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred.
 - vi. Where the root cause investigation indicates that the failure was related to operator activity, actions to limit the operator's activities, until retrained and requalified, should be taken.
 - vii. Production should resume only after completion of successful revalidation
252. All APS runs should be fully documented and include a reconciliation of units processed (such as units filled, incubated and not incubated). The justification for filled and non-incubated units should be included in the documentation. All interventions performed during the APS should be recorded, including the start and end time of each intervention and the involved person. All microbial monitoring data, as well as other testing data, should be recorded in the APS batch record.
253. An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases.
254. An aseptic process should be subject to a repeat of the initial validation when:
- i. the specific aseptic process has not been in operation for an extended period of time;
 - ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.
255. Routine production, after completion of the APS, should only commence after validated procedures have been completed in accordance with the CCS, to ensure that there is no risk to the product

Quality Control

256. There should be a sufficient number of personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation needed to assess the impact of microbiologically linked events on the quality and safety of the sterile product.
257. Specifications for raw materials, components and products should include requirements for microbial, particulate and endotoxin/pyrogen limits when the need for this has been indicated by monitoring or by the CCS.
258. The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilized products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the final sterilizing grade filter or the terminal sterilization process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst-case scenario (for example, at the end of hold time). Where overkill sterilization parameters are set for terminally sterilized products, bioburden should be monitored at suitable scheduled intervals.
259. For products authorized for parametric release, a supporting presterilization bioburden monitoring programme for the filled product prior to initiating the sterilization cycle should be developed and the bioburden assay should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilizing process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.
260. The sterility test applied to the finished product should only be regarded as the last in a series of critical control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or validation parameters. The test should be validated for the product concerned.

261. The sterility test should be performed under aseptic conditions. 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:

- i. For products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples (for example, taken after critical interventions) should be considered based on risk.
- ii. For products that have been heat sterilized in their final containers, samples taken should be representative of the worst-case locations (for example, the potentially coolest or slowest to heat part of each load).
- iii. For products that have been lyophilized, samples should be taken from different lyophilization loads.

Note: Where the manufacturing process results in sub-batches (for example, for terminally sterilized products), then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. (Consideration should also be given to performing separate testing for the other parameters of the product.)

262. For some products, it may not be possible to obtain a sterility test result prior to release because the shelf-life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring or alternative test methods required to mitigate the identified risks should be assessed and documented.

263. Any substance or process (for example, vaporized hydrogen peroxide, ultraviolet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the outcome of the test.

264. Media used for product testing should be quality control tested according to the relevant pharmacopoeia before use. Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative in-house isolates. The end user should normally perform Media quality control testing. Any

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case.

265. Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification and release. A written procedure should be available that describes the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with a short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the compliance should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid or alternative methods.

266. Rapid and automated microbial methods should be validated.

ANNEX II- MANUFACTURING BIOLOGICAL MEDICINAL PRODUCTS

SCOPE

The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under the scope of this annex. Biological medicinal products manufactured by these methods include vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA). The production techniques may involve:

- a) Microbial cultures, excluding those resulting from r-DNA techniques.
- b) Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques.
- c) Extraction from biological tissues.
- d) Propagation of live agents in embryos or animals.

Principle

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

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

Control of biological medicinal products usually involves biological analytical techniques, which have a greater variability than physico-chemical determinations. In-process controls therefore take on a great importance in the manufacture of biological medicinal products.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

The special properties of biological medicinal products require careful consideration in any code of Good Manufacturing Practice and the development of this annex takes these points into account.

Personnel

1. All personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured should receive additional training specific to the products manufactured and to their work. Personnel should be given relevant information and training in hygiene and microbiology.
2. Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry.
3. chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the process concerned.
4. The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated where necessary with appropriate specific vaccines and have regular health checks. 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 infectious agents. Visitors should generally be excluded from production areas.
5. Any changes in the immunological status of personnel which could adversely affect the quality of the product should preclude work in the production area. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest X-ray.
6. In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products or different organisms are handled. If such passage is unavoidable, clearly defined decontamination measures, including change of clothing and shoes and, where necessary, showering should be followed by staff involved in any such production.

Premises and Equipment

7. The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the level of contamination of the starting materials and the risk to the finished product.
8. The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.
9. In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products.
10. Dedicated facilities should be used for the handling of *Bacillus anthracis*, of *Clostridium botulinum* and of *Clostridium tetani* until the inactivation process is accomplished.
11. Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.
12. Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by r-DNA techniques.
13. Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross-contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.
14. Positive pressure areas should be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of pathogens, they should be surrounded by a positive pressure sterile zone.
15. Air handling units should be specific to the processing area concerned and recirculation of air should not occur from areas handling live pathogenic organisms.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

16. The layout and design of production areas and equipment should permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures should be validated.
17. Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.
18. Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilization. The use of "clean in place" and "sterilize in place" systems should be encouraged. Valves on fermentation vessels should be completely steam sterilizable. Air vent filters should be hydrophobic and validated for their scheduled life span.
19. Primary containment should be designed and tested to demonstrate freedom from leakage risk.
20. Effluents which may contain pathogenic microorganisms should be effectively decontaminated.
21. Due to the variability of biological products or processes, some additives or ingredients have to be measured or weighed during the production process (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area.

Animal Quarter and Care

22. Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotropin (horses). In addition, animals may also be used in the quality control of most sera and vaccines, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).
23. Quarters for animals used in production and control of biological products should be separated from production and control areas. The health status of animals from which some starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in such areas must be provided with special clothing and changing facilities. Where monkeys are used for the production or quality control of biological medicinal products, special consideration is required as laid down in the current WHO Requirements for Biological Substances.

Documentation

24. Specifications for biological starting materials may need additional documentation on the source, origin, method of manufacture and controls applied particularly microbiological controls.
25. Specifications are routinely required for intermediate and bulk biological medicinal products.

Production Starting Materials

26. The source, origin and suitability of starting materials should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.
27. Where sterilization of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation).

Seed Lot and Cell Bank System

28. In order to prevent the unwanted drift of properties, which might ensue, from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture of propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.
29. The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the marketing authorization dossier. Scaling up of the process should not change this fundamental relationship.
30. Seed lots and cell banks should be adequately characterized and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks should be established, stored and used in such a way as to minimize the risks of contamination or alteration.
31. Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.

32. Evidence of the stability and recovery of the seeds and banks should be documented. Storage containers should be hermetically sealed, clearly labelled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded.
33. Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimize the risks of total loss.
34. All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned.

Operating Principles

35. The growth promoting properties of culture media should be demonstrated.
36. Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.
37. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live microorganisms is necessary.
38. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters should be used where possible.
39. Careful consideration should be given to the validation of any necessary virus removal or inactivation undertaken.
40. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non- treated products.
41. A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilized or

sanitized between batches. The use of the same equipment at different stages of processing should be discouraged. Acceptance criteria, life span and sanitization or sterilization method of columns should be defined.

