



GOOD COMPOUNDING PRACTICE

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INTRODUCTION

This guideline is used to provide guidance on compounding practice on the preparation used for treatment of any individual or aesthetic purposes. It will be used as a reference for inspection of compounding facilities in healthcare establishments.

In the compounding activity of medicinal products, overall control is essential to ensure that the consumer receives products of quality. The good practices outlined in these guidelines should be considered as general guides; whenever necessary, they may be adapted to meet individual needs, provided the established standards of product quality are still achieved.

In this guideline, **compounding** is defined as:

“to combine, mix of substances or alteration of dosage form or strength or delivery system of a medicinal product tailored to the needs and quantity of an individual; includes the combination of two or more compounded preparation or substances.”

Where relevant, the definition from the Poisons Act 1952 may be applicable. Technical requirements specified for sterile compounding preparation can be also refer to PIC/S Guide to Good Manufacturing Practice for Medicinal Product.

GLOSSARY

1. Active ingredient

Any substance or mixture of substances to which the effect of a finished medicinal product is adjudged, or which acts as such.

2. Batch

A defined quantity of starting materials, packaging materials or products processed in one process or series of processes so that it could be expected to be homogeneous.

3. Batch number

A distinctive combination of numbers, symbols and/or letters which specifically identifies a batch.

4. Beyond-use Date (BUD)

The date after which a compounded preparation should not to be used.

5. Clean area

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

6. Closed Procedure

A procedure whereby a sterile pharmaceutical product is prepared by transferring sterile ingredients or solutions to a pre-sterilised sealed container, either directly or using a sterile transfer device, without exposing the solution to the external environment.

7. Critical Zone

A work area where containers are opened and the product is exposed. Particulate and microbiological contamination should be reduced to levels appropriate to the intended use.

8. Cross contamination

Contamination of a material or product with another material or product.

9. Deviation report

A deviation report is a report of any deviation from standard procedures and documentation that occurs during the preparation process, and requires remedial action.

10. Dispensed Medicine

A medicine supplied by a registered medical practitioner, registered dentist or veterinary surgeon under and in accordance with section 19 of Poisons Act 1952 or supplied, for the purpose of medical, dental or animal treatment, of a particular individual by a licensed pharmacist on the premises specified in his license.

11. In-use expiry date

The end of the application period, in which a medical product may be taken or applied after the package has been opened, respectively after a first dose of the medicinal product has been taken from the package.

12. Packaging

All operations, including filling and labelling, which a bulk product should undergo to become a finished product.

13. Packaging material

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

14. Production

Part of preparation. It involves all processes and operations in the preparation of a product, from receipt of materials, through processing and packaging, to its completion as a finished product.

15. Pharmaceutical Isolator

A containment device which utilises barrier technology to provide an enclosed, controlled workspace.

16. Responsible Person

The person who is ultimately responsible for all aspects of the preparation of products including the release of these items.

17. Risk assessment

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

18. Self inspection

An assessment, undertaken under the responsibility of the same organisation in order to monitor the validity of the quality assurance system and its compliance with this guide. It can be conducted by designated competent person(s) from the organisation or assisted by external experts.

19. Starting material

A substance, used for the preparation of a compounded preparation excluding packaging material.

20. Validation

A risk-based, systemic, GMP compliant and documented evidence that a defined process actually leads reproducibility to the expected results.

CHAPTER 1 - GENERAL PRINCIPLES

- 1.1 Compounded preparations should only be provided if the preparation is safe and appropriate for an individual. The compounded preparation should be prepared in reference to international pharmacopoeias or references recognised by the Drug Control Authority (DCA), and must not be on testimonials and impressions.
- 1.2 A compounded preparation should be prepared only in circumstances when:
 - a) A registered product is unavailable in the market.
 - b) A registered product with similar therapeutic effect is unavailable in the market.
 - c) A registered product is unsuitable (e.g. if a patient experiencing allergy to an excipient in the registered product).
 - d) When undertaking research sanctioned by a recognised human research ethics committee.
 - e) A treatment requires tailored dosage strengths/forms for patients with unique needs (for example, an infant).
- 1.3 When a compounded preparation has no precedents in reputable references and lacks of published safety, efficacy, pharmacokinetic and clinical data; the compounded preparation must be justified with:
 - a) A basis for the assigned BUD of the intended formulation; and
 - b) A basis for the safety of the intended user.
- 1.4 Compounded preparations may include but not limited to:
 - a) Preparation containing hormones.
 - b) Preparations compounded for topical use that contain drugs for which oral use is well established.
 - c) Modified release medicines in the absence of good pharmacokinetic and clinical data on the precise formulation intended for use.
 - d) Preparation containing Dangerous Drugs, Psychotropic, and Precursor substances as permitted by relevant law and subject to approval.
- 1.5 Compounded preparations must not:
 - a) Contain substances which are prohibited by the Drug Control Authority (DCA) or substances stated in Group A of the Poisons List (Poisons Act 1952).

- b) Consist of parenteral medicine containing combinations of ingredients where there is no compatibility data.
 - c) Be intended for recreational purpose where the benefit of having the substances compounded is not proven (e.g.: nicotine).
- 1.6 Compounded preparations in anticipation of prescription drug orders, shall be allowable on the basis of routine, regularly observed prescribing patterns and must not exceed BUD as stipulated in international pharmacopoeia such as United States Pharmacopeia (USP) Pharmaceutical Compounding – Nonsterile Preparations Chapter <795> and Pharmaceutical Compounding – Sterile Preparations Chapter <797>.
- 1.7 Compounding may include the following:
- a) Preparation of drug dosage forms for human patients
 - b) Modification of registered products that may require the addition of one or more substances
 - c) Preparation of drugs or devices for the purposes of research (clinical or academic), teaching, or chemical analysis.
 - d) Sterile preparations and preparations which require special competencies, equipments, processes or facilities and containing ingredients that pose occupational health and safety hazard (such as cytotoxic or hormones). (Please refer to Annex 1: Guidelines on the Standards Required for the Sterile Compounded Preparations)
- 1.8 Compounding does not include the reconstitution, mixing, or other similar act that is performed pursuant to the directions contained in approved labelling provided by the manufacturer of a registered product.
- 1.9 The scope of compounding includes all activities of purchase of materials and products, production, quality control, release, storage, delivery of compounded preparation and the related control.

