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PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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**PIC/S GUIDE TO GOOD PRACTICES
FOR THE PREPARATION OF
MEDICINAL PRODUCTS IN
HEALTHCARE ESTABLISHMENTS**

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Document History

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A. Introduction

A.1 Purpose

The purpose of this Guide is to provide guidance on Good Practices on the preparation of medicinal products for human use.

A.2 Scope

Whereas PIC/S Guide PE 009 applies to industrial manufacture of distributed medicinal products, the basic requirements presented in this Guide apply to the preparation of medicinal products normally performed by healthcare establishments for direct supply to patients.

At the time of issue this document reflected the current state of the art. It is recognised that there are acceptable methods, other than those described in this Guide, which are capable of achieving the principles of the Guide. This Guide is not intended to place any restraint upon the development of alternate systems, new concepts or new technologies, which provide a level of Quality Assurance at least equivalent to those set out in this Guide.

National legislation and regulatory policies laid down by the relevant competent authority should always be referred to when determining the extent to which the provisions laid down in this document are binding. This document is a stand-alone document and it should be used for PIC/S related inspections.

A.3 Reference to GMP Guide for industry

This Guide is divided into 9 main chapters, thus following the structure from the GMP Guide for industry (PIC/S document PE 009). The main text is complemented with Annexes supplementing the main part of this Guide and specifying the general rules described in there for the preparation of specific types of medicinal products, such as sterile products (Annex 1), and non-sterile liquids, creams and ointments (Annex 2). The specification of the general rules may include the highlighting of important points from the main part as well as the completion with more specific guidance for the special situation covered by the Annex.

B. Glossary

Many of the definitions in this glossary are identical to the definitions from the PIC/S Guide PE 009, and are included to improve readability of the text.

1. Active pharmaceutical 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. Bulk product

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

5. Calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

6. 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.

7. 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.

8. Controlled work area

An enclosed work area constructed and operated in such a manner and equipped with appropriate air handling and filtration systems to reduce to a pre-defined level the introduction, generation and retention of contaminants. A controlled work area may also be used to protect the external environment from the materials being handled in it e.g. vaccines or cytotoxics.

9. Critical zone

That part of the controlled 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.

10. Cross contamination

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

11. Deviation report

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

12. Extemporaneous preparation

A product, which is dispensed immediately after preparation and not kept in stock.

13. Expiry date

The end of the shelf life period, in non-coded form, after which the medicinal product should not be used. Also called the use before date.

14. Finished product

A medicinal product, which has undergone all stages of production, including packaging in its final container.

15. Healthcare establishments

Establishments supplying medicinal products to their own patients in line with national legislation.

16. Intermediate product

A partly processed material, which should undergo further preparation steps.

17. In-use expiry date

The end of the application period, in which a medicinal 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.

18. Packaging

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

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

19. 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.

20. Preparation

All operations of purchase of materials and products, production, quality control, release, storage, delivery of medicinal products and the related controls.

Note: The simple provisioning of medicinal products according to authorised instructions and without necessitating pharmaceutical technical knowledge, where medicinal products are made ready for immediate application (e.g. dissolution of a powder for immediate application according to the instructions in the package leaflet of an authorised product), is normally not normally considered as preparation.

21. Processing

That part of the preparation of a medicinal product involving the dosage form.

22. Production

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

23. Production Supervisor

The person responsible for supervision should be in the department where the production takes place. He/she should be aware of what is going on and able to ensure that the process is carried out in the prescribed manner.

24. Products for immediate use

Products to be administered immediately after preparation, which do not undergo holding or storage.

25. Pharmaceutical Isolator

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

26. Qualification

The risk based systematic and documented evidence that facilities, rooms or equipment work correctly, are suitable for the intended purpose and actually give the expected results.

27. Quarantine

The status of starting or packaging materials, of material and substances, of intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or rejection.

28. Releasing Officer

The person who releases the prepared medicinal products. This person may be the Responsible Person.

29. Responsible Person

The person who is ultimately responsible for all aspects of the preparation of medicinal products including the release of these items. This person must have sufficient scientific and technical education and experience to perform this duty.

30. Risk Assessment

Consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable. 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)?

31. Self audit

An assessment, undertaken under the responsibility of the same organisation in order to monitor the validity of the quality assurance system and the compliance with

this guide. It can be conducted by designated competent person(s) from the organisation or assisted by external experts.

32. Specifications

See Chapter 4.

33. Starting material

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

34. Stock preparation

A product, which is prepared for stock and is available for dispensing.

35. Transfer Device

A fixed or removable device, which allows material to be transferred into and out of a container or a pharmaceutical isolator, without exposing it to the external environment.

36. Validation

The risk based, systematic, GMP compliant and documented evidence that a defined process actually leads reproducibly to the required results.

37. Working session

A defined period where available evidence indicates that the appropriate working conditions are maintained.

1. Quality assurance system

1.1 Principles

In order to protect public health, medicinal products should be of high quality, safe and effective. They should be prepared 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 reliably, there should be a comprehensively designed and correctly implemented quality assurance system, incorporating the principles of Good Preparation Practices as described in this Guide. The quality assurance system should be documented and its effectiveness should be monitored.

1.2 Quality assurance

1. Quality assurance represents the sum total of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended purpose. Its effectiveness and its suitability should be assessed regularly.
2. Quality assurance ensures that:
 - a. Medicinal products are designed and prepared according to the latest state of knowledge.
 - b. Production and control operations are clearly specified and implemented according to the principles of Good Preparation Practice.
 - c. Medicinal products are only supplied if they have been correctly processed, checked and stored in accordance with the defined procedures and released by an appropriately competent person (i.e. Responsible Person or Releasing Officer).
 - d. Adequate measures are in place to ensure that medicinal products are released, stored and handled in such a way that the required quality can be assured throughout their shelf-life and the in-use expiry date.
 - e. Documentation systems are in place and maintained.

1.3 Good Preparation Practice for medicinal products

1. Good Preparation Practice is that part of the quality assurance system which ensures that products are consistently prepared to appropriate quality standards.
2. In order to prepare medicinal products of consistent quality, the following basic requirements should be met:
 - a. Personnel should be qualified and trained in accordance with their function. Responsibilities and competencies should be clearly defined.
 - b. Premises and equipment should be suitable for their intended purpose.
 - c. All quality-assurance processes should be assessed on their suitability and described by appropriate instructions and procedures.

- d. Processes related to the preparation of medicinal products should be performed according to the principles of Good Preparation Practice as described in this guideline. Records should show that all the steps required were completed. The documentation should demonstrate the complete history of a medicinal product.
- e. The quality of prepared products should be assessed. The assessment should be documented and usually include:
 - A review of the preparation documentation
 - A comparison of test results, environmental results and specifications, where appropriate
 - An assessment of any deviations
- f. Medicinal products are only released after an appropriately competent person (i.e. Responsible Person or Releasing Officer) has certified that they comply with all specified requirements.
- g. Medicinal products, starting and packaging materials should be handled and stored so that their quality is ensured throughout their shelf life. Complaints of products are assessed, the cause of quality defects should be investigated, appropriate measures should be taken against incorrect preparation and precautions should be in place, in order to prevent a re-occurrence of the defects.