Quality Control

42. In-process controls play an especially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for quality (e.g. virus removal) but which cannot be carried out on the finished product should be performed at an appropriate stage of production.
43. It may be necessary to retain samples of intermediate products in sufficient quantities and under appropriate storage conditions to allow the repetition or confirmation of a batch control.
44. Continuous monitoring of certain production processes is necessary, for example fermentation. Such data should form part of the batch record.
45. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

Annex 3: Good manufacturing practices for medicinal gases

Introduction

Compressed medical gases (CMG or medical gases) include gaseous and liquid (cryogenic) forms stored in high-pressure cylinders that are administered as a gas. Types of compressed medical gases include, but are not limited to, oxygen, carbon dioxide, helium, nitrogen, nitrous oxide, medical air, and combinations of these gases.

Medical gases have unique properties impacting production and handling characteristics. The way the GMP regulations apply to medical gases may be different from other drugs. For example, when manufacturing a medical gas, the resulting gas may be used as a raw material, or it may be sold as a bulk drug or a finished packaged product.

Medical gases are regulated as finished pharmaceuticals regardless of the stage of processing. Medical gases must be manufactured (e.g., processed, filled, trans filled, mixed, purified, separated, cascaded, transferred, packaged, and distributed) using CGMP,

The methods of filling CMGs into refillable high-pressure cylinders or cryogenic vessels are unique to the drug industry, and the container/closure systems are unlike those used for other drug products. A set of strict prefill inspections is essential to give assurance that the container/closure systems are acceptable.

The Food Drug Authority of Ethiopia inspects establishments to assess their compliance with the mandate given by Proclamation 1112/2019 and associated regulations and directives. Regulators will use this document as a guide in assessing Manufacturer's compliance with GMP requirements.

Scope

- This guideline focuses on the production, control, storage and distribution of medicinal gases.
- This guideline apply to medicinal gases sold by commercial operations. This document does not cover the manufacture of medicinal gases in hospitals or at home for personal use. However, the principles contained in this document may be applied in those instances to ensure that oxygen generated at hospitals or at home is suitable for intended use and meets the appropriate quality standards.

Glossary

The definitions given below apply to the terms used in these guidelines.

active substance gas. Any gas intended to be an active substance for a medical product or medicinal gas.

air separation. The separation of atmospheric air into its constituent gases.

Compressed gas. A gas that, when packaged under pressure for transport, is entirely gaseous at $-50\text{ }^{\circ}\text{C}$; this category includes all gases with a critical temperature less than or equal to $-50\text{ }^{\circ}\text{C}$.

container. A cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel), a cylinder, a cylinder bundle or any other package that is in direct contact with a gas.

cryogenic gas. A gas that liquefies at 1.013 bar at temperatures below $-150\text{ }^{\circ}\text{C}$.

cylinder. A container, usually cylindrical, suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

cylinder bundle. An assembly of cylinders that are fastened together, interconnected by a manifold, transported and used as a unit.

evacuate. To remove residual gas from a container or system to a vacuum level of 0.84 bar absolute at sea level using a vacuum system.

gas. Any substance that is completely gaseous at 1.013 bar and $+20\text{ }^{\circ}\text{C}$ or has a vapour pressure exceeding 3 bar at $+500\text{ }^{\circ}\text{C}$.

home cryogenic vessel. A mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at a patient's home.

hydrostatic pressure test. A test performed, as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.

liquefied gas. A gas that, when packaged for transport, is partially liquid (or solid) at a temperature above $-50\text{ }^{\circ}\text{C}$.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

manifold. Equipment or apparatus designed to enable one or more gas containers to be emptied and filled at the same time.

maximum theoretical residual impurity. A gaseous impurity coming from a possible backflow that remains after a cylinder's pretreatment before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and supposes that these gases act as perfect gases.

medicinal gas. Any gas or mixture of gases classified as a medical product.

minimum pressure retention valve. A cylinder valve that maintains a positive pressure above atmospheric pressure in a gas cylinder after use in order to prevent any internal contamination of the cylinder.

mobile cryogenic vessel. A mobile thermally insulated container designed to maintain the contents in a liquid state.

non-return valve. A valve that permits flow in one direction only.

purge. To remove the residual gas from a container or system by first venting the residual gas from the container or system, then pressurizing the container or system to 2 bar and thereafter venting the gas used for purging to 1.013 bar.

tank. A static thermally insulated container designed for the storage of liquefied or cryogenic gas (also called a fixed cryogenic vessel).

tanker. A thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Valve. A device for opening and closing containers.

Vent. To remove the residual gas from a container or system down to 1.013 bar by opening the container or system to the atmosphere.

1. Quality Management system

1.1. Companies that are involved in the manufacture, control, storage and distribution of medicinal gases should document, implement and maintain a comprehensively designed and clearly defined quality management system. This is the responsibility of senior management.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 1.2. Senior management should also assume responsibility for the quality of the medicinal gases manufactured, controlled, released, stored and distributed.
- 1.3. All parts of the quality system should be adequately resourced and maintained.
- 1.4. The quality system should incorporate the principles of good practices (GxP), which should be applied to the life cycle stages of medicinal gases. This includes steps such as the receipt of materials, manufacturing, filling, testing, release, distribution and return of the container after use of a medicinal gas.
- 1.5. The quality system should ensure that:
 - medicinal gases are manufactured, controlled, stored and distributed in accordance with the recommendations in this document and other associated guidelines, such as good-quality control laboratory practices and good storage and distribution practices, where appropriate;
 - managerial roles, responsibilities and authorities are clearly specified in job descriptions;
 - operations and other activities are clearly described in a written form, such as standard operating procedures (SOPs) and work instructions;
 - supplier qualification is carried out and quality agreements are in place;
 - arrangements are made for the supply and use of the correct containers and labels;
 - all necessary controls are in place;
 - there is a system for quality risk management;
 - calibrations and validations are carried out where necessary;
 - the finished product is correctly processed and checked according to the defined procedures and specifications;
 - deviations, suspected product defects, out-of-specification test results and any other non-conformances or incidents are reported, investigated and recorded, and an appropriate level of root cause analysis is applied during such investigations in order to identify the most likely root cause;
 - proposed changes are evaluated and approved prior to implementation, considering regulatory notification and approval where required; after implementation of any such change, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 1.6. Appropriate corrective and preventive actions are identified and taken where required processes are in place to ensure the management of any outsourced activities that may impact product quality and integrity;
- finished products are not released and supplied before the authorized person has certified that each production batch has been manufactured and controlled in accordance with product specifications, the recommendations in this document and any other regulations relevant to the production, control and release of these products;
 - there is a system for handling complaints, returns and recalls from the market;
 - there is a system for self-inspection;
 - satisfactory arrangements exist to ensure that medicinal gases are filled, stored, distributed and subsequently handled so that their quality is maintained.
- 1.7. The system for quality risk management should cover a systematic process for the assessment, control, communication and review of risks in the production, filling, control, storage and distribution of medicinal gases and, ultimately, protect the patient from receiving a wrong or contaminated product.