CHAPTER 2 - QUALITY ASSURANCE SYSTEM

PRINCIPLES

In order to protect public health, compounded preparation should be of high quality and safety. They should be compounded in such a way that they are fit for their intended purpose and that their quality consistently complies with the defined requirements. To achieve this objective effectively, there should be a comprehensive designed and correct implementation of quality assurance system in place. The quality assurance system should be documented and its effectiveness should be monitored.

QUALITY ASSURANCE

- 2.1 Quality assurance represents the total sum of the organised arrangements made with the objective of ensuring that compounded preparation are of the quality required for their intended purpose. Its effectiveness and suitability should be assessed regularly.
- 2.2 Quality assurance ensures that:
 - a) Compounded preparation is formulated and compounded according to the latest available information to ensure the quality of the product is preserved when it reaches the patient.
 - b) Compounding and control operations are clearly specified and implemented according to the principles of this guideline.
 - c) Compounded preparation is only supplied if they have been correctly processed, checked and stored in accordance with the defined procedures and released by pharmacists, medical practitioner; veterinary practitioner; dental practitioner; as defined in relevant acts and regulations such as the Poisons Act 1952 and the Control of Drugs and Cosmetic Regulations 1984.
 - d) Adequate measures are in place to ensure that compounded preparations are released, stored and handled in such a way that the required quality can be assured throughout their BUD.
 - e) Documentation systems are in place and maintained.

CHAPTER 3 – PERSONNEL

PRINCIPLES

There should be an adequate number of personnel having knowledge, skill and capabilities relevant to their assigned function, in good health, and capable of handling their duties properly. They should have the attitudes for achieving the goals of Good Compounding Practice (GCP).

RESPONSIBLE PERSON

3.1 Compounding preparation shall be done by a Responsible Person as stated below:

- a) a pharmacist or a person working under the immediate personal supervision of a pharmacist.
- b) a person acting in the course of his duties who is employed in hospital or dispensary maintained by the Federal or any State Government or out of public funds or by a charity approved for the purpose of section 12(1)(b) of the Poisons Act 1952 or in an estate hospital and who is authorised in writing as provided in that section; and
- c) a fully registered medical practitioner or a dental practitioner or a veterinary practitioner or a person working under the immediate personal supervision of such a practitioner if the drug in question is for the use of such practitioner or of his patient.

Note: For poison compounding, it should be done in accordance with section 12 of the Poisons Act 1952.

QUALIFICATION

3.2 Responsible Person should possess the adequate knowledge, training and competency to perform compounding duties at the level at which they are involved and should maintain their competency but not limited to:

- a) possess suitable qualifications required for their jobs;
- b) have adequate experience and are technically competent; and
- c) regularly trained during their employment for the purpose of keeping up to date with any advancement or changes.

RESPONSIBILITIES

3.3 The Responsible Person shall:

- a) Ensure all compounding preparations of acceptable strength and quality to ensure the authenticity of the order.
- b) Ensure all compounding processes are conducted appropriately.
- c) Ensure the compounded preparation is supplied with appropriate packaging and labelling.
- d) Ensure all compounding processes have been documented accordingly.
- e) Ensure compliance to relevant acts and regulations.

PERSONNEL HYGIENE

3.4 Responsible Person involved in compounding preparation should prevent direct contact with any compounding components and substances during compounding process if they are in apparent illness or open lesion that may adversely affect the safety and quality of the compounded preparation.

3.5 Responsible Person engaged in compounding process should wear appropriate clean clothing during operations being carried out (e.g., hair covers, gowns, gloves, facemasks, aprons or other items) for self-protection from chemicals and prevention of substances contamination.

3.6 Instructions or procedures should be available relating to hygiene practices and clothing of Responsible Person.

3.7 In general, any unhygienic practice is forbidden within the compounding areas where compounded preparation might be adversely affected.

CHAPTER 4 - PREMISES AND EQUIPMENT

PRINCIPLES

There should be defined and reserved areas for the compounding activity. Compounding equipment should be adequate for the activities performed and should be placed and maintained in such a way to be easily available for its intended use.

FACILITIES

- 4.1 Responsible Person for the operation must ensure all compounding activities take place in premise that is adequately designed, equipped and maintained.
- 4.2 The compounding area should be isolated from potential interruptions, chemical contaminants and source of dust and particulate matter. The area should be located sufficiently away from routine dispensing and counselling functions.
- 4.3 The compounding facilities shall provide adequate place for equipments and materials to prevent mix-ups among ingredients, containers, labels, in-process materials, and finished preparations. That facilities shall be designed, arranged and used to prevent cross-contamination.
- 4.4 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either during the compounding activities and storage, or the accurate functioning of equipment.
- 4.5 Facilities should be designed and equipped to afford maximum protection against the entry of pests or other animals.
- 4.6 The work surface should be smooth, impervious, and free of cracks and crevices (preferably seamless) and non-shedding. Surface should be cleaned at both the beginning and the end of each compounding activity and should be free of drugs and chemicals used during previous compounding session.
- 4.7 Adequate facilities for washing hand and equipment should be easily accessible to the compounding area.
- 4.8 Hormones, cytotoxic and hazardous drugs shall be stored, prepared, and handled by Responsible Person under conditions that protect other personnel.