1.4 Quality control

Quality Control is that part of Good Preparation Practice, which is concerned with sampling, specifications and testing and with the organisation, documentation and release procedures, which ensure that the necessary and relevant tests are actually carried out and that starting and packaging materials as well as intermediate and finished products are only released, if their quality complies with the requirements.

2. Personnel

2.1 Principles

The establishment and maintenance of a quality assurance system and the correct preparation of medicinal products relies upon personnel. For this reason there should be sufficient and competent personnel to carry out all the tasks. Individual responsibilities should be documented and clearly understood by the individuals. All personnel should be aware of the principles of Good Preparation Practice and the system for quality assurance. Personnel should receive initial and continuing training, which should also include the necessary hygiene instructions.

2.2 General requirements

1. The Responsible Person is responsible for the quality of the prepared medicinal products and for compliance with these guidelines. Specific duties may be delegated to appropriately competent persons (e.g. Releasing Officer, Production

Supervisor). A deputy should be nominated in the absence of the Responsible Person.

2. The preparation establishment should have an adequate number of competent personnel, so that purchase, storage, production, control and release of pharmaceutical products are fully and appropriately controlled.

3. The competency level of personnel will depend on the duties and requirements of the activities undertaken by the organisation.

4. The preparation establishment should have an organisation chart showing the organisational reporting structure.

5. The duties and responsibilities of all personnel, including any deputies, should be laid down in a job function or description.

2.3 Training and continued education

1. New personnel should receive training in all areas that are necessary for the fulfilment of their duties, upon recruitment and on a continuing basis.

2. The continuing education of personnel should be given and documented and can take place internally or externally.

2.4 Hygiene

1. Instructions should be available for hygienic behaviour and for appropriate clothing of personnel. Personnel should be trained accordingly. Clothing should be adequate for the activities to be performed.

2. The risk of contamination of the product by personnel should be minimised by adequate methods. Personnel should notify the Production Supervisor about infectious diseases and open lesions on the exposed surface of the body. The Production Supervisor decides on the fitness of the relevant person to carry out activities in the area of preparation or the specific protective measures that should be taken to avoid contamination of the product. If no adequate protection is possible, the person should not be allowed to be involved in preparation activities.

3. It should be guaranteed that no risk of contamination exists, either for personnel or products. Eating, drinking or smoking in the preparation area should be prohibited.

4. Adequate precautions should be taken to prevent contamination of the product through contact with the operator. Additional protective measures (e.g. sanitisation of hands, wearing gloves etc.) should be taken for medicinal products having an increased risk of microbiological contamination.

3. Premises and equipment

3.1 Principles

Premises and equipment should be suitable for the intended activities and they should not present any hazard to the quality of the product.

3.2 General requirements

1. Premises and equipment should be appropriately designed, built, used, maintained and upgraded, ensuring that they are suitable for the intended activities and to minimise the risk of errors. The capacity should be sufficient to enable a logical workflow and appropriate segregation of activities.
2. In order to reduce the risk of contamination - for example by cross contamination or by the accumulation of dust and dirt – appropriately designed premises and equipment as well as careful and suitable working techniques should be used. The design should enable thorough cleaning. Special care should be taken when samples are taken or when equipment is cleaned and, where applicable, disinfected after repair or maintenance.
3. Adequate measures should be taken against the entry of insects and other animals (pest control).
4. Washing and cleaning activities should not themselves be a source of contamination.
5. Production, storage and quality control areas should be accessible to authorised personnel only.
6. Environmental conditions (temperature, humidity, light) during production, quality control and storage (including cold storage) should be defined and monitored and, if necessary, controlled. Monitoring results should be documented, assessed and retained. When conditions fall outside the defined limits, adequate corrective action should be taken.
7. All areas should be clean, orderly and well lit.

3.3 Production areas

1. Production areas should allow adequate segregation from other activities.
2. Separation of areas for specific dosage forms (e.g. dry and wet production facilities) should be considered. If separation of areas for specific dosage forms is not possible, there should be a documented risk assessment performed and appropriate measures taken, before different dosage forms are handled at the same time.
3. Dedicated rooms should be provided for hazardous products, e.g. cytostatics, penicillins, biologicals, radiopharmaceuticals, blood products. In exceptional cases

the principle of campaign working may be acceptable, provided that specific precautions are taken and any necessary risk assessments have been performed.

4. Materials and products should be stored and handled so that the risk of mix-ups of different products or of their ingredients is minimal, that cross contamination is avoided and that the risk of missing or incorrectly performing a processing step is reduced.

5. Weighing and sampling areas should be sufficiently separated from other preparation areas in order to avoid cross-contamination.

3.4 Storage areas

1. Storage areas should have sufficient capacity to allow orderly storage of the various categories of materials and products. Examples of these categories are: starting and packaging materials, intermediate and finished products, products in quarantine, released, rejected, returned or recalled products.

2. Starting and packaging materials should normally be stored outside the preparation areas, unless adequately segregated.

3. Materials and products that are in quarantine, rejected, returned or recalled should be stored in segregated areas and should be clearly marked as such.

4. The storage conditions (e.g. temperature, relative humidity), necessary in order not to adversely affect the material or product quality, should be specified and monitored. Control should be adequate to maintain all parts of the relevant storage area within the specified conditions. Storage areas should be equipped with recorders or other monitoring devices that will indicate when the specified conditions have not been maintained, so that out of specification situations can be assessed and appropriate measures taken.

3.5 Quality control areas

Normally, quality control activities should be performed in a dedicated area. If this cannot be achieved, steps should be taken to avoid errors and contamination.

3.6 Ancillary areas

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

2. Toilets and facilities for changing clothes and for washing should be easily accessible and appropriate for the number of users. Toilets should not be directly accessible from production or storage areas.

3.7 Equipment

1. The preparation equipment should be designed, located and maintained to suit its intended purpose.
2. Equipment should be constructed so that it can be easily and thoroughly cleaned. It should be stored in a clean and dry condition.
3. Measuring, weighing and control equipment should be of the required precision: it should be calibrated as well as checked for correct function and re-calibrated at appropriate intervals.
4. Defective equipment should be removed from production and quality control areas, or at least be clearly labelled as out of order.

4. Documentation

4.1 Principles

Good documentation on paper or in electronic form constitutes an essential part of the quality assurance system. Easily understandable and clearly written documentation prevents errors from spoken communication and permits traceability of a prepared medicinal product.

4.2 General requirements

1. Quality relevant data, including risk assessments, should be documented.
2. The term documentation summarises particularly:
 - a. **Specifications**
There should be appropriately authorised and dated specifications for starting materials, packaging materials, and finished products; where appropriate, they should also be available for intermediate or bulk products.
 - b. **Product specific instructions**
There should be processing, packaging, quality control and release instructions available to describe the composition, specifying all starting and other materials used and laying down all processing and packaging operations as well as quality control tests and release.
 - c. **Records**
Processing, packaging and quality control documents, which record the quality relevant facts of the history of a medicinal product during preparation.

d. General procedures and additional documentation

Instructions for the performance of standardised operations and other evidence which document the history and the quality of a medicinal product. Examples are the description of receipt of goods, sampling, reference samples of prepared products, testing, release, rejection, calibration, cleaning, disinfecting, performance of hygiene activities, personnel training, and operation of equipment.