2. Personnel

- 2.1. The medical gas manufacturer should have adequate, competent, qualified and appropriately trained personnel.
- 2.2. The manufacturer should have key personnel, including Technical Manager, Production Manager, Quality Assurance and Quality Control Manager, and maintenance manager, as required.
- 2.3. Personnel involved in the manufacture, control, release of a batch, storage and distribution of medicinal gases should possess qualifications, such as bachelor's degree in mechanical engineering, electrochemical engineering, Industrial engineering, Pharmacy, chemistry and should have practical experience appropriate for their required duties.
- 2.4. They should undergo medical examinations prior to employment and at periodic intervals thereafter, if required by national legislation.
- 2.5. Personnel should receive the appropriate training in relevant guidelines covering GxP and company procedures.
- 2.6. Personnel should be aware of potential hazards and risks to products and patients.

- 2.7. Personnel of outsourced service providers should be appropriately trained, especially where activities could influence the quality of medicinal gases and containers, such as the maintenance and cleaning of cylinders or valves.

3. Documentation

- 3.1. Specifications, SOPs and related documents, as appropriate for the manufacture, control, storage, and distribution of medicinal gases, should be established, implemented and maintained in accordance with the quality management system.
- 3.2. Documents should be designed, prepared, reviewed and distributed with care, in accordance with the quality management system.
- 3.3. Documents should be authorized (approved, signed and dated) by the appropriate responsible persons. No document should be changed without prior authorization and approval.
- 3.4. Documents should have unambiguous content and be laid out in an orderly fashion. The title, nature and purpose should be clearly stated.
- 3.5. Documents should be periodically reviewed and kept up to date.
- 3.6. Superseded documents should not be used.
- 3.7. Where documents require the entry of data, those entries should be clear, legible and indelible, in compliance with good documentation practices and data integrity requirements.
- 3.8. Records should be made or completed when any action is taken and in such a way that all significant activities are traceable. Records should be retained for a period of time as defined by internal procedures or national legislation, as appropriate.
- 3.9. Labels should be clear, unambiguous and in compliance with national or regional legislation, as appropriate.
- 3.10. Labels on the cylinders of medicinal gases should contain at least the information as recommended in the pharmacopoeia, where applicable, as well as the following information:
- the name of the medicinal gas
 - the batch number assigned by the manufacturer
 - the expiry or use-before date, if applicable

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- any special storage conditions or handling precautions that may be necessary directions for use
- warnings and precautions
- the name and address of the manufacturer
- test date (month and year).

3.11. Authorized specifications and testing procedures should be available.

3.12. Records should be maintained for each batch of gas manufactured.

Standard operating procedures and records

3.13. SOPs and associated records should be available for at least:

- Equipment
- analytical apparatus and instruments
- maintenance and calibration
- cleaning and sanitization
- personnel matters such as training, clothing and hygiene
- qualification and validation
- self-inspection
- complaints
- recalls
- returns.

3.14. The SOPs for sampling should specify the person or persons authorized to take samples and the sampling instructions.

3.15. The SOPs describing the details of the batch (lot) numbering system should ensure that each batch of medicinal gas is identified with a specific batch number.

3.16. Records of analysis should be maintained.

3.17. Written release and rejection procedures should be available, in particular for the release of the finished product for sale.

3.18. Records should be maintained of the distribution of each batch of medicinal gas.

3.19. Records should be maintained for major and critical equipment, as appropriate, of any qualifications, calibrations, maintenance, cleaning or repair operations, including the dates and the identities of the people who carried out those operations.

4. Complaints

- 4.1. There should be a written procedure describing the handling of complaints.
- 4.2. Any complaint concerning a defect of a medicinal gas should be recorded in detail and thoroughly investigated.
- 4.3. Where necessary, the appropriate follow-up action should be taken after the investigation and evaluation of a complaint. Where necessary, a recall of the batch or batches should be considered.
- 4.4. All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

5. Recalls

- 5.1. There should be a written, authorized procedure describing the managing of a recall of medicinal gases.
- 5.2. The manufacturer of medicinal gas should notify the regulatory authority, which product is recalled or withdrawn from the market in case of voluntary recall.
- 5.3. The recall of a medicinal gas should be documented. Records should be kept.

6. Returns

- 6.1. There should be a written authorized procedure describing the managing of returns of medicinal gases, which may include inspection or testing.
- 6.2. Once distributed, medicinal gases may only be returned under agreed conditions, as defined by the manufacturer.
- 6.3. Returned medicinal gases should be stored in a controlled manner, in a dedicated area. Returned goods should be clearly identified and kept until a decision is made as to what should be done with the returned goods.
- 6.4. Inventory records of returned medicinal gases should be kept.

7. Self-inspection, quality audits, and supplier audits and approvals

- 7.1. Self-inspections should be carried out according to a written, authorized procedure. The objective should be to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.
- 7.2. Self-inspections should be performed routinely and, in addition, may be performed on special occasions.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

7.3. Self-inspections should be done by a team of personnel with knowledge of the manufacture and control of medicinal gases and who are qualified to evaluate compliance with GxP

7.4. inspections should cover, for example:

- personnel
- premises
- maintenance
- equipment
- production
- quality control
- documentation, including label control
- sanitation and hygiene
- validation and qualification
- calibration
- batch release
- recall procedures
- complaints management
- results of previous self-inspections and any corrective steps taken.

7.5. A report should be made at the completion of a self-inspection.

7.6. Appropriate recommendations for corrective actions should be implemented and an effective follow-up program should be implemented. The effectiveness of corrective action taken should be verified.

7.7. Self-inspections may be supplemented by a quality audit and conducted by outside or independent specialists. The qualifications of external auditors should be documented.

7.8. Suppliers and contractors should be evaluated before they are approved and included in the approved list. The evaluation should consider a supplier's or contractor's history and the nature of the materials to be supplied or services to be contracted. If an audit is required, it should determine the supplier's or contractor's ability to conform with GMP or the applicable standards.

8. Premises

- 8.1. The premises where medicinal gases are manufactured should be located, designed, constructed and maintained to suit the operations to be carried out.
- 8.2. The layout and design of the premises should aim to minimize the risk of errors, mix ups, contamination and cross-contamination. In addition, it should allow effective cleaning and maintenance without any adverse effect on the quality of the products.
- 8.3. The premises should provide sufficient space for manufacturing, quality control testing and storage operations.
- 8.4. There should be:

- separate marked areas for different gases;
- clear identification and segregation of cylinders and mobile cryogenic vessels at various stages of processing (for example, “filled cylinders/mobile cryogenic vessels”, “awaiting checking”, “awaiting filling”, “quarantine”, “certified”, “rejected”, “prepared deliveries”, “empty cylinders/home cryogenic vessels”).

Note: The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used. The segregation of the products may be achieved electronically using a validated electronic system as long as the standards for the cylinders and the vessels intended for medicinal gases are maintained.