COMPOUNDING EQUIPMENT

- 4.9 The equipment needed to compound a preparation depends on the particular dosage form requested. Responsible Person is responsible for obtaining the required equipment and ensuring that equipment is properly maintained.
- 4.10 The equipment and utensils used for compounding shall have appropriate design and has the capacity according to dosage forms and the quantities compounded.
- 4.11 The equipment should be made of suitable materials. The surface of the contact component should be neither reactive nor additive so as not to affect or alter the purity of the compounded preparations.
- 4.12 Automated and other types of equipment used in compounding or testing of compounded preparations shall be routinely inspected, calibrated as necessary and checked to ensure proper performance.
- 4.13 Extra care should be practiced when cleaning equipment used in compounding preparation require special precautions (e.g. hormones, antibiotics, cytotoxic and other hazardous materials). When possible, dedication of equipment or single-use equipment should be practiced to reduce chances of bio burden and cross-contamination.

CHAPTER 5 - DOCUMENTATION

PRINCIPLES

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 of complementary preparation. Suitable control should be in place to ensure the accuracy, integrity, availability and legibility of documents.

GENERAL

- 5.1 Documentation, written or electronic, enables a Responsible Person, whenever necessary, to systematically trace, evaluate and repeat the compounding process of a compounded preparation.
- 5.2 The Responsible Person should document the compounding preparation in accordance with the relevant law.
- 5.3 Compounding documents should include:
 - a) Master formula
 - b) Compounding records
 - c) Standard operating procedures (SOPs) and its relevant records
 - d) Records such as the Certificates of Analysis (COA) and Material Safety Data Sheet (MSDS) of ingredients.
- 5.4 All records and reports should be retained for one year after BUD and in accordance with relevant law. The prescription for compounding poisons for individual or patient must be retained for at least two years.
- 5.5 All records and reports should be readily available for authorized inspection during the retention period.

MASTER FORMULA

- 5.6 This record shall include:
 - a) Official or assigned name, strength, and dosage form of the preparation
 - b) Calculations needed to determine and verify quantities of components and doses of active ingredients or substances

- c) Description of all ingredients and their quantities
- d) Compatibility and stability information, including references when available
- e) Equipment needed to prepare the preparation, when appropriate
- f) Mixing instructions
- g) Sample of labelling information of the compounded preparation, which shall contain legally required information
- h) Container used in compounding
- i) Packaging and storage requirement
- j) Description of final preparation
- k) Quality control procedures and expected results

COMPOUNDING RECORDS

- 5.7 Compounding records should include processing, packaging and quality control documents (when applicable), name of the person who does the compounding, date of compounding, reference to prescription or order, the quantity of stock received, balance stock, stock card for each compounded preparation and any other relevant documentation as required by the law.

STANDARD OPERATING PROCEDURES (SOPs)

- 5.8 All significant procedures performed in the compounding area should be addressed by written standard operating procedures (SOPs).
- 5.9 Procedures should be developed for the facility, equipment, personnel, preparation, packaging, and storage of compounded preparations to ensure accountability, accuracy, quality, safety and uniformity in compounding.

CHAPTER 6 - COMPOUNDING PROCESS

PRINCIPLES

With the facility and equipment provided, the compounding processes should be capable of producing compounded preparation which conform to their specification. Defined compounding procedures are necessary to ensure that compounding activities, quality control and other relevant personnel are instructed on the details of the processes concerned.

GENERAL

- 6.1 The quantity of compounded medicine to be supplied should be in a unit of use for the individual.
- 6.2 Responsible Person should evaluate the dose, safety and intended use in term of the chemical and physical properties of the components, dosage forms and therapeutics appropriateness and route of administration. Calculations are performed to determine the quantities of the ingredients needed.
- 6.3 A compounding record should be completed each time a preparation is compounded.
- 6.4 Only one preparation should be compounded at one time in a specific workspace.
- 6.5 Equipment needs to be inspected for cleanliness and functions correctly before being use in the compounding process.
- 6.6 A reliable BUD is established before preparation to ensure safety and quality.
- 6.7 The preparation is made in accordance with international pharmacopoeias or references recognised by the DCA.
- 6.8 Every critical process such as weighing, measuring or mixing has to be verified to ensure that compounded preparation is being prepared consistently according to the expected qualities.
- 6.9 The quality of final preparation is assessed (e.g. weight variation, adequacy of mixing, clarity, odour, colour, consistency and pH) and this information is recorded in Compounding Records.

- 6.10 The preparation is packaged and labelled with necessary information in accordance with current law.
- 6.11 Cleaning of compounding area and all equipment should be done immediately after the preparation.
- 6.12 The Compounding Records should be reviewed to prevent errors and ensure that the preparation is suitable for use.

INGREDIENTS

- 6.13 Sources of active ingredients may be derived from registered products.
- 6.14 The ingredients for the compounded preparation from registered product should be used accordingly to its indication and potential effect on the efficacy should be considered including strength, purity, stability, compatibility and quality.
- 6.15 To ensure consistent quality in compounded preparations, it is important to use the same suppliers of high-quality substance for compounding.
- 6.16 COA should be obtained and kept as record for documentation of quality substances used in compounding preparations.

PACKAGING, STORAGE AND LABELLING

- 6.17 The selection of container depends on the chemical and physical properties of the compounded preparations.
- 6.18 Packaging materials should not interact with the chemical and physical properties of the preparations to maintain the potency during storage. Storage of substances at any level of compounding process must comply with the relevant law and storage requirement.
- 6.19 The criteria for choosing a container should include inertness, visibility, strength, rigidity and moisture protection with suitable closure type.
- 6.20 Compounding preparations should be stored in tightly closed, light-resistant containers at room temperature or in accordance to the storage condition requirement as stipulated in the international pharmacopoeia references.
- 6.21 Temperatures of storage areas including refrigerator should be recorded and continuously monitored.