3. All specifications, instructions and procedures should be approved, signed and dated by the Responsible Person or by a person appointed by the Responsible Person.

4. All written documents should be legible, clear, unambiguous and up to date. Electronic records should be adequately protected against unauthorised changes and against data loss. The readability of electronically stored data needs to be guaranteed over the whole retention period.

5. The totality of these documents should ensure the complete traceability of the preparation process of a medicinal product.

6. Any alteration made to a document should be signed and dated. The alteration should permit the reading of the original information. The reason for alterations should be evident. Equivalent measures should be applied to electronic records.

7. Records should be retained for a sufficient period to satisfy national 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 at least five years after their use.

4.3 Documentation for extemporaneously prepared products

1. For extemporaneously prepared products, the minimum requirements are to specify the name, the strength and the expiry date. Approved starting materials should be used and relevant documentation should be available.

2. The prescription can represent the processing and packaging instructions. If no specific instruction is available, a general instruction for every type of preparation should be available, e.g. preparation of capsules, ointments, etc.

3. A record should be retained showing the key processing and packaging steps, including the name of the person responsible for each step. This record should comply with Chapter 4.4.3 where applicable.

4.4 Documentation for products prepared regularly or for stock

1. For medicinal products which fall within the scope of this Guide, there is normally no registration file approved by the regulatory authorities. Therefore, product specific documentation (a product file) should be kept, if products are

prepared extemporaneously on a more frequent basis or for stock. This will include specifications, instructions and records.

2. In order to establish product specific specifications, instructions and procedures, a pharmaceutical assessment of therapeutic rationale, safety data, toxicity, biopharmaceutical aspects, stability and product design should be carried out, before preparation takes place.

3. The product file should also include a product review (e.g. QC testing data, stability data, validation data), as soon as a product is used repeatedly or over longer periods.

4.4.1 Specifications

1. For starting and packaging material as well as for intermediate or finished products, approved specifications (for example references to the Pharmacopoeia) should be available.

2. Specifications for starting materials and, where applicable, packaging materials should include:

- a. Name (incl. reference to pharmacopoeia, where applicable)
- b. Description
- c. Procedures for sampling and testing with references
- d. Qualitative and quantitative requirements with the acceptance limits
- e. Where applicable, requirements concerning storage and precautions
- f. Shelf-life

3. Specifications for intermediate or finished products should include:

- a. Name
- b. Description of dosage form and strength
- c. Formula
- d. Package details
- e. Instruction for sampling and testing, or a reference to procedures
- f. Qualitative and quantitative requirements with the acceptance limits
- g. Storage conditions, microbiological requirements and any special handling precautions, where applicable
- h. Shelf-life

4.4.2 Instructions

Processing instructions

1. Processing instructions should include:

- a. Product name
- b. Description of dosage form and strength
- c. Batch size
- d. Type and quantity of all starting materials to be used

- e. Expected yield of intermediate or finished product
- f. Detailed instructions for the processing steps
- g. Instructions for in process controls with the acceptance limits
- h. Storage conditions (also for intermediate products) and precautions, where applicable

Packaging instructions

2. Packaging instructions should include:
 - a. Product name
 - b. Dosage form and strength
 - c. Package size
 - d. Labelling text or master label
 - e. List of all necessary packaging materials, including type, specification, size and quantity
 - f. Detailed instructions for the packaging steps
 - g. Instructions for in-process controls with the acceptance limits
 - h. Storage conditions (also for intermediate products) and precautions, where applicable

4.4.3 Records

Processing and packaging records

1. The processing and packaging records should include:
 - a. Qualitative and quantitative information of all materials used such as batch number of the material used or other references, enabling the traceability to further quality related documents (e.g. product, number of analysis, number of certificate)
 - b. Identification of the product (including batch number and preparation formula) and the date of preparation
 - c. Information on all operations and observations, such as documentation of cleaning, line clearance, weighing, yields of intermediate steps, readings and calculations, as well as sampling
 - d. Records on batch specific in process controls and on results obtained
 - e. Initials or signature of the responsible operators for significant processing steps and controls
 - f. Any deviations from the approved processing instruction
 - g. Yield of finished product
 - h. A specimen of the label used
 - i. Reconciliation of labels
 - j. Where applicable, name of patient or identification

2. The processing record should be finally assessed and approved by the Responsible Person or Releasing Officer, by dating and signing.

Quality control records

3. Quality control records should include:

- a. Product name
- b. Dosage form and strength
- c. Batch number
- d. Preparer or supplier
- e. Testing method; any deviations from the method should be justified
- f. Test results; where applicable the certificate of analysis from preparer or supplier including the date of the test
- g. Expiry date of starting material
- h. Date of the test
- i. Initials of the person performing the test
- j. Decision on release or rejection including the initials of the Responsible Person or Release Officer

4.5 General procedures and additional documentation

1. Written procedures should be available in particular for:
 - a. Receiving, sampling and releasing starting and packaging materials
 - b. Release and rejection of intermediate and finished products, including emergency release
 - c. Recalls of finished products
 - d. Calibration and qualification of equipment (e.g. autoclaves, dry heat sterilisers, thermometers, balances, equipment for melting point determination)
 - e. Validation of processes
 - f. Cleaning, disinfecting and maintenance of equipment (e.g. water demineralisation equipment, distillation equipment, refrigerator) and facilities
 - g. Training of personnel (e.g. related to the realisation of hygiene measures)
 - h. Operation of equipment, where applicable
 - i. Procedures for monitoring, including trending
 - j. Procedure for actions to be taken in the case of deviations and complaints
 - k. Self audits
2. The performance of these activities should be recorded, e.g. in the batch documentation, on a special form or in a log book.

5. Production

5.1 Principles

Production operations should guarantee the required quality and should be performed and supervised by competent people.

5.2 General requirements

1. Production should be performed by trained personnel.
2. Starting materials should be approved before use. The identity, weight and volume of all starting materials should be independently checked by a second person or by a validated computerised system (e.g. barcode check)
3. Except for the preparation for individual patients, production should be performed based on a written instruction, in which all relevant processes are laid down in detail.
4. To avoid mix-ups, all necessary technical and organisational measures should be taken.
5. The process steps which have been performed should be recorded.
6. Equipment and material used for all operations should be suitable for the intended use.
7. Products and materials should be protected against microbial and other contamination at all preparation steps.
8. At all times during preparation, all products should be identified. Labels or indications on containers and equipment should be clear and unambiguous.
9. At all times during preparation, the operational status (e.g. cleaned, in use) of rooms and equipment should be clear.

5.3 Prevention of cross contamination

To avoid cross contamination, the necessary technical and organisational measures should be taken.