- 8.5. Filled cylinders or mobile cryogenic vessels should be stored and transported in a safe manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used. Specific storage conditions should be provided as required (for example, for gas mixtures where phase separation occurs upon freezing).

9. Equipment and utilities

- 9.1. Equipment and utilities should be selected, located, constructed and maintained to suit the operations to be carried out.
- 9.2. The layout, design, installation and use of equipment and utilities should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

- 9.3. Equipment should be designed to ensure that the correct gas is filled into the correct container. There should normally be no cross-connections between pipelines carrying different gases. If cross-connections are needed (for example, when filling equipment with mixtures), qualification and controls should ensure that there is no risk of cross-contamination between the different gases. In addition, the manifolds should be equipped with specific connections. These connections may be subject to international or national standards. The use of connections meeting different standards at the same filling site should be carefully controlled, as well as the use of adaptors needed in some situations to bypass the specific fill connection systems.
- 9.4. Tanks and tankers should be dedicated to a single and defined type and quality of gas. Where non-dedicated tanks and tankers are used, risks of contamination should be assessed and controlled, including through the application of the same GxP in the production and having the same quality specification for industrial and medicinal gas.
- 9.5. A common system supplying gas to medicinal and industrial gas manifolds is only acceptable if there is a validated method to prevent backflow from the industrial gas line to the medicinal gas line.
- 9.6. Filling and distribution manifolds should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. In exceptional cases, filling gases used for other gases or other than medical purposes may be acceptable on manifolds dedicated to medicinal gases if justified and performed under control. In these cases, the quality of that gas or mixture of gases should be at least equal to the required quality of the medicinal gas, and GMP standards should be maintained. Filling should then be carried out by campaigns.
- 9.7. Repair, maintenance, cleaning and purging operations of equipment should not adversely affect the quality of the medicinal gases. Procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. It should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained.

9.8. A procedure should describe the measures to be taken when a tanker is taken back into medicinal gas service, for example, after transporting industrial gas or after a maintenance operation. This should include, for example, a change in service documentation and analytical testing. The methods should be validated.

10. Qualification and validation

10.1. The scope and extent of qualification and validation should be determined based on risk management principles.

10.2. Risk assessment should be carried out and should cover, for example, the premises, equipment, processing, filling, storage, and distribution of medicinal gases.

10.3. Authorized procedures, protocols, and records should be maintained.

11. Production

11.1. The manufacturing of medicinal gases should generally be carried out in closed equipment.

Note: Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (for example, in an air separation plant). Where air separation is used to manufacture active substance gases, the manufacturer should ensure that the ambient air is appropriate for the established process. Changes in ambient air quality should be documented and evaluated. Controls should be identified and implemented to exclude the risks of contamination.

11.2. Manufacturing data and information should be included in the records for each batch of cylinders or mobile cryogenic vessels produced.

11.3. Records should be maintained for each batch of gas manufactured. These records should include relevant information, as appropriate, such as the following:

- name of the product;
- batch number;
- identification of the person or persons carrying out each significant step;
- equipment used (such as filling manifold);
- quantity of cylinders or mobile cryogenic vessels before filling, including individual identification references and water capacity;
- prefilling operations performed;
- key parameters that are needed to ensure correct fill at standard conditions;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- results of appropriate checks to ensure the containers have been filled;
- specification of the finished product and the results of quality control tests (including reference to the calibration status of the test equipment);
- quantity of rejected cylinders or mobile cryogenic vessels with individual identification references and reasons for rejection;
- details of any problems or unusual events and signed authorization for any deviation from instructions;
- batch label, where applicable;
- specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment) by the responsible person, with date and signature;
- batch quantity;
- date of testing and certification statement;
- identification reference for the tank (tanker) in which the batch is certified;
- reference to the supplying tanker (tank), reference to the source gas, as applicable.

11.4. Each filled cylinder should be traceable to significant aspects of the production and filling operations.

11.5. Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in a manner that will prevent mix-ups. Controls should be appropriate and may include labelling,

11.6. Color coding, signage or separate areas to facilitate the segregation of industrial and medicinal cylinders and vessels.

11.7. There should be no exchange of cylinders or mobile cryogenic vessels used for medicinal and industrial gases in or from these areas unless all comply with the specifications of medicinal gases and the manufacturing operations are performed according to GMP standards.

11.8. Production through a continuous process, such as air separation, should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.

11.9. The transfer and delivery of active substance gases in bulk should comply with the same requirements as those for medicinal gases.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

11.10. The filling of active substance gases into cylinders or into mobile cryogenic vessels should comply with the same requirements as those for medicinal gases.

11.11. Requirements applying to cylinders should also apply to cylinder bundles (except storage and transportation under cover).

11.12. Records should be maintained for each batch of gas transferred to tankers. These records should include relevant information, as appropriate, such as the following:

- name of the product
- batch number;
- identification reference for the tank (tanker) in which the batch is certified;
- date and time of the filling operation;
- identification of the person or persons carrying out the filling of the tank (tanker);
- identification of the person or persons carrying out each significant step (such as line clearance, receipt, preparation before filling, filling);
- reference to the supplying tank (tanker) and reference to the source gas, as applicable;
- relevant details concerning the filling operation;
- equipment used (such as filling manifold);
- prefilling operations performed;
- key parameters that are needed to ensure correct fill at standard conditions;
- a sample of the batch label;
- specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
- details of any problems or unusual events, and signed authorization for any deviation from filling instructions;
- certification statement by the authorized responsible person, with date and signature.

Transfer and delivery of cryogenic and liquefied gas

11.13. The transfer of cryogenic or liquefied gases from primary storage, including controls before transfer, should be in accordance with validated procedures designed to avoid any contamination.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 11.14. Transfer lines should be equipped with non-return valves or suitable alternatives. Flexible connections and coupling hoses and connectors should be flushed with the relevant gas before use.
- 11.15. The transfer hoses used to fill tanks and tankers should be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should be adequately controlled.
- 11.16. Delivery of gas may be added to tanks containing the same quality of gas, provided that a sample is tested to ensure that the quality of the delivered gas is acceptable. This sample may be taken from the gas to be delivered or from the receiving tank after delivery.
- 11.17. Filling and labelling of cylinders and mobile cryogenic vessels
- 11.18. Before filling cylinders and mobile cryogenic vessels, a batch or batches of gas or gases should be determined, controlled according to specifications, and approved for filling.
- 11.19. In the case of continuous processes, adequate in-process controls should be performed to ensure that the gas complies with specifications.
- 11.20. Cylinders, mobile cryogenic vessels and valves should conform with appropriate technical specifications and any relevant requirements by the applicable regulatory authorities.
- 11.21. They should be dedicated to a single medicinal gas or to a given mixture of medicinal gases.
- 11.22. Cylinders should be color coded according to Ethiopian standard. They should preferably be fitted with minimum pressure retention valves unless other controls are in place to ensure the quality and integrity of the medicinal gas.
- 11.23. Cylinders, mobile cryogenic vessels and valves should be checked before first use in production and should be properly maintained. Checks and maintenance operations should not affect the quality and the safety of the medicinal gas. The water used for the hydrostatic pressure testing carried out on cylinders should be at least of drinking quality.
- 11.24. As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve to make sure they are not contaminated with water or other contaminants.