- 6.22 Labelling of compounded preparations must be in accordance with Regulation 12 of Poison Regulations 1952 (labelling of dispensed medicine) which includes information of but not limited to:
- a) Generic names of main active ingredients
 - b) Strength or quantity
 - c) Batch number; traceable to the compounded preparation
 - d) Beyond-use date (BUD)
 - e) Storage requirement
- 6.23 Compounding shall be specific for individual patient; thus the name of patient must be stated on the label of finished compounded preparations. Short name should be discouraged to prevent errors.
- 6.24 Written procedures should be prepared for excess preparation and additional quantities that might be used for future request must not exceed the BUD and must be labelled in accordance to paragraph 6 under this chapter.

CHAPTER 7 - QUALITY CONTROL

PRINCIPLES

Every compounding process should have a quality control system to ensure that compounding preparations are prepared in accordance with the established specifications.

GENERAL

- 7.1 All compounding records and final checks should be reviewed for accuracy and conduct in the process.
- 7.2 Written procedures such as listing of ingredients, quantities, order of mixing or preparation and detailed description of compounding process should be available including the equipment as well as the container closure system.
- 7.3 Operation at each step of weighing and measuring of compounding process should be counter checked by the Responsible Person.

BEYOND-USE DATE (BUD)

- 7.4 Sign of instability should be observed at all stages of compounding process.
- 7.5 Expiration date of a registered product that acts as active ingredients can be used in determining the BUD. However, it should be as stipulated in the international pharmacopoeias or references recognised by the Drug Control Authority (DCA) or supported by stability data. The expiry date also should not exceed the expiration date of any of its components.

CHAPTER 8 - COMPLAINTS AND RECALLS

PRINCIPLES

All errors, defects, complaints and other signs of quality problems should be reviewed carefully according to a written procedure. In order to be able to promptly and effectively recall compounded preparations which have severe deficiencies, a suitable procedure should be developed.

COMPLAINTS

- 8.1 Errors, defects, complaints and other signs indicating quality problems should be investigated. Appropriate measures should be in place to ensure that effective remedial action is taken. The source and content of deficiencies, remedial measures taken and tests performed should be documented in writing and added to the preparation record.
- 8.2 When a compounded preparation defect is reported, consideration should be given to check if other compounded preparation could be affected and to cease supply until the problem is fully investigated.

RECALLS

- 8.3 When deficiencies are potentially harmful to health, a recall should be initiated immediately and the relevant authority should be informed without delay.
- 8.4 A written procedure for a recall should be in place.
- 8.5 Recalled compounded preparation should be marked as such and stored in segregated areas.
- 8.6 It should be guaranteed that they cannot be supplied in error.
- 8.7 The progress of the recall should be recorded. A final report should be issued, including reconciliation between the delivered and recovered quantities of the compounded preparation. The report should be retained for five years, if national regulations do not require other retention times.

ADVERSE DRUG REACTION (ADR) REPORTING

- 8.8 Any adverse reactions arising from the use of compounded preparation should be investigated and reported to the relevant authority.

CHAPTER 9 – SELF INSPECTION

PRINCIPLES

The quality assurance system should include self inspection. These should be conducted in order to monitor implementation and compliance with the principles of GCP and to trigger necessary corrective and preventive measures.

GENERAL

- 9.1 The quality assurance system for personnel, premises, equipment, documentation, production, quality control, distribution of the compounded preparation, arrangements for dealing with complaints and outsourced activities, should be examined at regular intervals in order to verify their conformity as described in this Guide.
- 9.2 A self inspection programme should be established which considers the type and complexity of operations performed and includes an annual self inspection plan with records and evidence that adequate corrective actions are undertaken.

ANNEX 1

GUIDELINES ON THE STANDARDS REQUIRED FOR THE STERILE COMPOUNDED PREPARATION

INTRODUCTION

1. The sterile compounded preparation includes:
 - a) The preparation of terminally sterilized products
 - b) The aseptic preparation of products
2. This Annex is a supplement to the main part of this Guide and specifies additional rules for the preparation of sterile compounded preparation. The chapters of this Annex initially mention the rules which are valid for all types of sterile preparations mentioned above and are then followed – if necessary - by subsections containing specific guidance which is only applicable for one product category.
3. Sterile preparations are considered to be a high risk category, for example due to:
 - a) The increased potential for microbiological contamination in the compounded preparation prepared in uncontrolled environments;
 - b) The higher levels of microbial contaminants in uncontrolled environments
 - c) The increased risk of systemic infection associated with compounded preparation prepared in uncontrolled environments;
 - d) The increased risk of medication errors when preparing injections without responsible person supervision. The preparation should take place in well-controlled environments using well established, quality assurance driven procedures. This considerably reduces the risk linked to these products.
4. For individual compounded preparation examples of their more specific risk factors are:

Cytotoxic and radiopharmaceuticals: High level of hazard to the operator preparing the compounded preparation and high risk of preparation errors.

Total parenteral nutrition solutions: May be very complex depending on the

formula and the number of additions; Also there is a high risk of microbial contamination, and high risk of preparation error.

Epidurals and cardioplegia solutions: High risk associated with microbial contamination.

Infusers and ambulatory devices (e.g., patient controlled analgesia): Risk of microbial growth; some compounded preparation may be administered over significant periods of time at temperatures at or near body temperature during administration; technical complexity is also a risk.

Infusions, syringes and minibags: Risk of preparation errors and microbial contamination. Some solutions may promote bacterial and/or fungal growth. Some solutions may be administered over significant lengths of time.

Irrigations (excluding ophthalmic): Duration of administration.

Eye Preparations - unpreserved or preserved: Risk of microbial growth; complexity; risk of preparation error.

Others (e.g. biological, factor VIII): Should be assessed on an individual product basis.