5.4 Product risk assessment and demonstration of suitability

1. The risk potential for health damage in case of failures (e.g. quality defects) varies with different types of products and should therefore be assessed and documented by an appropriately competent person. The risk potential is mainly influenced by:

- a) The probability of occurrence of a mistake.

Examples for associated risk factors are:

- Low concentration of a non-dissolved active ingredient (risk of incorrect dosage due to non-homogeneity)
- High susceptibility for microbial growth (risk of microbial growth)
- Longer periods of storage or use (risk of chemical degradation or microbiological growth)

- Type of facility where a product is prepared in (risk of contamination in case of non-controlled working environment)
- Bad working technique (risk of mix-ups or contamination)

b) The probability of detection of a possible mistake.

Examples for associated risk factors are:

- Lack of control mechanisms, e.g. monitoring, in process and final controls (risk of non-detection of mistakes or defects)

c) The consequences of a possible mistake (health risk).

Examples for associated risk factors are:

- Scale of the operation (risk of affecting a larger number of patients due to extended use)
- Type of product prepared and route of administration, e.g. sterile preparations prepared for intravenous application (risk due to systemic consequences of microbiological contaminations)

Further information on the performance of risk assessments may be found in ICH Guideline Q9 (Quality Risk Management).

2. The measures which are necessary to adequately address the identified risk potential and to guarantee the required quality should be taken.

3. The need for demonstrating the suitability of the measures taken depends on the identified risk potential and should be assessed.

4. Where a demonstration of the suitability is found necessary, the related qualifications and validations should be performed. The principles of qualification and validation are described in Annex 15 of PIC/S document PE 009. If the same process is applied to a series of products (e.g. aseptic filling of comparable individual preparations), the validation approach might consider the performance of a single worst case study taking into account the relevant criteria for all the related products. This practice is termed “bracketing”.

5. The influence of changes of qualified facilities, rooms and equipment, the influence of changes in the composition or in the quality of starting materials and the influence of changes of validated processes on quality should be assessed by an appropriately competent person with regard to the necessity and the extent of a re-qualification or of a re-validation, before a change is made.

6. The appropriateness of existing validations should be checked at suitable intervals in accordance with a predetermined procedure. If the validation is no longer acceptable – for example due to a series of small changes, which were individually not be considered as relevant but when combined become significant – the process should be re-validated.

5.5 Starting materials

1. Starting materials used for the preparation of medicinal products should comply with the relevant specifications.

2. Starting materials should be stored in the original containers. If transferred into other containers, these should be clean and labelled with all batch specific information. In this regard quality should be guaranteed during the whole period of use. Mixing of different batches is prohibited.
3. The date of the first opening should be indicated for starting materials with a short in-use expiry date.
4. Outdated or obsolete starting material should be destroyed and the disposal recorded.

5.6 Processing operations

1. Before any processing operation is started, it is important to ensure (and document) that the work area and the equipment are clean and free from any starting materials and products not required for the current operation and that all equipment is functioning satisfactorily. Potential problems should be reported to key personnel.
2. Intermediate products should be stored under suitable conditions and labelled unambiguously.
3. Material superfluous for production should normally be destroyed. It should only be returned to stock after careful verification. Records should be kept.

5.7 Packaging material

1. Packaging material may only be used if suitable for the particular purpose. In particular there should be no risk that medicinal products are negatively influenced by containers or by closure systems. If applicable, the packaging material used should allow an anti-microbial treatment and sufficient protection against external influences and possible contamination.
2. Labels should comply with national legislation and normally include the following information:
 - a. Product name
 - b. Dosage form
 - c. Active pharmaceutical ingredient(s) and amounts(s)
 - d. Content (amount, e.g. grams, number of tablets etc.)
 - e. Batch number
 - f. Expiry date and, if necessary, application date
 - g. Preparer
3. Outdated or obsolete packaging material should be destroyed and the disposal recorded.

5.8 Packaging operations

1. Containers should be clean before use.

2. To exclude mix-ups or mislabelling, labelling should follow immediately after filling and closing. Otherwise, adequate security should be provided.

5.9 Rejected, recovered and returned materials and products

1. Rejected materials and products should be marked as such and stored in separate areas.

2. The reprocessing and recovery of non-compliant products should be by exception only and should be authorised by the Responsible Person. It should be carried out in accordance with written operating procedures and be recorded. A risk assessment should be performed, which includes possible consequences for the quality and the expiry date of the product, as well as the requirement for any additional tests.

3. The Responsible Person or Releasing Officer should decide whether to release reprocessed or recovered products after assessing any relevant documentation (and results of additional tests).

4. Dispensed products that have been returned and had left the control of the preparation establishment, should be destroyed unless there is no doubt their quality is satisfactory. They may exceptionally be considered for reprocessing or recovery only after they have been critically assessed under the responsibility of the Responsible Person or Releasing Officer in accordance with a written procedure. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use. Any action taken should be appropriately recorded.

6. Quality control

6.1 Principles

1. Quality control ensures that all requirements related to quality are met.

2. In particular it ensures that the necessary tests are carried out and that products are only released if they comply with the quality requirements.

3. The extent to which quality control tests are performed should take into account stability information and physical properties and should be defined on the basis of a risk assessment (cf. Chapter 5.4).

4. Quality control and release activities should be independent of preparation activities.

6.2 General requirements

1. Test equipment should be suitable for its intended use.

2. All operations should be performed in accordance with the defined procedures and recorded.

3. Test records should be retained for at least one year after the expiry date of the starting materials or of the finished product, whichever is the longest.

6.3 Sampling

1. Samples taken for analysis should be representative of the material being tested.

2. When finished products are subjected to analytical controls, an appropriate number of analytical reference samples should be retained for a suitable period of time after the expiry date.

6.4 Testing

Testing of raw materials

1. The quality requirements and tests should comply with the applicable Pharmacopoeia. If the Pharmacopoeia does not include a suitable monograph, other Pharmacopoeias may apply. Otherwise, formularies or professional standards, which may have been recognised by the competent authority, should be used. If no officially recognised standard exists, a standard should be defined based on local investigations or on specialised literature. In the latter case, the method should be validated.

2. The risk assessment to define the testing of raw materials should consider that confirming the identity of the content of every container is of special importance. In any case the label and inviolability of each container should be verified. Batch certificates should only be referred to, where the reliability of the manufacturer or supplier issuing the certificate was verified.

3. Released finished products used as starting materials are normally not tested.

Testing of finished products

4. The risk assessment to define the testing of finished products should especially consider product properties, the use of the product as well as risks associated with its preparation.

5. Normally, no quality control testing is performed for extemporaneously prepared products.

Laboratory reagents used for testing

6. Laboratory reagents prepared for stock should be marked with the preparation date and with the expiry date.

6.5 Release

1. The Responsible Person is ultimately responsible for the quality of the medicinal products prepared and released. The actual release can be delegated to another appropriately competent person (i.e. Releasing Officer).
2. Product release should include verification that the medicinal products comply with the valid specifications and that they have been prepared in accordance with valid procedures and with the principles of Good Practices for preparation described in this Guide.