11.25. An internal visual inspection should be done.

- when cylinders, mobile cryogenic vessels and valves are new and initially put into medicinal gas service;
- Following any hydrostatic statutory pressure test or equivalent test where the valve is removed;
- whenever the valve is replaced.

Note: After fitting, the valve should be kept closed to prevent any contaminant from entering the cylinder.

11.26. The maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medical product. If subcontracted, they should only be carried out by approved subcontractors, and contracts, including technical agreements, should be established. Subcontractors should be audited to ensure that the appropriate standards are maintained.

11.27. Where possible, a system should be implemented to ensure the traceability of cylinders and mobile cryogenic vessels.

11.28. Checks to be performed before filling should be done in accordance with an authorized procedure. The following checks should be observed:

- in the case of cylinders fitted with a minimum pressure retention valve, for a positive residual pressure in each cylinder;
- in the case of cylinders that are not fitted with a minimum pressure retention valve, to make sure it is not contaminated with water or other contaminants
- ensuring that all previous batch labels have been removed;
- the removal and replacement of damaged product labels;
- a visual external inspection of each cylinder, mobile cryogenic vessel and valve for dents, arc burns, debris, other damage, or contamination with oil or grease; cleaning should be done if necessary;
- on each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- for the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);
- on cylinders or mobile cryogenic vessels to ensure that any tests required by national or international regulations (such as hydrostatic pressure test or equivalent for cylinders) have been conducted and are still valid;
- ensuring that each cylinder is labelled as required.

11.29. A batch should be defined for filling operations.

11.30. Cylinders and mobile cryogenic vessels that have been returned for refilling should be prepared with care in order to minimize risk of contamination. These procedures, which should include evacuation or purging operations, should be validated.

11.31. There should be appropriate checks to ensure that each cylinder or mobile cryogenic vessel has been properly filled.

11.32. Each filled cylinder should be tested for leaks using an appropriate method prior to fitting the tamper-resistant seal or device. The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.

11.33. After filling, cylinder valves should be fitted with covers to protect the outlets from contamination. Cryogenic vessels should be fitted with tamper-resistant devices.

11.34. Each cylinder or mobile cryogenic vessel should be labelled. Patient information leaflets can be made available electronically.

11.35. In the case of medicinal gases produced by mixing two or more different gases (in line before filling or directly into the cylinders), the mixing process should be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.

12. Quality control

12.1. Each batch of medicinal gas (cylinders, mobile cryogenic vessels, tanks) should be tested in accordance with the marketing authorization, authorized specification or pharmacopoeia and a record of analysis should be maintained, for example a certificate of analysis.

Sampling

12.2. There should be an authorized sampling procedure with a sampling plan for testing medicinal gases.

12.3. In the case of a single medicinal gas:

- filled via a multi cylinder manifold, the gas from at least one cylinder from each manifold filling cycle should be tested for identity, assay and percent purity each time the cylinders are changed on the manifold.
- In the case of a single medicinal gas filled into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay.

Note: An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment and batch of gas to be filled.

12.4. In the case of a medicinal gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder should be tested for identity, and percent purity of each component.

12.5. For excipients, if any, testing on identity could be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle in the case of cylinders filled one at a time). Fewer cylinders may be tested in the case of a validated automated filling system.

12.6. Premixed gases should follow the same principles as single gases when a continuous in-line testing of the mixture to be filled is performed. Premixed gases should follow the same principle as medicinal gases produced by mixing gases in the cylinders when there is no continuous in-line testing of the mixture to be filled.

12.7. The testing for water content should be performed, where required (note the requirements in the pharmacopoeia and as specified by the regulatory authority).

12.8. Other sampling and testing procedures that provide at least an equivalent level of quality assurance may be justified.

12.9. Final testing on mobile cryogenic vessels should include a test for assay and identity on each vessel, unless otherwise authorized by the medicines regulatory authority. Testing by batches should only be carried out if it has been demonstrated that the critical attributes of the gas remaining in each vessel before refilling have been maintained.

Note: Where mobile cryogenic vessels are warm or returned from the market with residual product, the gas generated when filling the vessel is sufficient to purge the vessel adequately without any additional purging steps to remove any atmospheric contamination.

12.10. Cryogenic vessels retained by customers (hospital tanks or home cryogenic vessels) that are refilled in place from dedicated tankers do not need to be sampled after filling, provided that a certificate of analysis on the contents of the tanker accompanies the delivery.

12.11. Records of manual analysis should include at least the following:

- name of the medicinal gas;
- batch number;
- references to the relevant specifications and testing procedures, as approved in the marketing authorization;
- test results and reference to any specifications (limits);
- dates and reference numbers of testing;
- initials of the persons who performed the testing;
- date and initials of the persons who verified the testing and the calculations, where appropriate;
- a clear statement of release or rejection (or other status decision) and the date and signature of the designated responsible person.

12.12. Records of automatic analysis should include at least the following:

- Name of the medicinal gas, time and date, and the identity of the person initiating the test. Where access to the sampling and analysis system is controlled, the initials of the person initiating the test may be automatically recorded. The person initiating the test is not required to be part of the quality control department;
- batch number;
- test results, reference to the specification limits and a statement of passed or rejected;
- a clear statement of the change of status of the product being tested.

Note: For automated systems, the person initiating the testing may be the same person responsible for filling the cylinders. Formal approval of the test results

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

may be performed by the responsible person remotely to indicate approval or rejection.

12.13. For bulk medicinal liquid oxygen tankers used for the filling of cryogenic vessels at the customer's premises, the certification and release of batches by the responsible person may be performed retrospectively within a defined time frame, provided the medicinal gas manufacturer can demonstrate that the product being supplied is suitable for patient use

12.14. Reference and retention samples are not required, unless otherwise specified.

13. Product life cycle and continuous improvement

13.1. Manufacturers of medicinal gases should consider adopting a life cycle approach and continuous improvement. These principles should be applied in the relevant areas of the facility, equipment, instrument, utility, product and processes.

13.2. A means should be identified for continuous improvement to enable optimizing production and control whilst meeting current demands for supply and satisfying quality requirements of medicinal gases.

14. Storage and distribution

Storage

14.1. Precautions should be taken to prevent unauthorized persons from entering storage areas

14.2. Storage areas should be under cover with sufficient capacity to allow the orderly storage of the different medicinal gases.

14.3. In exceptional cases where this is not possible, as in the case of bundles of cylinders or large sized cylinders, the gas outlet should be protected from environmental contamination.

14.4. Storage areas should be appropriately designed, constructed and maintained. They should be kept clean and dry and there should be sufficient space and ventilation throughout.

14.5. Where special storage conditions are required, these should be provided, controlled, monitored and recorded.

14.6. Empty cylinders should be stored separately.

14.7. A written cleaning program should be available indicating the frequency of cleaning and the methods to be used to clean the storage areas.

14.8. There should be a written program for pest control.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

14.9. Broken or damaged cylinders that can no longer be used should be withdrawn from usable stock and stored separately.

14.10. Periodic stock reconciliation should be performed at defined intervals by comparing the actual and recorded stocks. Discrepancies should be identified and investigated. The appropriate corrective action should be taken.

Distribution

14.11. Filled gas cylinders and home cryogenic vessels should be handled in such a manner to ensure that they are delivered to customers in a clean and safe state.

14.12. Medicinal gases should be transported in accordance with the conditions stated on the labels.

14.13. Product, batch and container identity should be maintained at all times. All labels should remain legible.

14.14. Distribution records should be sufficiently detailed to allow recall when required.

14.15. Appropriately equipped vehicles should be suitable for the transport of medicinal gases, with sufficient space.

14.16. Vehicles should be kept clean and maintained.

14.17. Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.

14.18. Procedures should be in place for the operation and maintenance of all vehicles and equipment.

14.19. There should be written procedures, programs and records for the cleaning of tankers and vehicles. Agents used should not have any adverse effect on product quality or be a source of contamination.

14.20. There should be documented, detailed procedures for the dispatch of medicinal gases. Records for the dispatch should include relevant information to allow traceability. Such records should facilitate the recall of a batch of a medicinal gas whenever necessary.

14.21. Tankers and cylinders should be secured to prevent unauthorized access.

14.22. Procedures for transport should ensure that:

- the identity of the medicinal gas is not lost
- there is no risk of contamination of the medicinal gas
- precautions are taken against damage and theft

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- environmental conditions are maintained, if required.

14.23. The appropriate signs and warnings, where required, should be visible on tankers and vehicles.

Annex 4: Guideline on Good Manufacturing Practices for Radiopharmaceutical Products

Introduction

Radiation emitting radiopharmaceuticals are regulated under Proclamation No. 1112/2019. While the general principles of Good Manufacturing Practices (GMP) guidelines for pharmaceutical products apply to these drugs, their unique properties necessitate additional guidance.

Radiopharmaceuticals are compounds in which radioisotopes are bound to biological molecules capable of targeting specific organs, tissues, or cells within the human body. These products have distinct characteristics in terms of production, quality control, and handling. They are used not only for diagnostic purposes but also, increasingly, for therapeutic applications and as tools in biomedical research.

In addition to conventional chemical impurities, radiopharmaceuticals may contain impurities of radioactive origin such as radionuclide and/or radiochemical impurities. These can adversely affect the drug's utility, quality, safety, and diagnostic reliability. Moreover, such impurities may increase the radiation dose delivered to the patient, posing potential health risks

Most radioactive pharmaceuticals have a relatively short half-life and therefore a short shelf-life. They are often administered to patients within a short time after fabrication (production). The product may need to be released before certain quality control tests are completed, to maintain the appropriate radioactive dose regimen. For these reasons, it is vital to continually assess the effectiveness of the quality assurance program for radiopharmaceuticals.

These guidelines are meant to help industry and health care professionals understand how to comply with regulations. When we conduct an inspection, we will use this document as a guide in assessing your compliance with GMP requirements. These guidelines are not the only way GMP regulations can be interpreted and are not intended to cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

SCOPE

This guideline provides a general overview of the minimum good manufacturing practices (GMP) requirements for radiopharmaceutical products. The main principles of GMP are described in detail in the EFDA GMP guidelines related to pharmaceutical products.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

The procedures necessary to manufacture, prepare and control radiopharmaceutical products are in large part determined by the nature of these products, the methods of manufacture and their intended use. The recommendations in this guideline are applicable to:

- the production, preparation or compounding of radiopharmaceuticals in hospital radiopharmacies, including diagnostic and therapeutic products;
- the production or compounding of radiopharmaceuticals in centralized radiopharmacies;
- the production or compounding of radiopharmaceuticals in nuclear centres and institutes
- the production of radiopharmaceuticals by industrial manufacturers; and
- the production of cyclotron-based radiopharmaceuticals.

The scope of this guidance does not include:

- radiopharmaceutical dispensing (i.e. the drawing of a patient's specific unit dose from a bulk vial of a radiopharmaceutical product);
- regulatory authority-approved radiopharmaceutical preparation (i.e. the use of approved kits and approved generators in order to produce a radiopharmaceutical product as per instructions of the marketing authorization holder);
- handling of ready-to-administer radiopharmaceutical products (e.g. receipt, storage, assay, etc.);
- production or compounding of non-radioactive compounds, including cold kits; or
- production of investigational radiopharmaceutical products.

Glossary

The definitions given below apply to the terms used in this guideline and they may have different meanings in other contexts.

“as low as reasonably achievable”. ALARA is an acronym standing for “as low as reasonably achievable”, used to define the principle of underlying optimization of radiation protection. This is practiced based on the principles of time, distance and shielding, as well as an emphasis on creating adequate awareness among all stakeholders.

dispensing. The generation of a patient-specific unit dose, which involves physical withdrawal of the radiopharmaceutical from the bulk single-use or multidose vial into a

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

syringe; dilution with an appropriate diluent as necessary; measurement of the radioactivity content; and labelling of the syringe.

good manufacturing practices for radiopharmaceutical products. Good manufacturing practices (GMP) for radiopharmaceutical products are a set of practices, using a traceable process, that ensure that radiopharmaceutical products are consistently produced and controlled to the quality standards

appropriate for their intended use and designed to consistently yield radiopharmaceutical products. GMP fall under the umbrella of the overall quality management system (QMS).

manufacturing or production. Within the scope of this guidance, these terms refer to all the operations performed leading up to the finished radiopharmaceutical product, including the purchase of starting materials, production, quality control, release and storage of radiopharmaceuticals.

preparation or kit-reconstitution. Within the scope of this guidance, preparation or kit-reconstitution refers to all the procedures carried out as per instructions from a marketing authorization holder, which involves the addition of radionuclide solution approved by regulatory authorities to an approved cold kit.

primary packaging. Any packaging material that comes into direct contact with the finished radiopharmaceutical product (i.e. an immediate container, such as a vial or a syringe).

quality control. A set of analytical tests designed to demonstrate compliance of the quality of starting materials, intermediates and final radiopharmaceutical products with predetermined specifications for quality acceptance.

quality management system. An appropriate system encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will satisfy the given requirements for quality.

radiopharmaceutical compounding. This term refers to producing radiopharmaceuticals with no marketing authorization but pursuant to the order for a specific patient or patients from a physician certified/qualified for practice of nuclear medicine. In various regions of the world, this practice

may also be referred to as “in-house preparation”, “in-house-manufacturing” or “hospital preparation”.

Radiopharmaceutical product. Any pharmaceutical product that, when ready for use, contains one or more radio nuclides (radioactive isotopes) included for medicinal purposes.

Secondary packaging. The shielded container housing the primary packaging.

1. Quality management system

- 1.1. There should be a quality management system (QMS) that covers the organizational structure, job descriptions, procedures, processes, resources and actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will consistently yield a product of intended quality.
- 1.2. Principles of risk management should be applied in the establishment, implementation and management of the QMS and GMP.
- 1.3. Risk assessment should include a thorough identification and evaluation of all possible risks associated with the manufacturing process, and controls should be identified in order to minimize those risks to an acceptable level.
- 1.4. Risk assessment and risk controls should be commensurate with the complexity of the risk identified. Because radiopharmaceuticals are significantly different from “traditional” medicines, in both their characteristics and the production process, the GMP requirements applicable to the manufacture of “traditional” pharmaceuticals may often be different from those applied to the manufacture of radiopharmaceutical products.
- 1.5. Radiopharmaceutical-specific characteristics generally include the following:
 - a simple distribution chain, with direct delivery of the finished product from the manufacturer to the nuclear medicine department.
 - a small batch size.
 - a limited shelf-life of minutes to several days; and
 - a quality control (QC) sample representing the entire batch.

In addition:

- diagnostic radiopharmaceuticals often have a low potential to exert pharmacological or toxic effects, owing to the micro-dose levels administered.

- radiopharmaceuticals are often administered prior to completion of all QC testing. Tests such as sterility and determination of endotoxin content and radio-nuclidic purity may need to be performed post release. Hence, the application of GMP is essential in order to minimize possible risks to the quality that may not be identified through QC pre-release testing.
- 1.6. The risk assessment should cover the unique nature of these agents, with controls that are tailored to the actual production process, the nature of the radiopharmaceutical itself, the level of risk associated and the clinical indication. The preparation and control of these agents should be in compliance with applicable national radiation safety regulations and be based on the principles of ALARA (see Glossary).

2. Qualification and validation

- 2.1. Qualification of instruments and equipment and validation of procedures should be done.
- 2.2. Validation and qualification activities should be planned, organized and documented.
- 2.3. Qualification of premises, utilities, equipment and instruments should demonstrate that they have been designed, installed, operated and performed (as applicable) in accordance with the requirements of GMP and that they are appropriate for their intended use.
- 2.4. The extent of qualification and validation activities should be in accordance with a risk-based approach considering the complexity and critical aspects of the intended radiopharmaceutical production.
- 2.5. A schedule of planned preventive maintenance should be established. Procedures and records should be maintained.
- 2.6. There should be a schedule for regular calibration and verification. Procedures and records should be maintained.
- 2.7. Process validation should be carried out after all other qualification and validation have been successfully completed.
- 2.8. Process validation should be done by including an adequate number of batch preparations, or batches of preparations, of the intended radiopharmaceutical(s), following the same procedures, covering the intended range of batch size and with the same production and quality specifications as typically intended routine batches. The

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

number of batches and the range of batch size should be predetermined as part of a risk assessment performed prior to process validation.

- 2.9. Cleaning validation should be especially focused on surfaces that come into direct contact with the operators or with starting materials, intermediates and finished products.
- 2.10. Non-pharmacopoeia analytical procedures should be validated. Compendial analytical procedures should be verified for their suitability under actual conditions. This should be documented and records maintained.
- 2.11. General principles on validation of analytical procedures may be followed; however, the unique nature of radioactivity should be considered and specific adaptations should be made, where required.
- 2.12. Revalidation of certain processes (e.g. aseptic process simulation) should be performed on a periodic basis, in accordance with a written procedure. Requalification of equipment should be considered when appropriate, for example, in case of significant changes and/or of deviations.
- 2.13. Validation and qualification activities and results obtained, including the responsibilities of personnel, should all be documented. Records should be maintained.
- 2.14. Processes and procedures should be validated, as appropriate.

3. Product complaints

- 3.1. There should be a written procedure for handling and investigating product complaints.
- 3.2. The procedure should describe the actions to be taken in case of a complaint.

4. Product recall

- 4.1. There should be a written procedure to recall a radiopharmaceutical product, when required.
- 4.2. Since the return of radioactive products is generally not practical, the main purpose of recall procedures for radiopharmaceutical products should be to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with national and, where applicable, international transport regulations.

5. Outsourced activities

- 5.1. Contractors should be evaluated and qualified in accordance with a written procedure. Records should be maintained. The responsibilities of each party should be clearly described in a written agreement.

6. Personnel and training

- 6.1. The manufacturing establishment should have an adequate number of personnel to carry out the intended operations.
- 6.2. The responsibilities placed on any individual should not be so extensive as to present an increased risk to the quality of the product.
- 6.3. The manufacturing establishment and its personnel should be under the supervision of a responsible person(s) who has the appropriate qualifications and experience as required by national legislation.
- 6.4. Personnel should have appropriate qualifications, training and experience related to their responsibilities and job description.
- 6.5. Personnel should receive relevant training in GMP, procedural training and training related to the preparation and control of radiopharmaceutical products.
- 6.6. A written training program should be followed. Topics should also include the handling of radioactive materials and safety. Personnel should take periodic courses and receive training to keep abreast of the latest developments in their fields.
- 6.7. Training and assessment following training should be documented. Records should be maintained.
- 6.8. All personnel handling radioactive materials should be monitored for possible contamination and radiation exposure.
- 6.9. Personnel working in clean areas should observe good personal hygiene. They should report any personal medical condition that may adversely affect products.

7. Premises

- 7.1. Facilities should be located, designed, constructed, adapted and maintained, in order to suit the operations to be carried out. The laboratories for the handling of radioactive materials should be appropriately designed. Consideration should be given to radiation protection, ALARA compliance, a high level of cleanliness and the appropriate controls to minimize possible microbial contamination.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 7.2. Lighting, heating, ventilation and air-conditioning (HVAC) systems should be designed to maintain an appropriate temperature and relative humidity where required, in order to ensure the appropriate equipment performance, material storage, safety and comfort of personnel.
- 7.3. Facilities should be correctly maintained. Special precautions should be exercised, in order to ensure that facility repairs and maintenance operations do not compromise product quality. There should be adequate space for the operations to be carried out allowing for efficient workflow, effective communication and overall supervision. Facilities should also be designed in a manner that minimizes the risk of entry of insects, pests and vermin.
- 7.4. Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks. They should not shed particles and should allow for easy cleaning and decontamination.
- 7.5. Drains should be avoided wherever possible and should not be present in clean rooms. Where drains are required, these should be appropriately designed.
- 7.6. Sinks should be excluded from clean areas.
- 7.7. Pipes and valves should be appropriately marked, designed and located, in order to facilitate cleaning and decontamination. Vent filters should be appropriately controlled.
- 7.8. Technical area (e.g. rooms to access the rear of hot cells) access points should be configured in a way to minimize the entrance of maintenance and technical personnel to the production (clean) areas.
- 7.9. The HVAC system and pressure cascade design for the different areas should be appropriately designed and maintained, in order to minimize the risk of product contamination and to protect personnel from the risks of radiation exposure. The pressure differentials should be controlled, monitored and recorded. Appropriate controls should be put in place to promote the containment of radioactive gases and vapors.
- 7.10. Radioactive gas emissions should be effectively controlled and monitored, in order to minimize the risk of unnecessary radiation exposure to personnel and the surrounding environment. Alarm systems should be in place.
- 7.11. Radioactive gas should be removed through separate air-handling units fitted with the appropriate filters before being exhausted. These should be regularly checked for performance. The recirculation of radioactive contaminated air should not be allowed.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 7.12. All operations such as the handling, storage and distribution of materials and products, as well as waste disposal, should be performed in compliance with national regulations and guidance.
- 7.13. A dedicated area with the appropriate equipment should be used for the manufacture of any radiopharmaceutical product involving human blood or plasma.
- 7.14. QC laboratories should be separated from production areas.