SECTION 1 PERSONNEL

5. The Responsible Person should have relevant knowledge and current practical and theoretical experience in the preparation of sterile compounded preparation and an appropriate training in microbiology.
6. All sterile preparation should be carried out by appropriately trained personnel. Responsible Person for sterile preparation activities should be appropriately competent and should be authorised.
7. All staff working in sterile processing should be made fully aware of the potential consequences of any deviation from the validated procedures, both to the integrity of the compounded preparation and to the patient. Regular reminders of the critical nature of the process should be provided.
8. Before undertaking sterile work, all staff should be appropriately trained and have their competence assessed. In particular, radiopharmacy staff should achieve appropriate training in National law relating to Atomic Energy Licensing Act 1984.
9. All staff should receive training which will provide them with:

- a) an appropriate knowledge of Good Manufacturing Practice or Good Preparation Practice
 - b) knowledge of local practices, including health and safety
 - c) competence in the necessary sterile skills
 - d) knowledge of pharmaceutical microbiology
 - e) working knowledge of the department, compounded preparations, and services provided
10. Regular reassessment of the competency of each member of staff to undertake sterile manipulations should be undertaken, and revision or retraining provided where necessary.

Special requirements for aseptic preparation activities:

11. Supervisory personnel within the aseptic preparation department should have an adequate understanding of clean area and clean air device technology together with a thorough knowledge of all the particular design features in their department e.g. ventilation systems, position and grade of High Efficiency Particulate Air (HEPA) filters, type of workstation, isolator design etc.
12. Personnel involved in aseptic processing, should have specific competency and skills in aseptic technique. Their aseptic technique should be periodically assessed by performing media fill simulations (cf. Section 4). The justification for the frequency of these periodic assessments should be documented. This should be complemented by regular observation of aseptic technique to ensure that the operator can prepare dosage units precisely and safely.

SECTION 2 PREMISES AND EQUIPMENT

13. Premises should be situated in an environment which, when considered together with measures to protect the preparation, presents minimal risks of causing contamination of materials or compounded preparations. In case of the preparation of cytotoxic and radiopharmaceuticals, measures should also be taken to protect the operator from the materials being handled.

Clean areas for the preparation of sterile compounded preparations are classified in 4 grades (A, B, C and D) based on the required characteristics of the environment (cf. Section 6). The level of room classification should be specified according to the activities performed and the compounded preparation. Accordingly, for each clean area or suite of clean areas “in operation” conditions (installation is functioning in the defined operating mode with the specified number of personnel working) and “at rest” conditions (complete installation with production equipment but without personnel, i.e. unmanned) should be specified.

Appropriate air filtration (terminal HEPA filters for grades A, B and C) and sufficient number of air changes (cf. Section 6) should be defined in order to reach the specified conditions.

In order to meet “in operation” conditions, these areas should be designed to reach the “at rest” conditions after a short “clean up” period of 15-20 minutes (guidance value) after completion of operations.

14. Sterile preparations should be carried out in clean dedicated areas that have airlocks to allow the entry of personnel, materials and equipment. Changing rooms should be designed as airlocks.
15. Location and use of sinks should be carefully considered in view of their potential to cause microbiological contamination. Sinks or hand-washing facilities should not be available in preparation rooms or the final stage of the changing rooms. If present in adjacent areas, they should be regularly monitored and disinfected.
16. Standard Operating Procedures should be written and implemented for all equipment used for processing.
17. Where appropriate, equipment should be regularly calibrated and the accuracy of volume measuring devices checked.

Special requirements for preparation of terminally sterilised compounded preparations:

18. Preparation of components and most compounded preparations should be done in at least a grade D environment in order to reduce the risk of microbial and particulate contamination. Where there is an unusual microbiological risk with the compounded preparation, for example, because the compounded preparation actively supports the microbial growth, or it is held for a long period before sterilisation or is not processed in closed vessels, preparation should be done in a grade C environment.

Filling of compounded preparations for terminal sterilisation should be done in at least a grade C environment.

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

Table 2.1 gives examples of operations for terminally sterilised compounded preparations to be carried out in the various grades.

Table 2.1	
Grade	Examples of operations for terminally sterilised compounded preparations
A	Filling of compounded preparation, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of compounded preparation
D	Preparation of solutions and components for subsequent filling

Special requirements for aseptic preparation activities:

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

Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and compounded preparations should be done in a grade A environment.

Handling and filling of aseptically prepared compounded preparations (open and closed procedures) should be performed in a grade A environment in a laminar flow cabinet (LFC) or a positive pressure pharmaceutical isolator. The room should have a positive pressure (ideally 10 – 15 Pascals) and air flow relative to the surrounding areas of a lower grade in order to protect the compounded preparations from contamination.

Table 2.2 gives examples of operations for aseptic preparations to be carried out in the various grades.

Table 2.2	
Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

20. Preparation under negative pressure, protecting the operator and the environment from contamination should only be used for the preparation of hazardous pharmaceuticals (e.g. cytotoxic drugs, radiopharmaceuticals and radio labelled blood products), together with appropriate precautions against contamination of the medicinal product (e.g. appropriate background room air quality, positive pressure airlock systems). Laminar Flow Cabinets (LFCs) are

not suitable for the preparation of hazardous drugs. Biohazard safety cabinets (BSCs) should be used instead, with a vertical downward air flow exhausting vertically from the cabinet and not towards the operator

21. As there is no terminal sterilisation of aseptic compounded preparations the microbiological environment in which they are prepared is of the utmost importance. Therefore, the environment should be controlled and only authorised people should be allowed to have access. Unless there is a proper justification available, the background environment for LFCs and BSCs should meet grade B requirements, with grade D required for pharmaceutical isolators. Any justification for background environments of a lesser grade should be based on a documented risk assessment which should be performed with great care. Possible factors which could be considered in such a risk assessment include:
- a) Time between preparation and use
 - b) Use of a Closed Procedure (please see glossary)
 - c) Nature and composition of product

Table 2.3 gives an overview of the recommended minimal grades.