7. Work contracted out

7.1 Principles

1. Depending on the local situation and on national legislation, the work contracted out by a healthcare establishment may include activities, which are directly involved with preparation, such as processing, packaging or quality control, but also services, which are not directly involved with preparation, but which can nevertheless have a significant effect on the quality of the products prepared, or on any quality control results produced. Such services, which often are contracted out to another department or organisation, may include:
 - a. maintenance of the air handling system, water systems or other utility systems
 - b. maintenance of key equipment such as isolators, laminar air flow cabinets, sterilisers, balances
 - c. sterilisation of components and consumables such as mops, clothing, trays
 - d. environmental monitoring services
 - e. supply of microbiological consumables (e.g. settle plates)
 - f. handling of waste
 - g. pest control
2. Any work, which could affect the quality of the products prepared, and which is contracted out to a third party, should be the subject of a written technical agreement.
3. In an emergency, an individual, extemporaneously prepared medicinal product may be obtained without a written contract. This should be an exceptional occurrence.

7.2 General requirements

1. A technical service level agreement (contract) should specify the details of the work to be done, the specification which it should meet and the responsibilities of each party.
2. The contract should be authorised and signed by the contract acceptor (i.e. third party contractor) and by the Responsible Person of the contract giver.

7.3 Contract giver

1. In the contract, the contract giver should specify exactly what level of service is required and to what specification.
2. The contract giver should make sure that the contract acceptor is competent and – if necessary – authorised to carry out the service successfully. The extent to which contract acceptors are audited should be defined on the basis of a risk assessment. This risk assessment should include the existing evidence that a contract acceptor complies with the contract and with legal requirements (e.g. Good Preparation Practices). Audits of contract acceptors should be performed by the Responsible Person or someone nominated by the Responsible Person.
3. Any reports produced by the contract acceptor, summarising results or work carried out, should be formally reviewed and accepted by the contract giver as complying with the required specification. This review and formal acceptance should be detailed in the quality system procedures and the procedures should indicate who is authorised to review and accept these reports.

7.4 Contract acceptor

1. Any work should be performed in accordance with the contract.
2. Any service or results not complying with the required specification should be notified to the Responsible Person of the contract giver.
3. 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 should ensure that the preparation and critical information is made available in the same way as between the original contract giver and contract acceptor.

8. Complaints and product recalls

8.1 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 finished products which have severe deficiencies, a suitable procedure should be developed.

8.2 Quality problems

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.
2. When a product defect is reported, consideration should be given to check if other products could be affected and to cease supply until the problem is fully investigated.

8.3 Recalls

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

9. Self audits

9.1 Principles

1. The quality assurance system, including personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and work contracted out, should be examined at regular intervals in order to verify their conformity with the principles of Good Preparation Practice as described in this Guide.
2. A self audit programme should be established which considers the type and complexity of operations performed and includes an annual self audit plan with records and evidence that adequate corrective actions are undertaken.
3. Self audits should be conducted in an independent and detailed way by designated competent people.

ANNEX 1

GUIDELINES ON THE STANDARDS REQUIRED FOR THE STERILE PREPARATION OF MEDICINAL PRODUCTS

Introduction

1. The sterile preparation of medicinal products includes:
 - The preparation of terminally sterilized products
 - 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 medicinal products. 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 high risk category products, for example due to:
 - The increased potential for microbiological contamination for products prepared in uncontrolled environments;
 - The higher levels of microbial contaminants in uncontrolled environments;
 - The increased risk of systemic infection associated with products prepared in uncontrolled environments;
 - The increased risk of medication errors when preparing injections without pharmacy supervision.

The preparation should take place in well-controlled environments using well established, quality assurance driven procedures. This considerably reduces the risk linked with these products.

4. For individual product types examples of their more specific risk factors are:

Cytotoxics and radiopharmaceuticals: High level of hazard to the operator preparing the product 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 products 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. biologicals, 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 products and an appropriate training in microbiology.
6. All sterile preparation should be carried out by appropriately trained personnel. Production Supervisors for sterile preparation activities should be appropriately competent and should be authorised in writing by the Responsible Person.
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 product 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 legislation relating to Ionising Radiation Regulations.
9. All staff should receive training which will provide them with:
 - a) an appropriate knowledge of Good Manufacturing Practice or Good Preparation Practice
 - b) a knowledge of local practices including health and safety
 - c) competence in the necessary sterile skills
 - d) a knowledge of pharmaceutical microbiology
 - e) a working knowledge of the department, products, 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 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 HEPA filters, type of work station, 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 products. In case of the preparation of cytostatics and radiopharmaceuticals, measures should also be taken to protect the operator from the materials being handled.

Clean areas for the preparation of sterile products are classified in 4 grades (A, B, C and D) according to the required characteristics of the environment (cf. Section 6). The level of room classification should be specified according to the activities performed and the products prepared.

Accordingly, for each clean room or suite of clean rooms “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 a 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 inside 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 sterilized products:

18. Preparation of components and most products 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 to the product,

for example, because the product actively supports 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 products for terminal sterilisation should be done in at least a grade C environment.

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

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

Table 2.1

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

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 products should be done in a grade A environment.

Handling and filling of aseptically prepared products (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 product 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 operator and 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 products 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:

- Time between preparation and use
- Use of a closed system (please see glossary)
- 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. cytostatics, penicillins, 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 product 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:

- 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.
 - 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.
 - 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 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 micro organisms 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 processing records reproduced from a suitably approved master format 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 product.
35. Completed processing 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. Processing instructions and records will vary for each unit and should be designed to minimise the possibility of transcription errors. Processing instructions and records may be combined in one document (“worksheets”). Processing documentation should comply with the requirements given in Chapter 4.4 of the Main Part of this Guide.

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 product 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 product, which is not a simple aqueous or oily solution.
40. The preparation of different products 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 products 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 products are handled at the same time.

Preparation of terminally sterilized products

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 fibers should be kept to a minimum in clean areas.
45. Where appropriate, measures should be taken to minimise the particulate contamination of the end product.
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 tests 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 air flow, 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 products.
 - f) Removal of product 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 product and

selectivity, clarity, concentration and suitability for 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 interventions 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 products having high bioburdens or through the filtration of excessive volumes. The filter should be compatible with the product.
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 product residues from 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 licensed medicinal 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 product is prepared for a single patient, it is assumed that no end product 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 (cf. Chapter 5.4 of the Main Part of this Guide) and should comply with the requirements given in Chapter 6 of the Main Part of this Guide.
68. Samples for physical, chemical and microbiological analysis may be obtained from:
- a) Unused products
 - 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 issue may be a threat to product 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 products 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 (cf. Chapter 4) 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 product. 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 (cf. Chapter 5.4 of the Main Part of this Guide). This section includes recommendations on monitoring frequencies. Local procedures should always be justified and may deviate from these recommendations.

In addition to the risk factors given in Chapter 5.4 of the Main Part of this Guide, the following circumstances may lead to an increased monitoring frequency (i.e. more often than recommended in this section):

- Detected deviations (e.g. monitoring results which are out of specification)
- Changes
- Interventions in the environment (e.g. building work)
- 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:

- Use of closed systems during preparation
- Immediate use of prepared products
- Terminal sterilisation of products
- 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)

Laminar flow cabinets (LFCs) / Biohazard Safety Cabinets (BSCs):	
Particle counts	Yearly
Room air changes per hour	Yearly
Air velocities on workstations	Yearly
HEPA filter integrity checks	Yearly
Isolators:	
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 finished product is an essential part of the quality assurance of all sterile prepared products.

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. Particular 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)

Laminar flow cabinets (LFCs) / Biohazard Safety Cabinets (BSCs):	
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:	
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

83. Microbiological monitoring

Recommended frequencies of microbiological monitoring (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 end product testing, microbiological monitoring plays an extremely vital role in confirming that the product is unlikely to be contaminated. Many products 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)

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)

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.

ANNEX 2

GUIDELINES ON THE STANDARDS REQUIRED FOR THE PREPARATION OF NON-STERILE LIQUIDS, CREAMS AND OINTMENTS

Introduction

1. This Annex is a supplement to the main part of this Guide and specifies the general rules described therein for the preparation of non-sterile liquids, creams and ointments. Where only single containers are produced for immediate use there may be scope to reduce some of the requirements below.

Principle

2. Liquids, creams and ointments may be particularly susceptible to microbial and other contamination during preparation. Therefore special measures should be taken to prevent any contamination.

Premises and Equipment

3. The use of closed systems for processing and transfer is recommended in order to protect the product from contamination. Production areas where the product or open clean containers are exposed should normally be effectively ventilated with filtered air.
4. Production areas should not be used for other activities.
5. Measures to reduce the risk of contamination should be taken and may include:
 - a) The use of dedicated garments and hair covers.
 - b) Where open procedures are used it is recommended that there is local air filtration and gloves are worn.
 - c) Prompt cleaning of used equipment.
 - d) Rinsing equipment that contacts the product with an appropriate grade of water after washing (purified water or bottled water for injection or irrigation may be suitable if used within 24 hours of opening).
 - e) Ensure that residues of cleaning and sanitising agents are removed (e.g. hypochlorites).
 - f) Check if equipment is clean and dry before being stored.
 - g) Careful storage of cleaned equipment.
 - h) All materials brought into the production area should be clean.
 - i) Sanitising critical surfaces before use with alcohol.
 - j) Checking containers and lids to ensure they are clean and dry before use.
 - k) Final product containers should not be re-used.
 - l) Mops and cloths should not shed fibres, they should be sanitised each day if they are reused and should not be used to clean other areas.
 - m) If more than one activity is undertaken in the production area at a time, there should be adequate segregation to prevent cross contamination and mix-ups. A risk assessment should be

- performed.
- n) The use of dedicated equipment is recommended for potent substances, penicillins, cephalosporins, sensitising agents, cytotoxics, ectoparasiticides and other substances that are very hazardous or difficult to clean. These materials should be identified and a risk assessment performed.
6. Tanks, containers, pipe work and pumps should be designed and installed so that they may be readily cleaned and if necessary sanitized. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.
 7. The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for parts coming into contact with product. Where glass equipment is used, it should be checked for damage before and after use.

Production

8. The chemical and microbiological quality of water used in production should be specified and monitored.

It should be specified according to the “Note for guidance on quality of water for pharmaceutical use”, issued by the European Agency for the Evaluation of Medicinal Products (EMA), and should comply with pharmacopoeial requirements.

Where appropriately certified sterile bottled water for injection or irrigation is used, there is no need to perform microbiological or chemical tests. For routine monitoring of water systems, general tests such as bioburden (total viable aerobic count), conductivity, total organic carbon (TOC) or comparable readings, should be periodically recorded (typically weekly). Specific chemical analysis should be performed occasionally (typically 3 monthly). Care should be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. After any chemical sanitisation of a water system, a validated flushing procedure should be followed to ensure that the sanitising agent has been effectively removed.

9. Materials likely to shed fibres or other contaminants, like cardboard or exposed untreated wood, should not be present in areas where products or clean containers are exposed.
10. Care should be taken to maintain the homogeneity of mixtures, suspensions, etc. during filling. Mixing and filling processes may require validation, and mixing times and speeds should be recorded. Special care should be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained.
11. When the finished product is not immediately packaged, the maximum period of storage and the storage conditions should be specified and adhered to. It is recommended that product is packaged as soon as possible (the same day).
12. The extent to which physical, chemical and microbiological quality control tests are performed should be defined on basis of a risk assessment (cf. Chapter 5.4 of the Main Part of this Guide). If possible, samples of the finished product

should be visually examined before release.

13. Expiry dates (use by dates) should be set and justified for the unopened product. Once the container is opened, it may be necessary to recommend an in-use expiry date.

ANNEX 3

GOOD PRACTICES FOR THE PREPARATION OF RADIOPHARMACEUTICALS IN HEALTHCARE ESTABLISHMENTS

Introduction

1. There are various types of radiopharmaceuticals prepared in healthcare establishments including:

- Sterile products with a marketing authorisation which are aseptically prepared in the healthcare establishment. These are typically used for routine diagnostic purposes in nuclear medicine and include: Technetium-99m radiolabelled ligands obtained by the combination of the kit component with [^{99m}Tc]pertechnetate from a radionuclide generator.
- Radionuclide precursors with a marketing authorisation, for example Yttrium-90 which are used as starting materials for synthesis.
- Sterile products without a marketing authorisation which are synthesised, radiolabelled, purified and formulated for diagnostic or therapeutic use. The radionuclides, especially short lived ones, may be produced on site with a cyclotron, for example: Fluorine-18, Oxygen-15 or Carbon-11. Alternatively they can be supplied as radiochemicals, for example Iodine-123, Iodine-124, Lutetium-177.

Also the Germanium-68 / Gallium-68 radionuclide generator system can supply on site Gallium-68 as a PET radionuclide.

Attention should also be given to the non radioactive cold chemical precursor which derives in most cases as a chemical substance from external suppliers. As this chemical precursor designates on first hand the pharmacokinetic behaviour of the radiolabelled active substance special attention should be given to the identity and purity. Impurities also might mask the radionuclides instead of the chemical precursors.

- Oral products with or without marketing authorisation which are prepared as capsules or solutions which the patient takes for diagnosis or therapeutic use (e. g. Iodine-131 for thyroid treatment).
 - Inhalation products with or without marketing authorisation, as gas, aerosols or particles, (for example [^{81m}Krypton], [^{99m}Tc]-DTPA, [^{99m}Tc]-Graphite).
2. Radiopharmaceuticals are different from other pharmaceutical products due to the safety issues inherent with these products and they should comply with any national requirements for radiological protection and GMP. Moreover a demanding technical difference and challenge is that in most cases, diagnostic radiopharmaceuticals need to be prepared, controlled and used within a short time of a few hours or even minutes due to the physical half life of the radionuclides.

3. Some countries may have already established a licensing framework for the preparation of radiopharmaceuticals in healthcare establishments. Routine inspections are often carried out based on national requirements at regular intervals.

Purpose

4. The purpose of this Annex is:
 - To supplement and amend current guidance for the preparation of radiopharmaceuticals. This Annex does not repeat any guidance for sterile product preparation which is already contained in Annex 1 of this Guide.
 - To supplement any guidance already developed by national competent authorities

The purpose is not:

- To provide detailed technical information about radiopharmaceuticals which are available from other literature sources.
- To replace any guidance already developed by national competent authorities.
- To alter any specifications and quality control testing procedures for radiopharmaceuticals which are already specified in a national pharmacopoeia.
- To provide detailed guidance on radiological safety and protection.

Scope

5. This Annex covers the preparation of radiopharmaceuticals in healthcare establishments only.

It does not cover:

- The manufacture of radiopharmaceuticals with a marketing authorisation.
- The manufacture of radiopharmaceuticals for research or for clinical trials as some healthcare establishments and universities may share common facilities or have specific national authorisations relating to the preparation of these products.

SECTION 1

Personnel

6. Personnel including contract staff should have a detailed knowledge of the risks of working with ionising radiation and have knowledge of radiological protection. Personnel should be monitored regularly and their exposure to ionising radiation minimised.

7. The preparation and release of product should be carried out by suitably qualified and trained personnel with detailed knowledge of Good Practice for the Preparation, aseptic processing and radiochemistry.
8. Due to the small number of personnel working in healthcare establishments there must be a clear separation of responsibilities for QC and production activities. It would be unacceptable for one person to perform both tasks for the same product. There should also be specific release procedures for working outside normal working hours.
Note: For products prepared from licensed kits and generators in accordance with the manufacturer's instructions, where QC testing is not required, one person could make the product but the release to the patient should be performed by an independent person.
9. There should be sufficient personnel to run the production unit without compromising quality. Factors such as the number of personnel available and the available production time should be used to develop a capacity plan to ensure that the quality system is not stressed.
10. Some units attached to universities or major clinical centres may prepare doses for patient administration and also for research. It is important that research personnel do not make routine patient doses unless specifically trained in GMP for which written training records are available.

SECTION 2

Premises and equipment

11. Radiopharmaceuticals should be prepared in dedicated facilities.
12. Radiopharmaceutical preparations for injection should be prepared in an environment which protects the product from microbial contamination. At the same time the environment should also be protected from ionising radiation.
13. Where both research and preparation activities are carried out at the same location these should be physically or organisationally separated from each other to avoid research personnel impacting on GMP tasks.
14. The appropriate equipment should be in place for the detection and monitoring of personnel for radiation exposure.
15. Due to health and safety requirements to ensure the rapid removal of contamination from personnel, suitable methods such as sinks and/or showers may have to be located closer to clean rooms than for normal aseptic operations depending on national safety requirements. Appropriate controls for the design and maintenance of the sinks and/or showers should be considered. Other methods of decontamination according to local requirements may also be used.
16. Labelling of blood cells should be done in a separate room from other preparation activities. The risk of using common changing rooms for the two activities should be assessed and documented.

17. Wherever possible, products should be prepared using closed method of preparation such as transfer from one sealed sterile container to another. The aseptic puncturing of the vial stopper should be minimised as much as possible.
18. Operations should be carried out either in laminar flow workstations, hot cells or in closed radiological protection workstations. If open workstations are used for example safety cabinets, these will require a higher surrounding air classification depending on whether the product is aseptically prepared or terminally sterilised.
19. Visual inspection of gloves for isolators and hot cell manipulator sleeves, for hot cells should be carried out prior to use. Leak testing of hot cells, where possible, and isolators should be carried out at the intervals defined in Annex 1.
20. It is expected that any open method of preparation and handling of aseptic products is done in a grade A environment. In the case of closed method of preparation used for the filling of the final product into a single container for immediate use, a grade C area may be adequate for the filling operation, based on a risk assessment.
21. For products which can be terminally sterilised these should be filled in a grade C environment. For pre-filling steps e.g. radiochemical synthesis, a grade C environment should be used or otherwise justified through a risk assessment.
22. Materials should be transferred into the workstation through transfer hatches which are interlocked, where applicable.
23. Generators should be placed in a suitable area or workstation adjacent to the preparation workstation. The required classification should be based on a risk assessment to minimise any potential contamination during elution.
24. Where an isolator is used for the preparation of radiopharmaceuticals, air from the isolator should not generally be re-circulated.
25. The grade required for the **surrounding room** will depend on various factors which should be evaluated in a documented risk assessment and will include the type of workstation containment system and the method of product preparation. In the table below minimum expected standards for a range of activities are given.

	Open workstation	Closed (isolator)
Preparation method		
Open aseptic	B *Note	D
Closed aseptic	C	D
Open terminally sterilised	D	D
Closed terminally sterilised	D	D

Closed workstations are defined as Isolators and hot cells which can be leak tested. Open workstations are defined as laminar air flow cabinets which are partially open at the front.

If an aseptically prepared radioactive medicinal product in an open vial, on any occasion, during production is handled outside of the workstation, the room should comply with grade B.

* Note: Immediate administration may allow a C grade area to be used, subject to a risk assessment.

26. Radioactive materials are required to be stored in shielded outer packages such as Lead/Tungsten pots or equivalent containers for radiological protection.
27. Depending on the microbial risk to the product, the preparation of capsules and other non sterile products should be carried out in a controlled environment with the appropriate radiological protection.

SECTION 3

Documentation

28. The general documentation requirements in this Guide apply.
29. Where product with a marketing authorisation is used e.g. vials where Technetium is added, the requirements in the product information leaflet should be complied with.
30. If electronic documents are used, data integrity must be maintained. Documents should be retrievable in a timely manner and sufficient access control should be in place. The same general requirements for paper documents should also apply.

SECTION 4

Production

31. Although there is a section on starting materials in Annex 1 of this Guide, some further clarification is included for radiopharmaceuticals. Starting materials include generators, chemicals for synthesis such as Mannose, Acetonitrile, Ion exchange resins etc., packing components and consumables such as syringes and needles. All materials should be received in accordance with national requirements and any formal receipt process should involve an inspection of the documentation, confirmation that the material is obtained from an approved supplier and quality control testing where appropriate.

The following additional guidance is given for the different types of components:

- Some consumables may have a medical device authorisation in some countries and this should be confirmed on receipt.
- It is expected that, although some generators are licensed products, some testing is done on receipt to confirm that they comply with specification e.g. Molybdenum breakthrough and Aluminium if this is not already indicated on the product information leaflet.
- Chemicals such as Mannose for radiopharmaceutical synthesis / manufacturing may already be pre-packed in cassettes or supplied in bulk

and chemical testing for identity/purity should be carried out unless otherwise justified. Chemicals in pre-packed cassettes may not require to be tested if the healthcare establishment has a robust supplier approval process in place where an audit of the supplier has been carried out.

