National Guidelines for Aseptic Compounding in Irish Hospital Pharmacy Practice

(H-PIC\S)

Version 1.0

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Developed by: Working group of the HPAI Aseptic Services Special Interest Group (ASSIG)

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Preface

European legislation for aseptic manufacturing is developed with a particular focus on the pharmaceutical industry. With certain exceptions, manufacturers of human medicines are required to hold a Manufacturer's Authorisation. To obtain an authorisation to manufacture medicinal product, compliance with the principles of Good Manufacturing Practice (GMP) must be demonstrated.

Aseptic compounding in Irish hospital pharmacy is exempt from holding a Manufacturer's Authorisation provided certain criteria are met (Medicinal Products (Control of Manufacture) Regulations, 2007. Section 5 – S.I. No. 539 of 2007). However, the ethos of GMP is equally paramount to ensure that all products compounded are of high quality, safe and effective. It is important, therefore, that the underpinning principals of GMP can be translated transparently and safely into the hospital pharmacy aseptic compounding unit.

In the absence of nationally agreed guidelines for aseptic compounding in Irish hospital pharmacy the Hospital Pharmacist Association of Ireland (HPAI) submitted a project to develop guidelines to the Medication Safety Forum in 2010. All pharmacy departments with compounding facilities were invited to contribute.

Through consultation with the Health Information and Quality Authority (HIQA) and the Irish Medicines Board (IMB), the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (PE 010/3) was chosen as the most appropriate guidance to apply to aseptic compounding in Irish hospitals.

These guidelines were written by pharmacists working in aseptic compounding and reflect a consensus of the combined knowledge of these pharmacists. They are guidelines of professional practice as developed by practitioners and have been endorsed by Chief Pharmacists (Head of Departments) on 7th March 2013 and by the HPAI Executive on 7th November 2013.

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INTRODUCTION

Purpose

The purpose of this document is to provide guidance on Good Practices for the aseptic preparation of medicinal products in Irish Hospitals.

Scope

Aseptic reconstitution in isolators situated in a clean room, where licensed products or products from licensed manufacturers, are used to compound, on receipt of a prescription, patient specific products, that are released by a releasing officer.

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.

Glossary

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. HIQA
The Health Information and Quality Authority (HIQA): HIQA is the independent Authority established in May 2007 to drive continuous improvement in Ireland's health and social care services.

17. HPAI
Hospital Pharmacists Association of Ireland (HPAI): The Hospital Pharmacists Association of Ireland (HPAI) is a voluntary organisation that represents it members on issues relevant to hospital pharmacists.

18. IMB
Irish Medicines Board (IMB): The objective of the IMB is to ensure in so far as possible, consistent with current medical and scientific knowledge, the quality, safety and efficacy of medicines available in Ireland and to participate in systems designed to do that throughout the European Union.

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

20. 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.

21. Medication Safety Forum
The Medication Safety Forum is comprised of a number of organisations with a particular interest in medication safety including the Department of Health, Health Services Executive, Pharmaceutical Society of Ireland, Irish Medicines Board, Health Information & Quality Authority, professional bodies and patient representatives. The Forum is chaired by the Chief Pharmacist, Department of Health.

22. 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.

23. 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.

24. PIC\S
Pharmaceutical Inspection Corporation Scheme (PIC/S): The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP. PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products."

25. 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.

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

27. 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.

28. 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.

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

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

31. 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.

32. 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.

33. Releasing Officer
The person who releases the prepared medicinal products. This person may either be the Responsible Person or are acting under the direction of the Responsible Person.

34. 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. This individual must be a Pharmacist.

35. 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)?

36. 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.

37. Shall
Term used to indicate that the requirement is mandatory

38. Should
Term used to indicate that the requirement is considered and application requirement assessed.

39. Specifications
See Chapter 4.

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

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

42. 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.

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

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

Chapter 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 (see 1.3 below)
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
f) Change control – There should be a formal procedure for recording all implemented alterations to documents, equipment, process, procedures or specifications.

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 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 the prepared products should be assessed. The assessment should be documented and usually include:

- A review of the preparation documentation (e.g. worksheet)
- A comparison of test results, environmental results and specifications, where appropriate
- An assessment of any deviation(s)

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 microbial sampling, product specifications and environmental testing and with the organisation, documentation and release procedures, which ensure that the necessary and relevant tests are actually carried out and that starting materials as well as intermediate and finished products are only released, if their quality complies with the requirements.

Chapter 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.
In order to manage workload the preparation establishment should have a capacity plan. Capacity planning is used to examine volume and complexity of workload, time available and the staff and facilities required.
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 Continuing 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 (Annex 1 No. 21- 23)
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 contamination risk is minimised, 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.

Chapter 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 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 isolators (and where applicable, rooms) should ideally be provided for hazardous products, e.g. cytostatics, penicillins, biologicals, radiopharmaceuticals, blood products, gene therapy. Procedural controls shall be in place to minimise risk to patients. The principle of campaign working should be used where possible, 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 recalibrated 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.