Table 2.3		
	Working environment	Background environment
LFC/BSC	Grade A	Grade B
Isolators	Grade A	Grade D

22. In order to minimise the risk of cross-contamination, facilities should be dedicated. Rooms should be provided for hazardous products e.g. cytostatic, penicillin, biologicals, radiopharmaceuticals and blood products. In exceptional cases the principle of campaign working may be acceptable, provided that specific precautions are taken and the necessary risk assessments have been performed.

Clothing

23. 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 compounded preparation from contamination.

Dedicated clothing should be worn in areas used to process blood products, radiopharmaceuticals and live viruses.

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

- a) Grade D: Hair, arms and, where relevant, beard and moustache should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
 - b) Grade C: Hair, arms and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.
 - c) Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face-mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.
24. Outdoor clothing should not be brought into the changing rooms leading to grade B and C areas. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each working session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session.

Special requirements for aseptic preparation activities:

25. It is important to visually check that garments are in good condition and that the seams are sealed. Periodic monitoring for particles and bioburden (contact plates) should be considered (cf. Section 6). The justification for the frequency of these periodic tests should be documented.

The frequency of laundering should be appropriate to the activity undertaken and the use of biocidal washes or gamma irradiation should be used for grade C and B areas respectively.

Cleaning

26. Clean areas should be regularly cleaned according to a documented and approved procedure. Any staff performing cleaning duties should have received documented training, including the relevant elements of GMP and should have been assessed as competent before being allowed to work alone.
27. Dedicated equipment should be used and stored to minimise microbiological

- contamination. Mop heads should be disposed of or re-sterilised after each cleaning session.
28. Cleaning and disinfecting agents should be free from viable microorganisms and those used in Grade A and B areas should be sterile and spore free.
 29. The effectiveness of cleaning should be routinely demonstrated, by microbiological surface sampling e.g. contact plates or swabs.
 30. Periodic use of sporicidal cleaning agents should be considered to reduce contamination from spore forming microorganisms.
 31. Virucidal cleaning agents should be used to decontaminate areas where blood products or viruses are handled.
 32. For sterile alcohol sprays and other materials brought into clean areas an in- use expiry date should be defined.

SECTION 3 DOCUMENTATION GENERAL ISSUES

33. The general GMP guidelines on documentation should apply to all quality systems associated with sterile processing.

Processing Instructions and Processing Records

34. Individual processing instructions and compounding records reproduced from a suitably approved master formula should be used and approved prior to use. They should be sufficiently detailed to allow traceability of starting materials and components to establish an audit trail for the compounded preparation.
35. Completed compounding records should be retained for a sufficient period to satisfy legislative requirements. In any case, records should be retained at least one year after the expiry date of the relevant finished product. Procedures and preparation instructions (including prescriptions) should be retained for at least five years after their use.
36. Compounding records will vary for each unit and should be designed to minimise the possibility of transcription errors. Compounding records may be combined in one document (“worksheets”).

SECTION 4 STERILE PROCESSING

37. All manipulative steps in the sterile process should be controlled by comprehensive Standard Operating Procedures to ensure the output of the process is a sterile compounded preparation of the requisite quality.
38. All sterilisation processes should be validated. The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made to the process or equipment.
39. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the Pharmacopoeia, or when it is used for a compounded preparation, which is not a simple aqueous or oily solution.
40. The preparation of different compounded preparations with different formulations, in the same workstation at the same time should be avoided. Before commencing the next activity, a line clearance should be performed, i.e. all material should be removed from the area to prevent cross contamination and mix-ups. Where a sequence of similar compounded preparations is prepared during the same working session for a series of patients (e.g. different concentrations of a cytotoxic preparation), particular care should be taken to avoid errors.
41. Where there is more than one workstation in a room, there should be a documented risk assessment performed and appropriate measures taken, before different compounded preparations are handled at the same time.

Preparation of Terminally Sterilized Compounded Preparations

42. Precautions to minimise contamination should be taken during all processing stages.
43. Microbiological contamination of starting materials should be minimal.
44. Materials liable to generate fibres should be kept to a minimum in clean areas.
45. Where appropriate, measures should be taken to minimise the particulate contamination of the end compounded preparations.
46. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not re-contaminated.

Sterilisation by Moist Heat

47. Sterilisation records should be available for each sterilisation run. They should be approved as part of the release procedure.
48. For effective sterilisation the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved. The validity of the process should be performed initially as well as subsequently on a regular basis, according to the risk, and whenever significant modifications have been made to the equipment or to the process.
49. Validated loading patterns should be established. It is recommended that photographs or detailed drawings are used in procedures to ensure that loads are packed in a consistent way.
50. Temperature and pressure should be recorded during each sterilisation cycle and periodically checked with steam tables. The independent temperature and pressure gauges on an autoclave should be monitored and logged during mid cycle and compared with the chart readings for similarity.
51. Air removal tests and leak tests on the chamber should also be frequently performed with porous load cycles.
52. Clean steam should be used where contact with critical surfaces is expected. Steam quality testing should periodically be performed including superheat, dryness value and tests for non-condensable gases.
53. Thermal indicators should be used to indicate whether a load has been sterilised (in order to avoid a mix up with non-sterile product).

Aseptic Processing

54. The key elements of the aseptic process include:
 - a) Maintaining the integrity of the aseptic processing area, and care of the workstation and its environment.
 - b) Handling and preparation of starting materials, especially any disinfection processes.
 - c) Entry of materials into the processing area.
 - d) Standard aseptic processing techniques, including not-touching critical surfaces, correct positioning of materials within the laminar airflow, and use of specific pieces of equipment and regular sanitisation of gloves.
 - e) Segregation and flow of materials to ensure no accidental cross-

- contamination or mix up of prescriptions or compounded preparations.
 - f) Removal of compounded preparation and waste materials from the processing area.
 - g) All aseptic processing should be carried out by competent staff who are authorised to perform their work by the Responsible Person.
 - h) The number of people present in the room should be kept to a minimum (however, during media fills the maximum permitted number of people should be present so as to present a worst case challenge).
 - i) Only sterile materials should be taken into grade A or B areas e.g. settle plates, swabs, and cleaning materials. Product solutions that are non-sterile should be filtered through a sterile filter of nominal pore size of 0.22 micron (or less) before being taken into Grade A or B areas. When this is not possible, adequate decontamination measures should be taken.
55. Process validation of aseptic procedures should be performed by using broth or a similar nutrient media to simulate the aseptic procedure (media fills) and should be performed initially as well as subsequently on a regular basis, according to the risk, and whenever significant modifications have been made to the equipment or to the process. The process simulation test should imitate as closely as possible routine aseptic procedures (i.e. manipulations that are normally conducted) and include all the critical production steps. Selection of the nutrient medium should be made based on dosage form of the compounded preparation and selectivity, clarity, concentration and suitability for the sterilisation of the nutrient medium.
56. Media fill vials should be incubated at an appropriate temperature taking care to invert containers periodically to ensure contact with all surfaces. Further guidance is given in PIC/S document PI 007. Any contamination should be fully investigated even if the container integrity is suspect.
57. Any interventions occurring during the preparation process should be recorded on batch documents. There should be an intervention policy with approved interventions that are simulated during media fills.
58. The in-use expiry date of any bulk solution used as an ingredient (e.g. a bag of parenteral infusion or a vial of cytotoxic agent) should be justified. Any containers of unpreserved products used as starting materials should not be used beyond 24 hours after first opening. They should be protected against contamination or deterioration at all times.
59. Sterile disposable components such as filters, needles, tubing etc should not be used beyond one working session and should be removed at the end of each day or session.
60. Where multiple containers are filled, filter integrity tests should be performed on

- every batch and care exercised to ensure that the capacity of the filter is not exceeded by compounded preparations having high bioburdens or through the filtration of excessive volumes. The filter should be compatible with the compounded preparation.
61. The transfer of materials into the Grade A workstation is usually done by disinfection or sanitisation rather than sterilisation and therefore it is important to have a written, validated Standard Operating Procedure for this process. It is essential to validate this method by practical studies that demonstrate the effective removal of viable organisms from all surfaces. Spraying and wiping is considered more effective than only spraying to sanitise surfaces.
 62. Purchasing bulk gamma irradiated or sterile components in double/triple wrapped form is recommended rather than spraying many individual components into the grade A zone (e.g. packs of syringes).
 63. The cleaning procedure should also effectively remove compounded preparation residues from the surfaces of the workstation.

SECTION 5 QUALITY CONTROL

64. All starting materials, components and packaging materials should be visually checked before use to ensure that they comply with the required specification.
65. If starting materials are themselves approved registered products then it is not usually necessary to test these before use, however, for some materials such as radiopharmaceuticals some testing may be required.
66. If a compounded preparation is prepared for a single patient, it is assumed that no end compounded preparation testing will be required except for radiopharmaceuticals where the activity is measured in each dose.
67. The extent to which physical, chemical and microbiological quality control tests are performed should be defined on the basis of a risk assessment and should comply with the requirements given in Chapter 7 of the Main Part of this Guide.
68. Samples for physical, chemical and microbiological analysis may be obtained from:
 - a) Unused compounded preparations
 - b) Additional samples that were specially prepared
 - c) An in-process sample taken at the end of the compounding procedure before the final seals are in place and before removing from the critical zone

69. Microbiological analysis is not necessary on each batch. Alternatively, a regular programme of microbiological analysis of the units produced over a certain period of time or a regular programme of media fills (i.e. process validation using broth) may be acceptable.
70. Any growth should be investigated and documented in a deviation report.
71. Sampling of the final container after completion of preparation and prior to the issue may be a threat to the compounded preparation integrity and is therefore not recommended. However, containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing
72. The testing laboratory should be fully conversant with the technical background and requirements of sterile preparation and have validated methods for analysing the compounded preparations and samples. The responsible person should ensure that the testing laboratory has a comprehensive knowledge of microbiology and that quality assurance systems are regularly reviewed. Off-site testing facilities should be regularly audited.
73. Methods of analysis should be stability indicating and validated appropriately.

SECTION 6 Monitoring

74. In addition to media fill simulations monitoring is performed to obtain evidence that the process, operators and facility are operating under control. Monitoring consists of qualification activities (classification “at rest”) and environmental monitoring of units in use (environmental monitoring “in operation”). For pharmaceutical applications, the major criteria upon which the sterile facilities are assessed should be the risk of microbiological contamination of the compounded preparation. However, because of the imprecision and variability associated with microbiological test methods it is recommended to complement microbiological environmental control with more practical physical monitoring.
75. The extent to which monitoring is performed should be defined and based upon a risk assessment. This section includes recommendations on monitoring frequencies. Local procedures should always be justified and may deviate from these recommendations. The following circumstances may lead to an increased monitoring frequency (i.e. more often than recommended in this section):
 - a) Detected deviations (e.g. monitoring results which are out of specification)
 - b) Changes
 - c) Interventions in the environment (e.g. building work)
 - d) Increased workload (more operational activities to be observed)

Potential circumstances which may justify a reduced monitoring frequency (i.e. less often than recommended in this section) include:

- a) Use of closed systems during preparation
 - b) Immediate use of compounded preparations
 - c) Terminal sterilisation of compounded preparations
 - d) Decrease of workload (less operational activities to be observed)
76. A written report of the test data indicating the significance of the results and recommended action should be brought to the attention of all relevant staff and full records kept on file for future reference.

Classification “at rest”

77. All areas associated with the sterile preparation process should be assessed by the Responsible Person for compliance with the relevant clean area grade in the unmanned state:
- a) On commissioning
 - b) Following changes or maintenance procedures, as appropriate
 - c) Routinely at an agreed frequency
78. Classification tests recommended frequencies for classification tests (Table 6.1)

Table 6.1	
Laminar flow cabinets (LFCs) / Biohazard Safety Cabinets (BSCs):	Frequency
Particle counts	Yearly
Room air changes per hour	Yearly
Air velocities on workstations	Yearly
HEPA filter integrity checks	Yearly
Isolators:	Frequency
Isolator alarm functional tests	Yearly
Isolator leak test	Yearly
HEPA filter integrity checks	Yearly

Environmental Monitoring “In Operation”

79. Regular monitoring of the environment, process and compounded preparation is an essential part of the quality assurance of all sterile compounded preparations.

Standards and guidelines are available for many of the physical and microbiological aspects (cf. PIC/S and EU GMP Guide for industrial manufacture). The Responsible Person and key personnel should refer to and have an understanding of these documents with particular emphasis on the sections relating to sterile processing.

80. Particulate importance should be attached to obtaining meaningful results, monitoring trends and setting 'in-house' standards and action limits. Information should be actively and knowledgeably assessed and not merely filed for record purposes.
81. Each unit should have a programme of periodic testing (e.g. sessional daily, weekly, monthly, quarterly and annual) with all results documented and retained for inspection. Recommended frequencies of physical and microbiological monitoring are shown for guidance in Tables 6.2 and 6.3. The optimum frequency for testing will depend upon the individual unit and the activities undertaken. The monitoring programme should confirm that the environment meets the appropriate standard. It is not a substitute for the continual vigilance of operators in ensuring the correct functioning of all equipment.
82. Physical monitoring recommended frequencies of physical monitoring (Table 6.2)

Table 6.3	
Laminar flow cabinets (LFCs) / Biohazard Safety Cabinets (BSCs):	Frequency
Pressure differentials between rooms	Before beginning of work, usually daily
Pressure differentials across HEPA filters (workstation)	Before beginning of work, usually daily
Particle counts	Quarterly in the operational state
Isolators:	Frequency
Pressure differentials across HEPA filters	Before beginning of work, usually daily
Isolator glove integrity	Visual checks every session

Isolator pressure hold test (with gloves attached)	Weekly
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83. Microbiological monitoring recommended frequencies of microbiological monitoring (Table 6.3)

Table 6.3		
	Direct working environment (Grade A zone)	Background environment
Settle plates	Every working session	Weekly
Glove finger dabs	At the end of each working session	At the end of each working session
Surface samples (swabs or contact plates)	Weekly	Monthly
Active air samples	Quarterly	Quarterly

It should be borne in mind that in the absence of compounded preparation testing, microbiological monitoring plays an extremely vital role in confirming that the compounded preparation is unlikely to be contaminated. Many compounded preparations are used before any microbiological results associated with its preparation, are known. The first indication that contamination has occurred in the workstation may well be a patient exhibiting pyrexia or septicaemia. Frequent monitoring and prompt reporting of results to the Responsible Person should help to reduce this possibility.

Test limits for monitoring

84. Microbiological test results require very careful analysis to elucidate any underlying trends. The relative imprecision of the methods used and the low levels of contamination seen do not lend themselves to easy interpretation. Warning or alert levels should be established that are well within the guideline limits provided in Tables 6.4 and 6.5, which are based on the requirements given in Annex 1 of the PIC/S and EU GMP Guide for industrial manufacture and in EN/ISO14644. Exceeding warning levels on isolated occasions may not require any more action than an examination of control systems. However, the frequency at which the limit is exceeded should be examined and should be low. If the frequency is high or shows an upward trend, then remedial action should be taken.
85. Physical monitoring limits for physical monitoring of controlled areas and devices (Table 6.4)

Table 6.4							
Grade	Maximum permitted number of airborne particles / m ³ equal to or above				Air changes (number per hour)	Air flow velocity (m/s ± 20%)	Pressure differential to adjacent low-class room (Pa)
	At rest		In operation				
	0.5 µm	5.0 µm	0.5 µm	5.0 µm			
A	3 520	20	3 520	20	N/A	0.45 HLF 0.30 VLF	N/A LFC >15 Isolator
B	3 520	29	352 000	2 900	>20	N/A	>10
C	352 000	2 900	3 520 000	29 000	>20	N/A	>10
D	3 520 000	29 000	Not defined	Not defined	>10	N/A	>10

Notes: N/A = not applicable LFC = laminar flow cabinet HLF = horizontal laminar flow; VLF = vertical laminar flow

For classification purposes in Grade A zones, a minimum sample volume of 1m³ should be taken per sample location. This will ensure that the classification process is not adversely affected by false counts associated with electronic noise, stray light, etc. For Grade A, the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥ 5.0 µm. For Grade B the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.

Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of loss of particles ≥ 5.0µm in remote sampling systems with long lengths of tubing. Isokinetic sample heads should be used in unidirectional airflow systems.

“In operation” monitoring may be performed 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.

86. Microbiological monitoring

Recommended limits for microbiological monitoring of clean areas in operation (Table 6.5)

Table 6.5				
Grade	Recommended limits for microbial contamination (a)			
	Air sample (cfu/m ³)	Settle plates, diam. 90mm (cfu/4hours) (b)	Contact plates, diam. 55mm (cfu/plate)	Glove print, 5 fingers (cfu/glove)
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes: (a) These are average values (b) Individual settle plates may be exposed for less than 4 hours in which case the limits should be appropriately reduced.

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