- As the non radioactive chemical precursor will determine the pharmacokinetic behaviour of the finished product, the identity and purity of the chemical precursor should be demonstrated by appropriate means such as supplier qualification, testing on receipt etc. and documented.
 - The product information leaflet contains important information on the preparation of the product. It is therefore essential to have a process on receipt to confirm that there have been no changes to the preparation instructions.
 - Where dilution is required, diluents which are already licensed should be used.
32. Synthesis is considered as the first part of preparation for some radiopharmaceuticals. As synthesis units may be used for different products, the risk of cross contamination should be considered and the appropriate measures taken to prevent this through the use of dedicated components, equipment or an assessment of cleaning effectiveness where appropriate.
 33. Synthesis processes should preferably be computer controlled and the computerised system should be validated. If the synthesis processes are under manual control detailed written instructions for each process step are required.
 34. Wherever possible a licensed generator or product should be used, however due to the clinical need of the patient and availability of supply this may not be possible. In these circumstances, a risk assessment should be carried out to determine if products from other countries could be used taking into account any national regulatory requirements.
 35. There should be a procedure for the transfer and sanitisation of the generator and any other materials into the preparation area to reduce the risk of contamination.
 36. Generators should be used in accordance with the manufacturer's instructions or based on appropriate practices to maintain sterility, if an unlicensed generator is used.
 37. The number of components or consumables stored in the workstation should be kept to a minimum to avoid air flow disruption.
 38. All components used for aseptic processing such as tubing, filters etc. must be sterile before use and used once only. Components should preferably be assembled and sterilised before use to minimise the number of aseptic connections.
 39. Different products should not be prepared in the same workstation at the same time to prevent product mix ups. The potential for cross contamination should be considered where powders or gases are prepared and there are multiple workstations in the room.

40. Product is normally eluted or filled into sterile vials which are supplied by the manufacturer or purchased locally. The sterility of these vials should be confirmed through the receipt documentation.
41. The labelling of radiopharmaceuticals must take into account the specific requirements of any national regulatory or pharmacopoeial requirements.
42. When required, vials used in preparation should be labelled. Lead/Tungsten pots or equivalent containers must be labelled with the appropriate information after preparation.
43. Containers used for the radiological protection of the vial or syringe should be checked to ensure that all previous labels have been removed prior to use.
44. Containers used for radiological protection of the vial or syringe should be cleaned and sanitised prior to reuse in the workstation. Tungsten or similar materials are the preferred material due to the shedding of lead particles.
45. Filter integrity testing must be performed for aseptically filled products. Pre-filtration integrity testing may not be possible for radiopharmaceuticals especially if a vented filter is used but post integrity testing should be done for all products.
46. Where automatic delivery systems after preparation are used, for example for PET products, these must ensure that the vial is not damaged or cracked during transit into the receiving container. Any seals at the bottom of the container to protect the vial from damage or any reflectors should be present.
47. Cleaning of critical areas such as workstations should be carried out by production personnel. Rooms may be cleaned by contract staff having the appropriate training in GMP. See Annex 1 for more information on cleaning frequency.
48. Dose calibrators should be checked daily or before use for constancy. They should also be checked using national standards and linearity confirmed at regular intervals.

SECTION 5

Quality control

49. Appropriate tests on generators such as Molybdenum breakthrough and Aluminium should be carried out on unlicensed generators. Sterility testing may be carried out during the life of the generator, where appropriate, depending on the usage, whether the generator is licensed or unlicensed and any other relevant factors. Products prepared from licensed generators and kits would not normally require QC testing unless stated in the manufacturer's instructions.
50. Where a monograph is available in the Pharmacopoeia, QC testing of an unlicensed radiopharmaceutical should be based on this, or otherwise justified based on any likely impurities, residual solvents from the manufacturing process and the risk to the patient. Consideration should also be given to the

method of manufacture of the generator as this may vary from that used to prepare the material used in developing the monograph.

51. The half life of the product requires that QC testing must be completed within a short period of time and some time consuming tests such as sterility must be completed retrospectively. Sessional monitoring results (see section 6) may also not be available at the time of batch release. It is therefore important to build up a history of acceptable performance to provide confidence that the product can be released for safe administration to the patient.
52. It should be recognised that there may be multiple releasing steps for some radiopharmaceuticals; release for despatch to the site of administration, release for administration to patients and final release when all test results including sterility testing are available.
53. There should be a system established at the site preparing the product and at the receiving healthcare establishment, if remote from the preparation site, to ensure that radiopharmaceuticals are not administered before the release for administration. Products should be transported in accordance with local radiological legislation and responsibilities should be defined in a technical agreement with the transport company if used.
54. Initial detailed investigation of an Out of Specification (OOS) result may not be possible within the short timescale for release and therefore the most appropriate action may be to reject the batch and start again.
55. A procedure should also describe the measures to be taken by the responsible person if OOS test results are obtained after release for administration. Such events should be investigated to include the corrective and preventative actions taken to prevent future events. This process must be documented and the responsible physician informed as soon as possible to determine the impact on the patient.
56. For products administered before final release e.g. PET trending of production parameters and QC results are an important part of batch release to confirm that the batch is within the acceptable range and can be released for administration to patients. Out of trend results should be investigated and any subsequent release justified.
57. Sufficient retention samples should be stored for a period of time which is scientifically justifiable to be of benefit. Samples are not normally required for products prepared from licensed kits and generators.

SECTION 6

Monitoring

58. For aseptic injectable products, the media fill must simulate the method of preparation exactly and will mainly involve the transfer of product by syringe from one container to another and dilution or removal of samples from the product vial. It is not normally required to perform media fill for any synthesis steps. If there are any differences in the way licensed kits are handled, e.g. there is an extra dilution step; this should be taken into consideration when designing the media fill programme.

59. During the preparation of non sterile products, environmental monitoring should be performed if there are any possible risks to patients.
60. It is expected that the environmental monitoring is carried out at the frequency defined in Annex 1 of this Guide.
61. The aim should be to perform particulate monitoring during filling.

GLOSSARY

(This only includes terminology which is not already mentioned in this Guide.)

Workstation – A dedicated place where work is carried out in a protected environment. This could be an isolator or a hot cell which is completely sealed from the surrounding environment or a safety cabinet which is open to the environment as the front may not be completely closed.

Open method of preparation – preparation where material may be handled or transferred using open vials exposing the product to the environment.

Closed method of preparation – refer to main document but, for clarification, the elution from a generator into a sealed vial and then drawing the contents into a syringe through the septum would be classified as a closed method of preparation.

Reference sources

- (1) PIC/S Guide PE 009: Guide to Good Manufacturing Practice for Medicinal Products ⇒ <http://www.picscheme.org>
- (2) Eudralex Volume 4 - Medicinal Products for Human and Veterinary Use: EU Guidelines to Good Manufacturing Practice
⇒ <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex>
- (3) ICH Guideline Q9: Quality Risk Management, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Geneva ⇒ <http://www.ich.org>
- (4) EN/ISO 14644: Clean rooms and associated controlled environments, European Committee for Standardization (CEN), Brussels ⇒ <http://www.cen.eu>
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Revision history

Date	Version Number	Reasons for revision
1 April 2008	PE 010-2	Correction of a misprint at paragraph 54 of Annex 1
1 October 2008	PE 010-3	Correction of a misprint at paragraph 85 of Annex 1
1 March 2014	PE 010-4	Addition of Annex 3