8. Equipment

- 8.1. Equipment should be appropriately qualified for its intended use. This includes user requirement specifications, design qualification (if applicable), installation qualification, operational qualification and performance qualification. Equipment and devices, as appropriate, should be calibrated and maintained. Consideration should be given to reducing the risk of product contamination, minimizing the risk of staff radiation exposure and optimizing ergonomics, in order to facilitate the operation, maintenance and cleaning of equipment. Records should be retained.
- 8.2. Equipment, maintenance, qualification and calibration operations should be recorded and the records maintained.
- 8.3. Computerized systems, such as those controlling equipment, should be included in validation.
- 8.4. The dose calibrator (also known as the activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose-calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dial setting.

9. Starting materials

- 9.1. Starting materials of appropriate quality should be used for radiopharmaceutical production. Written procedures for material acceptance should be established for starting materials to be subsequently used in radiopharmaceutical production.
- 9.2. Specifications for starting materials should be established. Specifications should include, for example, the identity, purity or certification of origin (if applicable) and any other parameters or characteristics required in order to make the material suitable for its intended use.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 9.3. Starting materials should be accepted by performing in-house testing. Where this is not possible, and in lieu of testing, a review of the certificate of analysis supplied by the reliable material manufacturer to confirm compliance with the specification may be acceptable.
- 9.4. The status of materials should be clear. This includes:
 - a) accepted materials.
 - b) quarantined materials; and
 - c) rejected materials.
- 9.5. Rejected materials should be securely stored in an area that is separate from other materials.
- 9.6. Waste materials should be disposed of in accordance with the national requirements.

10. Documentation

- 10.1. Good documentation practices should be followed.
- 10.2. Documents should ensure the traceability of radiopharmaceutical production (including the processes and the product).
- 10.3. The processing records of regular production batches must provide a clear and complete account of the manufacturing history of each batch of a radiopharmaceutical product, showing that it has been manufactured, tested, dispensed into containers and delivered in accordance with the applicable standard operating procedures (SOPs).
- 10.4. A controlled system of written SOPs must be created, in order to cover the requirements for major aspects of radio-pharmaceutical manufacturing. The SOPs should be approved, signed and dated by the appropriate responsible person(s). No approved SOP document should be changed without an appropriate review, evaluation and approval by the person responsible(s). The SOPs should be reviewed periodically, in order to ensure applicability.
- 10.5. Documentation should be retained for a period appropriate to the nature of the document content.

11. Good practices in production

- 11.1. Access to restricted areas should be by authorized and trained personnel only.
- 11.2. Only the minimum number of personnel required should be present in clean areas.

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- 11.3. Processes should be designed to minimize the risk of contamination, cross contaminations and mix-ups. The following measures may be adopted to minimize these risks:
- processing and filling in segregated areas;
 - avoiding the manufacture of different products at the same time, either in the same dedicated space or by the same personnel;
 - performing decontamination and visual pre-checks of the manufacturing area; and
 - using manufacturing “closed systems”, whenever possible.
- 11.4. The critical aseptic operations, such as final product vial assembly, vial filling or sterility testing, should be carried out under aseptic conditions of a clean area of grade A in grade B background .
- 11.5. Both raw materials and final radiopharmaceutical products should be stored under appropriate controlled conditions.
- 11.6. The stability and shelf-life of the finished product should be defined in a written protocol in agreement with the competent authority.
- 11.7. The expiration dates and times for radiopharmaceutical products should be based upon the results of an adequate number of stability studies.

12. Good practices in quality control

- 12.1. radiopharmaceutical’s final product acceptance criteria, including criteria for release, should be established and documented in a written SOP.
- 12.2. Sampling procedures should consider the nature and characteristics of the material being sampled (e.g. a small batch size and/or its radioactive content), in order to make sure that the samples are representative of the radiopharmaceutical batch.
- 12.3. The QC procedures should be described in written SOPs.
- 12.4. QC samples should be prepared, handled and stored in a way to ensure adequate identification and segregation of the test samples, to avoid mix-ups and cross-contamination.
- 12.5. A final radiopharmaceutical product that fails to meet the acceptance criteria should be rejected and segregated. Such events should be investigated and the investigation outcome and proposed actions documented.
- 12.6. The release of a batch should be performed by a responsible person. Under certain circumstances (e.g. radiopharmaceuticals with an extremely short radioactive half-life

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

and/or shelf-life), a final radiopharmaceutical drug product may need to be released and delivered prior to completion of all final drug product characterization testing. Under these circumstances, a SOP that clearly describes the required release process should be established and documented.

- 12.7. Batch release by the manufacturer should be carried out by a responsible person who is independent of the person carrying out the production and QC.

13. Labelling

- 13.1. Finished radiopharmaceutical products should be clearly labelled.
- 13.2. Whenever possible, a portion of the primary packaging container should be left uncovered, in order to allow for inspection of the contents.
- 13.3. The content of the labels for radiopharmaceutical products should comply with national legislation and international agreements, where applicable.
- 13.4. In the absence of regulatory authority requirements, the following information should be listed on the primary packaging container label:
- the name of the product and batch number;
 - the name of the manufacturer;
 - the amount of activity in SI units;
 - for liquid radiopharmaceuticals, the total activity or the radioactive concentration per milliliter at the calibration date and time, and the volume of liquid;
 - for capsules, the radioactivity of each capsule at the calibration date and time, and the number of capsules in the container;
 - where relevant, the international symbol for radioactivity;
 - the expiration date and time; and
 - cautionary statements, e.g. “Caution: radioactive material”.

Note: reporting information about an activity on a primary label may not always be possible, for reasons of radiation protection. In this case, the information may be reported on the secondary packaging label.

- 13.5. In the absence of regulatory authority requirements, the following information may be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:

Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles

- the qualitative composition;
- excipient information;
- the route of administration;
- any special storage instructions; and
- the address of the manufacturer.

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