Chapter 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.
There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded, or documented on media from which data may be rendered in a human readable form.

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. Effective and review dates should be defined.
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 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.

4.3.1 Specifications

1. For starting and packaging material as well as for intermediate or finished products, approved specifications (for example Summary of Product Characteristics) 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) Qualitative and quantitative requirements with the acceptance limits
d) Where applicable, requirements concerning storage and precautions
e) 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

4.3.2 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

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

4.3.3 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.

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 (e.g. environmental monitoring)
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

4.4 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.

Chapter 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. 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.

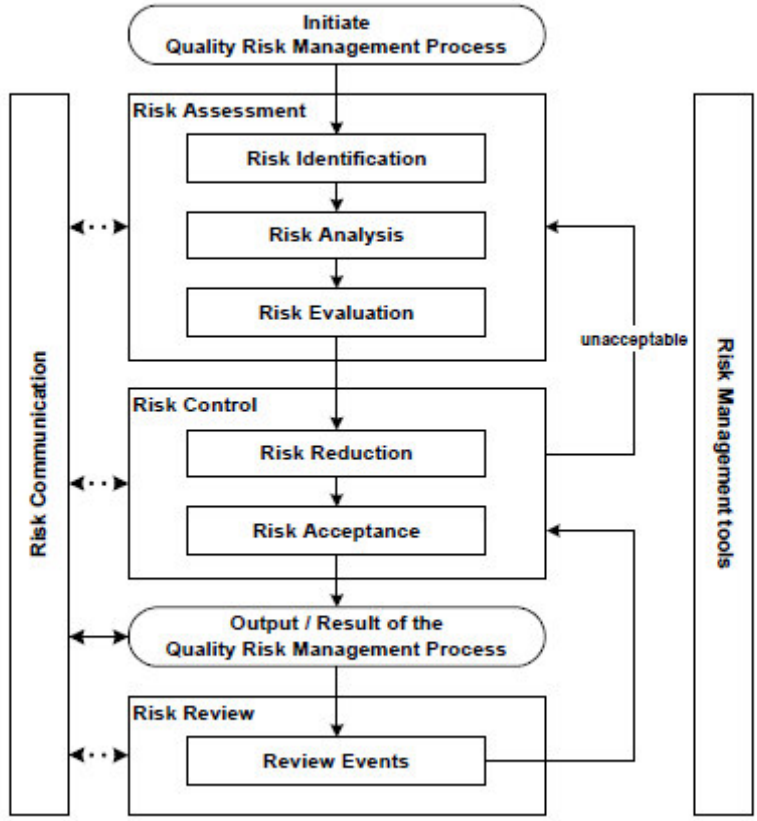
Examples for associated risk factors are:
• Low concentration of a non-dissolved active ingredient (risk of incorrect dosage due to non-homogeneity)
• High susceptibility for microbial growth (risk of microbial growth)
• Longer periods of storage or use (risk of chemical degradation or microbiological 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) (*Summary figure 1*).

Figure 1: Overview of a typical Quality risk management process



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.

3. The date of the first opening should be indicated for starting materials with a short in-use expiry date. A risk based assessment should be completed if vials are reused. Consideration should be given to the use of a closed system.

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 where appropriate.

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 amount(s)
d) Content (amount, e.g. grams, millilitres etc.)
e) Batch number
f) Expiry date and, if necessary, application date
g) Preparer (e.g. name of hospital, department name, contact number)

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.

Chapter 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 (e.g. particle counter, air sampler)

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 Inspection

Inspection of raw materials

1. Where possible use licensed starting materials. Where not available, obtain information supporting the quality of the starting materials, e.g. Professional standards, which may have been recognised by the competent authority, should be used.

2. The risk assessment to define the inspection 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, but should be inspected before use.

Inspection of finished products

4. The risk assessment to define the inspection 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 compounded products.

6.4 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.

Chapter 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, to include contract laboratory work.
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.

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 (reflects the nature of the service provided and potential of GMP impact) 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.

Chapter 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, if applicable, 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.

Chapter 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 trained 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 only 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 for aseptic processing.

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: High level of hazard to the operator preparing the product and high risk of preparation errors.
-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.

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, 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 (microbiological) 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 aseptic preparation activities:
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.
Aseptic compounding of products (open and closed procedures) should be performed in a grade A environment in a pharmaceutical isolator ideally with laminar flow and pressurised positive or negative as appropriate. 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 2.1 gives examples of operations for aseptic preparations to be carried out in the various grades.

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

Examples of operations for aseptic preparations
Aseptic Compounding – Grade A environment
18. Preparation under negative pressure, protecting operator and environment from contamination should only be used for the preparation of hazardous pharmaceuticals (e.g. cytotoxic drugs) together with appropriate precautions against contamination of the medicinal product (e.g. appropriate background room air quality, positive pressure airlock systems).

19. 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 minimum background environment for pharmaceutical isolators is grade D. 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 2.2 Overview of the recommended minimal grades

	Working environment	Background environment
Isolators	Grade A	Grade D

20. 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

21. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.
The description of clothing required for each grade is given below:
- 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.

22. Outdoor clothing should not be brought into changing rooms leading to grade B and C areas. 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:

23. It is important to visually check that garments are in good condition and that the seams are sealed. Periodic monitoring of people, clothing and hand, 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

24. 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. An effective sanitisation programme for routine and non-routine (e.g. breach) cleaning of isolators and clean room should be developed.

25. Dedicated equipment should be used and stored to minimise microbiological contamination. Mop heads should be disposed of or re-sterilised after each cleaning session.

26. 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.

27. The effectiveness of cleaning should be routinely demonstrated, by microbiological surface sampling e.g. contact plates or swabs.

28. Periodic use of sporicidal cleaning agents should be considered to reduce contamination from spore forming microorganisms.

29. For sterile alcohol sprays and other materials brought into clean areas an inuse expiry date should be defined.

Section 3

Documentation

General Issues

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

Processing instructions and processing records

31. 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.

32. 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.

33. 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 4.3 of the Main Part of this Guide.

Section 4

Aseptic processing

34. All manipulative steps in the compounding process should be controlled by comprehensive Standard Operating Procedures to ensure the output of the process is a sterile product of the requisite quality.

35. All sanitisation processes including transfer disinfection and cleaning 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.

36. 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.

37. 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.

38. 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.

39. 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 ensure ability to retrieve contaminating micro-organisms that may be there.

40. 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.

41. Any interventions/deviations 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.

42. 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 ideally not be used beyond 24 hours after first opening. They should be protected against contamination or deterioration at all times.

43. 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.

44. 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.

45. 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.

46. 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).

47. The cleaning procedure should also effectively remove product residues from surfaces of the workstation.

Section 5

Quality Control

48. All starting materials, components and packaging materials should be visually checked before use to ensure that they comply with the required specification.

49. If starting materials are themselves licensed medicinal products or products from licensed manufacturers then it is not usually necessary to test these before use.

50. If a product is prepared for a single patient, it is assumed that no end product testing will be required.

51. 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.

52. Samples for 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

53. 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.

54. Any growth in a media fill or critical zone should be investigated and documented in a deviation report.

55. 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.

56. 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 audited at appropriate intervals.

Section 6

Monitoring

57. Methods of analysis should be stability indicating and validated appropriately if doing end product testing or in support of extended product shelf life.

58. 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.

59. 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) should be based on a risk assessment and include:
• Use of closed systems during preparation
• Immediate use of prepared products
• Decrease of workload (less operational activities to be observed)

60. 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"

61. 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

62. Classification tests – not in operation (i.e. validation).

Table 6.1 Recommended frequencies for classification tests

	Pharmaceutical Isolator	**Rooms**
Particle counts	Every 6 months	Yearly
Air changes per hour	Every 6 months	Yearly
Air velocities on workstations	Every 6 months	Yearly
HEPA filter integrity checks	Every 6 months	Yearly
Isolator alarm function tests	Every 6 months	N/A
Isolator leak test	Every 6 months	N/A

Environmental monitoring "in operation"

63. Regular monitoring of the environment, process and finished product is an essential part of the quality assurance of all aseptic compounding. 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 aseptic compounding.

64. 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.

65. Each unit should have a programme of periodic testing (e.g. sessional, daily, weekly, monthly, quarterly and annually) 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.

66. Physical monitoring

Table 6.2 Recommended frequencies of physical monitoring

Rooms	Pressure differentials between rooms	Before beginning of work, usually daily. Ideally system should be alarmed
	Pressure differentials across HEPA filters	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 between every preparation
	Isolator pressure hold test (with gloves attached)	Weekly if equipment allows and if equipment open/breached.

67. Microbiological monitoring

Table 6.3 Recommended frequencies of microbiological monitoring

	Direct working environment (Grade A zone)	**Background environment**
Settle Plates	Every working session	Weekly
Glove finger dabs	At the end of each working session	N/A
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

68. 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.

69. Physical monitoring

Table 6.4 Action Limits for physical classification of controlled areas and devices.

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				
	0.5µm	5.0 µm	0.5µm	5.0 µm			
A	3 520	20	3 520	20	N/A	0.45 HLF O.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 $1m^3$ 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 micrometre. 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 ≥ 5.0micrometre 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.

70. Microbiological monitoring

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

Recommended limits for microbial contamination (a)				
Grade	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.

References

1. PIC/S 010-03: Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (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. Alison M. Beaney (Editor): Quality Assurance of Aseptic Preparation Services, 4th Edition, London: Pharmaceutical Press, 2006 (http://www.pharmpress.com)

4. S.I. No. 539/2007 - Medicinal Products (Control of Manufacture) Regulations 2007 (http://www.irishstatutebook.ie/2007)

5. ICH Guideline Q9 (Quality Risk Management) (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf)