Professional Standards

ROYAL PHARMACEUTICAL SOCIETY

Quality Assurance of Aseptic Preparation Services: Standards

Part A | Fifth edition

Edited by
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On behalf of the Royal Pharmaceutical Society and the NHS Pharmaceutical Quality Assurance Committee

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Fifth edition

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This publication is intended as professional standards and may not include all information relevant to the subject matter. You should interpret all information and advice in light of your own professional knowledge and all relevant literature and guidelines. Nothing in this publication constitutes legal advice and cannot be relied upon as such. Whilst care has been taken to ensure the accuracy of content the Royal Pharmaceutical Society excludes to the fullest extent permissible by law any liability whether in contract, tort or otherwise arising from your reliance on these standards, information and advice.

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Acknowledgements, news and updates. Available at: **www.rpharms.com/qaaps**

In 2016 additional supporting resources to aid implementation of the standards will be developed into a handbook. The handbook will provide part A – standards and part B – support resources. Further news and updates on access to part B and its planned launch as part of "Quality Assurance Aseptic Preparation Services: Standards Handbook" is available at: **www.rpharms.com/qaaps**

PREFACE

These standards for the quality assurance of aseptic preparation services are a joint initiative between the Royal Pharmaceutical Society and the NHS Pharmaceutical Quality Assurance Committee. We share an aim to develop national standards that support best practice and the care of patients. Pharmacy aseptic preparation services are supporting the care of some of the most critically ill patients.

All the standards have been revised and updated for this fifth edition. The standards are well established and widely used by UK hospital pharmacy departments. Their origin goes back prior to 1993, when the first edition of *Quality Assurance of Aseptic Preparation Services* was published by the NHS Quality Control Sub-Committee.

The relationship between the Royal Pharmaceutical Society and the NHS Pharmaceutical Quality Assurance Committee extends over many years and our publishing division, the Pharmaceutical Press (RPS Publishing), has previously published the third and fourth editions of *Quality Assurance of Aseptic Preparation Services*.

Since 2010 the Royal Pharmaceutical Society has become a body akin to a Royal College. As such, it is appropriate for us to produce and host these standards as part of our library of professional standards. The standards have particular relevance to the RPS leadership roles, including our vision for the pharmacy workforce (RPS 2015).

I would like to join the editor, Dr Alison M Beaney, in thanking the contributors. These standards are a result of the hard work and dedication of many experts from across the UK.

In the UK these nationally agreed quality standards and an audit programme are in place to assure the quality of pharmacy aseptic units (unlicensed) within the NHS. The standards are primarily intended for use within the NHS but they will also be of use to students, licensed units, individuals and organisations in other countries as well as the UK.

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President Royal Pharmaceutical Society

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CHAPTER 1 INTRODUCTION

Aseptic preparation of medicines is an important part of the service provision by pharmacy departments to facilitate accurate and timely administration of injectable medicines for patients. It is a complex and demanding activity requiring skilled staff, appropriate facilities and close monitoring and control.

Standards to guide and monitor the safe and accurate delivery of these services have evolved gradually, reflecting the changing expectations and needs for maintaining the high quality of aseptic products in the context of rising workload pressures, often reduced resources, and the increasing complexity of modern medicines.

The standards contained herein address these issues in a practical way and should assist both those providing these services and those whose role it is to audit them.

Aseptic preparation in the UK is only exempt from the licensing requirements of the *Medicines Act 1968* and subsequent amendments provided all of the following conditions are met (MCA 1992):

- The preparation is done by or under the supervision of a pharmacist, who takes full responsibility for the quality of the product
- The preparation uses closed systems
- Licensed sterile medicinal products are used as ingredients or the ingredients are manufactured sterile in licensed facilities
- Products will be allocated a shelf life of no more than one week. The shelf life should be supported by stability data
- All activities should be in accordance with defined NHS guidelines.

The term 'preparation' is therefore used to denote activity without a manufacturing licence from the Medicines and Healthcare products Regulatory Agency (MHRA), whilst 'manufacture' is used to denote licensed activity.

The first edition of the *Quality Assurance of Aseptic Preparation Services* (Quality Control Sub-Committee 1993) gave advice to ensure consistent quality of products prepared in unlicensed hospital aseptic preparation units. It provided the 'defined National Health Service (NHS) guidelines' required by the then Medicines Control Agency (MCA) in their publication *Guidance to the NHS on the licensing requirements of the Medicines Act 1968* (MCA 1992).

Updated and expanded versions of these guidelines have been published by the NHS Quality Control/ Assurance Committee (Lee 1996, Beaney 2001, Beaney 2006). This new edition has similarly been updated and significantly expanded to provide the NHS with up-to-date standards for aseptic preparation.

Since 2006 there have been significant changes to practice that are reflected in this new edition of the *Quality Assurance of Aseptic Preparation Services*. The NHS Pharmaceutical Quality Assurance Committee works closely with MHRA to maintain equity of standards between licensed and unlicensed units. Patients treated with products made in the NHS in either of these types of unit are entitled to expect the same level of safety from the products that they receive.

This fifth edition of the *Quality Assurance of Aseptic Preparation Services* (now published as a standards handbook) includes many new and revised standards in all chapters and places greater emphasis on requirements for pharmaceutical quality systems in EU Good Manufacturing Practice (GMP) (EC 2015) and for quality risk management (ICH 2005). For example, the scope of the Documentation chapter (Chapter 8) has been expanded to reflect this, and the chapter has been renamed. This new edition has been reformatted into two parts: Part A – Standards (contained in the chapters) and Part B – support resources (contained in what were previously termed appendices). In line with EU GMP (EC 2015) the chapters, although standards, use 'should' rather than 'must' throughout. All support resources (which are now published separately) have been revised and updated with the aim of standardising best practice and providing guidance across the NHS on ways of achieving the standards in the chapters. The information in Part B on Computer Validation, for example, has been used as the basis for an advisory document (PQAC 2015) to assist with, amongst other systems, validation of electronic prescribing and so is applicable to an expanded audience.

The standards are applicable to all products prepared aseptically in unlicensed NHS units across the UK for administration to patients. Parenteral nutrition solutions, cytotoxic injections, radiopharmaceuticals and additives for parenteral administration are the most common examples of such products. As such, the products are of a critical nature and standards for their preparation have a significant impact on patient safety. These standards enable pharmacists supervising unlicensed aseptic activity to implement safe systems of work and to prepare products of appropriate quality.

Executive Letter (97)52 (NHS Executive 1997) introduced a requirement in England for regular external audit of all unlicensed aseptic units by Regional Quality Assurance Specialists to ensure appropriate standards were achieved and maintained. This requirement still applies and similar arrangements are in place in the other home countries. The standards in the fourth edition of the *Quality Assurance of Aseptic Preparation Services* (Beaney 2006) are the basis for this ongoing audit programme at the present time, and those in the fifth edition will replace them.

Although *Quality Assurance of Aseptic Preparation Services* is primarily used as the basis of the above audit programme across the UK, the text is also used as standards in several other countries worldwide. Additionally, it is used for undergraduate and postgraduate pharmacy teaching in academia.

The editor, Alison M Beaney, would like to thank all contributors to this edition for their hard work and dedication in preparing these standards. She would like to acknowledge the helpful comments and suggestions received from members of the NHS Pharmaceutical Quality Assurance Committee, the NHS Pharmaceutical Aseptic Services Group, the UK Radiopharmacy Group, the NHS Technical Specialist Education and Training group, and the Medicines and Healthcare products Regulatory Agency.

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CHAPTER 2 DEFINITIONS / GLOSSARY OF TERMS

ACCOUNTABLE PHARMACIST

The pharmacist responsible for all aspects of the services within an aseptic preparation unit. The duties of the Accountable Pharmacist include the approval of all systems of work and documentation used in the unit. This person is also an Authorised Pharmacist.

ACCREDITED PRODUCT APPROVER

An Authorised Pharmacist or a person who has been approved through a nationally recognised accreditation programme for product approval.

ACTION LEVEL

Established microbial or particulate monitoring results requiring immediate follow-up and corrective action. This term is occasionally called an action limit. (BSI 2011).

(*BS EN ISO 13408-1:2011 Aseptic processing of health care products – General requirements*).

ALERT LEVEL

Established microbial or particulate monitoring results giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which could require follow-up investigation. This term is occasionally called alert limit. (BSI 2011).

(*BS EN ISO 13408-1:2011 Aseptic processing of health care products – General requirements*).

ASEPTIC PROCESSING

Aseptic processing is the manipulation of sterile starting materials and components in such a way that they remain sterile and uncontaminated whilst being prepared for presentation in a form suitable for administration to patients.

ASEPTIC SERVICES VERIFICATION

The process of verifying that the clinical pharmacy verification of the prescription has been carried out, that the prescribed constituents are compatible and the formulation is stable, and that the product is the correct presentation for the intended route of administration.

ASEPTIC WORK SESSION

A period of time where a process or series of processes are performed which can reasonably be expected to present a uniform risk of contamination to the final product(s). Typically a session is the period of continuous work within the aseptic area between breaks and is no longer than a morning or afternoon.

AUTHORISED PHARMACIST

The person designated in writing by the Accountable Pharmacist to supervise the aseptic process and release the product for use.

BIOBURDEN

Population of viable microorganisms on or in the product and/or sterile barrier system. Bioburden is used in aseptic preparation to refer to room surfaces, the surface of items taken into a clean room, product microbial contamination pre filtration or sterilisation. (ISO 2006).

(International Standards Organisation (ISO) Technical Committee (2006). *ISO/TS 11139-1:2006 Sterilisation of health care products – Vocabulary*).

CAMPAIGN BASIS

A campaign basis means that two or more doses may be drawn up from the same vial or the same pool of vials as long as these doses are made sequentially, that no other products are present in the work zone throughout the process, and that the vials stay within the grade A work zone throughout the process.

CHANGE CONTROL

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of the facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

CHIEF PHARMACIST

The pharmacist responsible for the pharmacy services within a corporate body. In the context of this handbook, for aseptic facilities not under the direct management control of the chief pharmacist, this responsibility lies with the most senior pharmacist.

CLEAN AIR DEVICE

A clean air device is a piece of equipment that provides a controlled workspace such as horizontal or vertical laminar air flow cabinets, Class II safety cabinets, cytotoxic cabinets, negative and positive pressure isolators.

CLEANING

The removal of organic or inorganic materials from objects or surfaces. This is generally accomplished by a process of wiping using water, detergents or disinfectants. Cleaning is essential before disinfection or sanitisation to remove organic and inorganic materials that may remain on surfaces that potentially interfere with the effectiveness of the process.

CLEAN ROOM

A clean room is a room in which the number and concentration of viable and non-viable airborne particles is controlled. The room is constructed and used in a manner that minimises the introduction, generation and retention of particles inside the room, and other relevant parameters, e.g. temperature and humidity, are controlled as necessary.

CLINICAL PHARMACY VERIFICATION

The process of verifying against the prescription that the product is clinically appropriate for the particular patient.

CLOSED PROCEDURE

A closed procedure is a procedure whereby a sterile pharmaceutical 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.

The use of a solution from a sealed ampoule can be regarded as a closed procedure when a single withdrawal is made from the ampoule, immediately after opening, using a sterile syringe and needle or equivalent device.

The above assumes that, for aseptic preparation and dispensing activities, all closed procedures are performed within a EU GMP Grade A (EC 2015) environment.

CLOSED SYSTEM TRANSFER DEVICE

A drug transfer device that mechanically prohibits the transfer of environmental contamination into the system and the escape of hazardous drug or vapour concentrations outside the system. (NIOSH Alert 2004).

COMMISSIONING

Commissioning is the process of advancing a system from physical completion to an operating condition. It will normally be carried out by specialist commissioning contractors working in conjunction with equipment suppliers. Commissioning will normally be the responsibility of the main contractor. (DH 2007).

COMPONENT

A disposable item that comes into direct contact with the product during preparation.

COMPUTERISED SYSTEM

A set of software and hardware components which together fulfil certain functionalities. For example, the system used to perform parenteral nutrition (PN) labelling may consist of the labelling software, the PC on which the software runs, the server where the database of ingredients is stored and the label printer which produces the final label. It is essential that all of these components work as expected otherwise the desired outcome (a clear, accurate, legible label to put on a product) cannot be achieved.

CONSUMABLE

A disposable item that does not come into contact with the product during preparation.

CONTAMINATION

The presence of viable microorganisms or chemicals, residues and the like (for example dirt and dust) on a surface or within a space.

CONTROLLED WORKSPACE

A controlled workspace is that volume of a clean air device constructed and operated in such a manner and equipped with appropriate air-handling and filtration systems to reduce to a predefined level the introduction, generation and retention of contaminants.

CORRECTIVE AND/OR PREVENTATIVE ACTION (CAPA)

A system that eliminates the cause of a detected deviation or other undesirable situation (corrective action) or the cause of a potential deviation or other undesirable potential situation (preventative action).

CRITICAL ZONE

The critical zone is that part of the controlled workspace where the aseptic manipulation is carried out. Particulate and microbiological contamination should be reduced to levels appropriate to the intended use, normally EU GMP Grade A (EC 2015).

DESIGN QUALIFICATION

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the user requirements specification (URS) and GMP.

DOP

DOP is an abbreviation for Dispersed Oil Particulate and is an aerosol used to test the integrity of high efficiency particulate air (HEPA) filters, usually produced using poly alpha olefin oil.

DETERGENT

A cleaning agent that has wetting and emulsifying properties, used to aid the removal of residues, microorganisms and soiling from a surface.

DISINFECTION

The process of reducing the number of vegetative microorganisms in or on an inanimate matrix by the action of an agent on their structure or metabolism, to a level judged to be appropriate for a specified, defined purpose.

EXTERNAL AUDIT

An external audit is undertaken by staff who are not managerially accountable within the corporate structure in which the aseptic preparation unit is situated, and are independent of any service provision to the unit.

FINGER DAB

A print of 5 digits from a gloved hand on an agar plate. EU GMP (EC2015) uses the term "glove print". (EC 2015).

GASEOUS BIODECONTAMINATION

A sanitisation technique using disinfectants in a vapour phase often used in specially designed isolators. Biodecontamination is the removal of microbiological contamination or its reduction to an acceptable level. There are a number of vapours available for gaseous biodecontamination; the most common is hydrogen peroxide. MHRA refer to these devices as gassed or gassing isolators (MHRA 2015). (ISO 2005).

(International Standards Organisation (ISO) (2005). *ISO 13408-6:2005 Aseptic processing of health care products – Isolator systems*).

GENE THERAPY

Introduction into the human body of genes or cells containing genes foreign to the body for the purposes of treatment, diagnosis or curing disease. (See Part B – 6).

HAND WASH-STATION

A built-in sink used for washing and usually drying hands prior to entry into the clean room.

HIGH EFFICIENCY PARTICULATE AIR (HEPA) FILTER

A filter with classification H13 to H14 when tested according to BS EN 1822-1. H13 filters have an efficiency of 99.95% at most penetrating particle size (mpps). H14 filters have an efficiency of 99.995% at mpps. This does not relate to the DOP test limits. The classification of filters is a factory test using particles of a defined size whereas the DOP test is an in situ test using a range of particle sizes. If replacement H14 filters are ordered for clean rooms operated at EU GMP Grade B (EC 2015), the supplier should be informed that they need to pass the DOP test limit of 0.001% in situ. There is a move to reclassify filters. (BSI 2009).

(British Standards Institute BSI (2009). *BS EN 1822-1:2009 High Efficiency Air Filters (EPA, HEPA and ULPA) – Classification, performance testing, marketing*).

HIGH-RISK PRODUCTS

Those (medicinal) products whose preparation and/or administration in clinical areas have been identified by risk assessment as most likely to pose a significant risk to patients. (NPSA 2007).

HORIZONTAL AUDIT

The most familiar type of audit that examines one element of the standard on more than one item, e.g. documentation.

IMPACT ASSESSMENT

The process of identifying the anticipated or actual impacts of an intervention on those social, economic and environmental factors which the intervention is designed to affect or may inadvertently affect product quality.

INSTALLATION QUALIFICATION (IQ)

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

INTERNAL AUDIT

An internal audit is undertaken by staff who are a part of the management organisational structure of the department. This is sometimes termed self-inspection.

LINEAR AUDIT

A process whereby the auditor follows the process from beginning to end (trace forward), or in reverse (trace back), if appropriate.

LIQUID BIODECONTAMINATION

A sanitisation technique using liquid disinfectants either impregnated onto wipes or in a spray bottle or canister. When used in combination the process is called spray and wipe. (Cockcroft et al 2001).

LOW-RISK PRODUCTS

Those (medicinal) products whose preparation and/or administration have been identified by risk assessment as least likely to pose a significant risk to patients. (NPSA 2007).

MANAGEMENT REVIEW

A periodic review with the involvement of senior management. A review of the operation of the pharmaceutical quality system to identify the opportunities for continual improvement of products, processes and the system itself to ensure its continuing suitability and effectiveness.

MANUFACTURE (IN RELATION TO CLINICAL TRIALS)

In relation to an Investigational Medicinal Product (IMP), includes any process carried out in the course of making the product but does not include dissolving or dispersing the product in, or diluting it or mixing it with, some other substance used as a vehicle for the purpose of administering it. (*The Medicines for Human Use (Clinical Trials) Regulations 2004*).

OPERATIONAL QUALIFICATION (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges. Tests should confirm upper and lower operating limits.

PERFORMANCE QUALIFICATION (PQ)

The documented verification that systems and equipment can perform effectively and reproducibly based on the approved process method and product specification.

PHARMACEUTICAL ISOLATOR

A pharmaceutical isolator is a containment device that utilises barrier technology for the enclosure of a controlled workspace for the preparation of aseptic products.

PHARMACEUTICAL ISOLATOR TRANSFER DEVICE (TRANSFER HATCH)

Mechanism to effect movement of material into or out of isolators while minimising ingress or egress of unwanted matter. Isolator transfer devices are often referred to as isolator hatches (MHRA 2015). (BSI 2004).

(BS EN ISO 14644 – 7:2004 Cleanrooms and associated controlled environments. Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)).

PHARMACEUTICAL QUALITY SYSTEM (PQS)

A management system to direct and control pharmaceutical operations with regard to quality. (ICH 2008).

PRIMARY PACKAGING

The packaging that immediately encloses a single unit. In the case of a sterile component the primary packaging will maintain the sterility of the individual unit.

PROCESS VALIDATION (PV)

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes. (EC 2015).

QUALITY REVIEW

An activity that checks whether the Pharmaceutical Quality System (PQS) is capable of achieving its established objectives. The use of Key Performance Indicators (KPIs) for both process, and quality, e.g. number of overdue audit actions, is beneficial, including a regular review with senior management.

READY-TO-ADMINISTER INJECTABLE PRODUCTS

These products require no further dilution or reconstitution and are presented in the final container or device, ready for administration or connection to a needle or administration set, e.g. an infusion in a bag with no additive required. (NPSA 2007).

READY-TO-USE INJECTABLE PRODUCTS

These products require no further dilution or reconstitution before transfer to an administration device; for example, a liquid within an ampoule or vial, of the required concentration, that only needs to be drawn up into a syringe. (NPSA 2007).

RECOMMISSIONING

The process of repeating the commissioning tests for a specific facility at a defined frequency to demonstrate continued compliance with operating conditions. This is often carried out immediately after servicing a piece of equipment.

RISK

The combination of the probability (likelihood) of occurrence of harm and the severity (consequence) of that harm (based on ISO/IEC Guide 51) (ISO 2014). (ICH 2005).

RISK ACCEPTANCE

The decision to accept risk (ISO Guide 73) (ISO 2009). (ICH 2005).

RISK ANALYSIS

The estimation of the risk associated with the identified hazards. (ICH 2005).

RISK ASSESSMENT

A systematic process of organising information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. (ICH 2005).

RISK COMMUNICATION

The sharing of information about risk and risk management between the decision maker and other stakeholders. (ICH 2005).

RISK CONTROL

Actions implementing risk management decisions (ISO Guide 73) (ISO 2009). (ICH 2005).

RISK EVALUATION

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk. (ICH 2005).

RISK IDENTIFICATION

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description. (ICH 2005).

RISK MANAGEMENT

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk. (ICH 2005).

RISK REDUCTION

Actions taken to lessen the probability of occurrence of harm and the severity of that harm. (ICH 2005).

RISK REVIEW

Review or monitoring of output/ results of the risk management process considering (if appropriate) new knowledge and experience about the risk. (ICH 2005).

SANITISATION

Sanitisation is the process of achieving pharmaceutically clean objects and surfaces by cleaning and disinfection processes.

SECONDARY PACKAGING

The packaging that encloses multiples of individual units. The secondary packaging may be removed without affecting the characteristics of the product, e.g. loss of sterility.

In the context in which the term is used in this handbook, any packaging that encloses, for example, a single ampoule or vial is considered to be secondary packaging.

SHORT-TERM USE

Products for short-term use should commence administration within 24 hours of preparation on condition that stability data is satisfactory. They will have been prepared under controlled conditions complying with the guidance in Part B – 4.

SPORICIDE

A chemical that can penetrate the outer wall of a spore and kill the microorganism.

STANDARD OPERATING PROCEDURES

Standard operating procedures are detailed written documents formally approved by the Accountable Pharmacist. They describe the operations to be carried out, the precautions to be taken and the measures to be applied that are directly or indirectly related to the preparation and supply of the product. They give directions for performing certain operations, e.g. cleaning, changing, environmental monitoring and equipment operation, to ensure that they are performed to a consistent standard.

STARTING MATERIAL (INGREDIENT)

Any substance used in the preparation of a medicinal product, excluding components and consumables.

STERILITY ASSURANCE LEVEL

Sterility assurance level (SAL) is the probability that a process makes something sterile. A sterilisation process must deliver a SAL of 1 in a million (10^{-6}).

STERILISATION

Sterilisation is the process of killing all microorganisms present. It is an absolute term.

SUPPORT ROOM

The support room is a dedicated room that is used for activities that are ancillary to the aseptic preparation process. Such activities may include component assembly, generation of documentation, labelling, checking and packaging.

Note: The support room may be known by other terms, e.g. preparation room, layup room, collation room and there may be more than one, i.e. inner and outer support rooms.

USER REQUIREMENTS SPECIFICATION (URS)

The set of owner, user and engineering requirements necessary and sufficient to create a feasible design, meeting the intended purpose of the system.

VALIDATION

The accumulation of documentary evidence to show that a system, equipment or process will consistently perform as expected to a predetermined specification, and will continue to do so throughout its life cycle.

It establishes documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

VALIDATION MASTER PLAN (VMP)

A co-ordinating document describing the validation of a total system comprising individual pieces of equipment and/or process.

The VMP should begin with policy and strategy for total system validation and show how different items of equipment and processes are to interact to form a total system. It should list all associated validation documents, including individual validation plans and protocols, and should include those documents in existence and those to be created to complete the validation study.

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CHAPTER 3 MINIMISING RISK WITH INJECTABLE MEDICINES

Risks to patients are greater when injectable medicines are prepared in clinical areas, such as wards and operating theatres, than when they are prepared in pharmacy under appropriate standards (Austin and Elia 2009). Risks of medication errors and microbiological contamination have been well documented (Crowley et al 2004, Argo et al 2000). Instances of harm to patients continue to be reported, however (NHS England 2013).

Standards for aseptic preparation in pharmacy are clearly defined in this text and others across Europe (EC GMP 2015, PIC/S 2014).

Ideally all injectable medicines should be prepared in pharmacy under these defined and inspected standards (NHS Executive 1997). Unfortunately, however, aseptic capacity within pharmacy to prepare medicines in ready-to-use or ideally ready-to-administer form, is limited. As a consequence, the majority of "aseptic" manipulation is carried out in clinical areas where environmental standards and preparation practices are variable (Beaney and Goode 2003) and risks of medication errors and microbiological contamination exist (Austin and Elia 2009).

A survey on quality assurance standards for preparation across the EU (Scheepers 2010) also showed a gap in standards between pharmacy and ward preparation.

There should be a risk management system across the organisation to minimise risks to patients from injectable medicines (ICH 2005). This involves the following components:

- Risk assessment
- Risk reduction and control
- Risk acceptance and communication
- Risk review.

The use of a risk assessment tool is recommended to identify high-risk products being prepared in clinical areas to target them for pharmacy preparation. A risk assessment tool was developed (Beaney et al 2005) which became the basis of a Patient Safety Alert (NPSA 2007) requiring risk assessment of practices and individual injectable products prepared in clinical areas. There is an ongoing requirement to audit injectable medicines practices in clinical areas (NPSA 2007). Additionally, NHS England created a list of serious preventable patient safety incidents that should never occur (NHS England 2013).

One of these stated that a patient should not come to severe harm as a result of a wrongly-prepared high-risk injectable medicine. This required hospitals to use the NPSA risk assessment tool (NPSA 2007) to identify their own list of high-risk medicines. (A list has been published by the NHS Pharmaceutical Aseptic Services Group (PASG) and UK Medicines Information (UKMI), and is available on their websites. This may be helpful as a basis for a hospital's own list.) Risk assessment allows prioritisation of products of higher risk for pharmacy preparation to make best use of the limited capacity in pharmacy aseptic units.

The EU survey on quality assurance standards for preparation (Scheepers 2010) led to a Council of Europe Resolution, CM/ResAP(2011)1 (EC 2011) which requires risk assessment for aseptic products. This risk assessment mentions similar risk factors to those identified in earlier UK publications (Beaney and Goode 2003, Beaney et al 2005, NPSA 2007). The Resolution CM/ResAP(2011)1 (EC 2011) also states that high-risk products should be prepared in pharmacy, but that low-risk products can be prepared in clinical areas. Further advice is available to assist organisations with these decisions (Scheepers et al 2015).

Even for low-risk products, pharmacy has a role to play in the training of nurses to raise awareness of the risks to patients from preparation and to give advice on "non-touch" techniques (Beaney et al 2005, Beaney and Black 2012). Other risk reduction measures for example, the provision of dose calculation tools or step-by-step preparation methods, can also reduce risks to patients from preparation in clinical areas.

MANAGEMENT OF THE RISKS

3.1 Risk assessment

3.1.1 There should be an up-to-date injectable medicines policy across the organisation defining roles and responsibilities and multi-disciplinary management arrangements.

3.1.2 Risk assessments and option appraisals for the site of preparation i.e. pharmacy or clinical areas, should be performed and documented for preparation of all injectable medicines within the organisation.

3.1.3 The location of all aseptic preparation should be appropriate in relation to the level of risk as determined by use of the risk assessment tool (NPSA 2007). There should be evidence of pharmacy involvement in this process.

3.1.4 An up-to-date list of high-risk injectable medicines for the specific hospital should be maintained reflecting the local situation. Best practice is that a list of NPSA 20 risk ratings should be available for all injectable medicines prepared in clinical areas.

3.1.5 There should be a system for evaluating risks for injectable medicines before they are introduced to the organisation, for example by assessment by drug and therapeutics or formulary committees.

3.2 Risk reduction and control

3.2.1 There should be a pharmacy strategy to effectively manage risks associated with injectable medicines wherever they are prepared (pharmacy, outsourced, or in clinical areas). Pharmacy support should be provided to clinical areas to reduce risks to patients from preparation in those locations. This should be defined in the injectable medicines policy.

3.2.2 An appropriate pharmacy aseptic product list (catalogue) should be maintained and updated regularly. This should include all aseptic products supplied from pharmacy (either prepared in-house or outsourced). This catalogue should be available in all clinical areas to ensure products are not inappropriately prepared there.

3.2.3 Robust arrangements should be in place to specify and monitor the quality of any outsourced aseptic products (see Part B – 3).

3.2.4 Additions to parenteral nutrition solutions (aqueous or lipid phase) contained in infusion bags and/or syringes should only be made in a pharmacy aseptic unit (DH 2011).

3.2.5 Arrangements should be in place for the provision of parenteral nutrition when the pharmacy aseptic unit is closed. Ward-based preparation or additional manipulation of parenteral nutrition components should not occur (DH 2011).

3.2.6 Arrangements for the preparation of intrathecal chemotherapy should comply with national guidance (DH 2008).

3.2.7 Arrangements for intrathecal chemotherapy should comply with Patient Safety Alert NHS/PSA/D/2014/002 (NHS England 2014).

3.2.8 Arrangements for the handling of concentrated potassium chloride solutions should comply with NPSA requirements (NPSA 2002). Ready-to-administer products should be provided to clinical areas wherever possible.

3.2.9 Preparation should use closed systems. An MHRA licence is required for open systems (MCA 1992).

3.2.10 For unlicensed units, the expiry period allocated should not exceed one week (MCA 1992). The shortest practical expiry period should, however, be allocated to minimise the time between preparation and administration and thereby reduce the risk of any microbial contamination multiplying and of chemical degradation (see Chapter 6: Formulation, stability and shelf life). The shelf lives of products should be appropriate and consider microbiological risk as well as physico-chemical stability.

3.3 Risk acceptance and communication

3.3.1 Any residual risks relating to injectable medicines that have not been appropriately controlled as described above should be accepted by the organisation, e.g. by recognising them on the risk register.

3.3.2 There should be a system for communicating decisions about which products are to be made by aseptic units and which can be made in clinical areas so all are aware of their responsibilities.

3.3.3 There should be an effective process in place to communicate any heightened risks, e.g. invoking of contingency plans.

3.4 Risk review

3.4.1 All risks (including risk register entries) should be regularly reviewed at defined time intervals and risk ratings updated as appropriate.

3.4.2 There should be a system to review any errors or incidents in relation to injectable medicines across the organisation and put risk reduction and control measures in place in response to these.

3.4.3 There should also be a system to learn from these type of events that occur external to the organisation and for responding to alerts from national bodies e.g. patient safety bodies.

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CHAPTER 4 PRESCRIBING, CLINICAL PHARMACY AND ASEPTIC SERVICES VERIFICATION

Prescribing of aseptically-prepared medicines requires all the care and attention which would normally be accorded to any prescribing activity, and the nature of the products and routes of administration also bring additional risks. Risks exist from inadvertent administration by the incorrect route e.g. inappropriate intrathecal administration of vinca alkaloids (NPSA 2008), from inappropriate rate of infusion or dilution e.g. potassium (NPSA 2002) or neonatal parenteral nutrition (PN) (DH 2011), and the inherent toxicity of cytotoxic drugs. Checks of the prescription during the clinical pharmacy and aseptic services verification processes are required to reduce these risks and to ensure that the prepared medicines are appropriate for the patient. For the purposes of these standards these checks will be referred to as 'clinical pharmacy verification' and 'aseptic services verification'. It is recognised that there are other terms in common use to describe these processes e.g. 'clinical checking' or 'screening of prescriptions' or 'prescription validation' etc. The checks required and terminology used may vary according to the medicine, route and organisational arrangements.

4.1 Prescribing

4.1.1 All prescriptions should be signed by an approved prescriber who has successfully completed appropriate training. This may be a doctor or non-medical prescriber.

4.1.2 A current approved list of non-medical prescribers should be available.

4.1.3 Organisational policies and associated procedures should be available and adhered to cover the following where applicable:

- Prescribing preparation and administration of Injectable Medicines (NPSA 2007)
- Prescribing of paediatric and neonatal Parenteral Nutrition (DH 2011)
- Prescribing of adult Parenteral Nutrition
- Prescribing of Chemotherapy (DH 2014)
- Prescribing and use of Unlicensed Medicines (MHRA 2014)
- Prescribing of Radiopharmaceuticals (ARSAC 2014)
- Intrathecal chemotherapy (DH 2008 and local organisational policy)
- Intravenous Administration of Potassium (NPSA 2002).

These policies, that may be available separately or in combination in an overall medicines policy, should clearly define the roles and responsibilities of doctors, pharmacists and other healthcare professionals in the prescribing of aseptic products. A multi-disciplinary approach to prescribing of PN should be considered (see Chapter 3: Minimising risk with injectable medicines).

4.1.4 All staff involved in any stage of the prescribing and verification processes should have ready access to appropriate information and reference sources when undertaking these tasks. This should include the current *British National Formulary* and an injectable medicine guide (local guidelines or a database such as the *NHS Injectable Medicines Guide*. **www.medusa.wales.nhs.uk**). For clinical trials, a copy of the current approved protocol should be available.

4.1.5 Prescribing for paediatric and neonatal patients should be made with reference to specialised neonatal and paediatric dose guidelines. This should include the *BNF for Children* (current edition).

4.1.6 All chemotherapy regimens should be documented and authorised by the appropriate multidisciplinary team (MDT), or consultant or follow an approved trial protocol.

4.1.6.1 This document should include details of:

- critical tests required
- cumulative doses for specific named drugs
- regimen and individual drug identification
- diluents and dilution volumes, and any hydrations
- supportive drugs
- administration route and duration.

4.1.6.2 In the event of a deviation from the agreed algorithms there should be a procedure for recording this and it should include:

- the regimen used or change in order of the regimens
- the reason for the deviation.

4.1.6.3 There should be a document control system to ensure the current approved versions of regimens are in use (see Chapter 8: Pharmaceutical Quality System) although this might not be under the control of the aseptic unit.

4.1.7 Radiopharmaceuticals are Prescription Only Medicines. Therapeutic radiopharmaceuticals and certain radioactive medical devices should be requested and approved on an individual patient basis by the Administration of Radioactive Substances Advisory Committee (ARSAC 2014) certificate holder for that therapy.

Requests received in nuclear medicine departments for diagnostic procedures are often for a named procedure rather than for a particular radiopharmaceutical and so may not include all on the information that would be required on a prescription.

4.1.7.1 Diagnostic radiopharmaceuticals may be supplied for use in specific patients against Nuclear Medicine requests provided that the following conditions are met:

- The request includes the patient details (as for a prescription)
- The request states which procedure is to be carried out
- The request has been approved for that procedure by an ARSAC certificate holder or their designated deputy, in compliance with *The Medicines (Administration of Radioactive Substances) Amendment Regulations 2006*
- A protocol is in place for the procedure which includes the name and dose of the radiopharmaceutical to be used
- The protocol has been approved by an ARSAC certificate holder and ratified by the organisation's Medicine Management Committee
- The requestor and/or the approver are named on the protocol and have been appropriately trained, with approval from the ARSAC certificate holder.

4.1.7.2 The pharmacist verifying the dose request should be familiar with the protocol for the procedure and confirm that the approver has authority to approve the request.

4.1.7.3 A number of nuclear medicine procedures require the administration of non-radioactive medicinal products in order to optimise the biodistribution of the radiopharmaceutical. The protocol for the procedure should clearly indicate the circumstances where these non-radioactive adjuncts can be prescribed.

4.1.8 All clinical trial protocols should be documented and authorised. There should be a document control system to ensure the current approved versions are in use (see Chapter 8: Pharmaceutical Quality System). The Accountable Pharmacist should ensure that the activities involved in the trial are in compliance with requirements of *The Medicines for Human Use (Clinical Trials) Regulations 2004*. In practice this means that no manufacture of an investigational medicinal product (IMP) as defined by *The Medicines for Human Use (Clinical Trials) Regulations 2004* can be carried out unless the site has a MIA(IMP) authorisation. Labelling may, however, be carried out without a MIA(IMP) authorisation if the requirements of the hospital exemption in Section 37 of this legislation are met.

4.1.9 Whether generated manually or electronically, prescriptions should be clear, unambiguous and accurate.

4.1.10 Approved standardised prescription formats should be used for each product type.

4.1.11 Where a computerised system is used for prescribing or dose calculations, the system and all of its outputs should be fully validated (see Part B – 2.6) before being put into routine use. In addition:

- The roles and responsibilities of staff using the system should be clearly defined so that the status of the prescription is understood at all stages of the prescribing, validation and verification process
- Electronic prescribing systems should be subject to the same standards of security and viewed as having the same legal status as a paper prescription
- It should be possible to demonstrate a full audit trail of changes made to the electronic prescription and any associated calculations or doses.

4.2 Clinical pharmacy and aseptic services verification

4.2.1 The pharmacist in the aseptic unit may not be the most appropriate person to verify the prescription from a clinical perspective. Clinical pharmacy verification is the process of verifying against the prescription that the product is clinically appropriate for the particular patient and aseptic services verification is the process of verifying that the clinical pharmacy verification of the prescription has been carried out, that the prescribed constituents are compatible and the formulation is stable, and that the product is the correct presentation for the intended route of administration.

A pharmacist in the clinical area with a greater knowledge of the patient or with specialised clinical expertise may be better placed to perform the clinical verification. The clinical and aseptic services verification may, in certain cases, be carried out by the same person.

4.2.2 A written organisational policy and supporting procedures should be available and in use which cover the arrangements and accountability for clinical and aseptic services verification. For example, the roles and responsibilities of the nutrition team should be defined, if applicable. The policy should include the course of action if changes are made to the prescription by the pharmacist during either clinical pharmacy or aseptic services verification.

4.3 Clinical pharmacy verification

The checks required to clinically verify a prescription may vary according to the product type and individual medicine.

4.3.1 There should be clinical pharmacy verification procedures which include checks for the following against the **original** prescription:

- Prescriber's details and full signature (may be electronic if an electronic prescribing system is in use)
- Prescriber is authorised to prescribe the medicine(s) (e.g. chemotherapy should only be prescribed by authorised prescribers, paediatric and neonatal parenteral nutrition should be initiated by a senior clinician)
- Intrathecal chemotherapy is only prescribed by authorised prescribers on the Intrathecal Register
- Patient details (e.g. full name, hospital number, consultant, ward, date of birth)
- Patient demographics (age, height and weight) where appropriate have been correctly recorded on the prescription
- Where body surface area (BSA) or creatinine clearance (CrCl) is used in the dose calculation it has been correctly calculated, taking into account recent patient parameters
- Correct dose calculation
- Doses are appropriate with respect to renal and hepatic function and any experienced toxicities
- Drug interactions (including with food) or conflicts with patient allergies
- Method of administration is appropriate
- Administration details (route, diluent, volume, rate, duration).

For electronic systems there is no need to manually check calculations e.g. doses, BSA, CrCl etc. on each occasion so long as the electronic system has been appropriately validated (see Part B – 2.6).

4.3.2 Additional checks are also required for the following:

For chemotherapy additional checks should include (BOPA 2013):

- Where there is access to either clinic notes, treatment plan or electronic record on first cycle, check the regimen is intended treatment and is appropriate for patient's diagnosis, medical history, performance status and chemotherapy history
- The timing of administration is appropriate i.e. the interval since last treatment
- Cumulative dose and maximum individual dose as appropriate
- Reason for and consistency of any dose adjustments, e.g. reduction(s) or escalations and ensure the reason is documented
- Laboratory values e.g. full blood counts, urea and electrolytes and liver function tests are within accepted limits, if appropriate (see below)
- Other essential tests have been undertaken, if appropriate
- Supportive care e.g. anti-emetics, steroids etc. is prescribed and it is appropriate for the patient and regimen.

4.3.3 In general, chemotherapy doses should not be released from the aseptic unit until these checks are complete. However, some services may allow dose checking of prescriptions in advance without access to laboratory values. This may not take into account the patient's blood counts or toxicities and hence policies should be in place clearly defining who is responsible for checking full blood count results and monitoring toxicities for chemotherapy prepared in advance before administration is authorised.

4.3.4 For parenteral nutrition additional checks (DH 2011) are also required for the following:

- For paediatric and neonatal parenteral nutrition the prescription has been initiated by a senior clinician
- Where an individualised parenteral nutrition (as opposed to a standard formulation) is prescribed, it is clinically appropriate
- The route of administration is appropriate for the glucose concentration of the parenteral nutrition.

4.3.5 Technical issues such as the stability of components, the osmolality (see Chapter 6: Formulation, stability and shelf life) may require a modification of the prescription in the pharmacy aseptic unit. In this instance, a pharmacist familiar with PN should carry out the final verification of the amended regimen, discuss any changes with the prescriber if necessary and ensure they are recorded on the prescription.

4.3.6 For radiopharmaceuticals, additional checks (IR (MER) 2000) are also required:

- The patient radioactive dose prescribed is in accordance with the Diagnostic Reference Level for that procedure (ARSAC 2014)
- Paediatric radioactive dose prescribing is in accordance with national guidelines (ARSAC 2014)
- For certain procedures, that the patient's concomitant medication has been withheld or administered for the appropriate period prior to the procedure being undertaken.

4.3.7 If the prescription is not available in the unit at the time of preparation (e.g. use of facsimiles, scanned documents, order forms) there should be a robust system for ensuring that the above checks have been made against the original prescription before the product is released.

4.4 Aseptic services verification

4.4.1 The Authorised Pharmacist should carry out the aseptic services verification process and as part of this ensure that a clinical verification has been completed in accordance with the specific organisational policy.

4.4.2 The aseptic services verification should include the following checks:

- The prescription has been clinically verified
- The prescribed constituents are compatible and the formulation is stable (see Chapter 6: Formulation, stability and shelf life)
- The product is the correct presentation for the intended route of administration.

4.4.3 A record should be made on the worksheet indicating who carried out the verification of each prescription.

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CHAPTER 5 MANAGEMENT

Aseptic units should ensure that the products they prepare are fit for their intended use, comply with the standards in this text, and do not place patients at risk due to inadequate safety or quality.

Achieving this objective is the responsibility of senior management and requires the commitment, understanding and participation of all staff who are involved in the ordering, preparation, storage and supply of aseptic products.

There should be a comprehensive and correctly implemented Pharmaceutical Quality System (PQS), incorporating the principles of Good Manufacturing Practice (GMP) (EC 2015) and quality risk management (EMA 2006).

The standards in this chapter are interrelated with those in Chapters 3, 8 and 9 on Minimising risk with injectable medicines, Pharmaceutical Quality System, and Personnel, training and competency assessment respectively.

5.1 General issues

5.1.1 All departments undertaking aseptic preparation activities should have an appropriate documented organisational structure that indicates clearly the responsibilities and accountability of each member of staff.

5.1.2 Aseptic units should be under the management of an Accountable Pharmacist who should ensure that a system of quality assurance is implemented that incorporates the principles set down in these standards. Routine monitoring of the adherence to procedures in the form of internal audit should be undertaken.

5.1.3 All staff working in the aseptic unit should be professionally accountable, either directly or indirectly, to the Accountable Pharmacist.

5.1.4 To assist Chief Pharmacists to discharge their overall responsibility for the PQS and associated quality indicator monitoring, the Accountable Pharmacist should be directly accountable to the Chief Pharmacist.

5.1.5 There should be a system for capturing staff suggestions for improvement and implementing regulatory changes.

5.1.6 All aseptic preparation should be carried out by, or under the supervision of, a pharmacist authorised by the Accountable Pharmacist. (The Accountable Pharmacist is also an Authorised Pharmacist by definition). Pharmacists supervising any aseptic preparation carried out outside normal working hours to the same quality system should be Authorised Pharmacists.

5.1.7 The responsibility for the release of an aseptically-prepared product should be taken by an accredited product approver in accordance with the criteria set down in Chapter 14: Product approval. This may not necessarily be the same Authorised Pharmacist who supervised the preparation of the product.

5.1.8 The Accountable Pharmacist should authorise the Standard Operating Procedures. Any deviation from these procedures should be approved and should be fully documented in accordance with the PQS.

5.1.9 Senior managers should ensure that all staff who are involved in the preparation and supply of aseptically-prepared products clearly understand their level of responsibility and accountability, and are competent to carry out their role.

5.1.10 The Chief Pharmacist has overall responsibility for medicines management within the organisation. In practice, this means that they are ultimately responsible for ensuring that effective governance arrangements are in place across the organisation for all injectable medicines, whether prepared in clinical areas, in pharmacy or outsourced.

5.1.11 The Chief Pharmacist holds ultimate responsibility for the adequate resourcing of the aseptic preparation service to ensure that it meets the defined national standards as described in this text. This needs to be formally documented in an organisational policy (such as the injectable medicines policy).

5.1.12 The Chief Pharmacist is also responsible for ensuring that a policy on aseptic preparation is in place and that, where this allows delegated product approval in line with Nationally Recognised Competency Framework requirements (ASAWG 2014), this has specific, formal, organisation board-level agreement.

5.1.13 There should be an appropriate reporting structure so that all accredited product approvers are accountable directly to the Accountable Pharmacist for this activity and that this is reflected in their job description (see Chapter 14: Product approval).

5.1.14 Where delegated product approval is in place, the Chief Pharmacist and Accountable Pharmacist should agree a suitable management structure within the aseptic unit to ensure that the requirements of the Nationally Recognised Competency Framework (ASAWG 2014) are met at all times that the unit is operational.

5.2 Pharmaceutical Quality System

5.2.1 The PQS (see Chapter 8: Pharmaceutical Quality System) should be fully documented and its effectiveness monitored.

5.2.2 All elements of the PQS should be adequately resourced with competent personnel, suitable and sufficient equipment and facilities.

5.2.3 Senior managers should ensure that quality indicators, e.g. complaints, errors, microbiological non-conformances, are recorded, investigated and regularly trended. Any adverse trends should be acted on in a timely manner.

5.2.4 There should be regular (normally monthly) quality management meetings to review the PQS. It is the responsibility of the Chief Pharmacist to ensure that there are adequate resources to enable this review to take place. The Chief Pharmacist should be aware whether the quality system is functioning correctly, e.g. by participation in, or reports from, these meetings. An example agenda would include: deviations; change controls; errors; complaints; capacity; audit (internal and external); microbiological out-of-specifications; planned preventative maintenance (PPM) for facilities and equipment.

5.2.5 Units should continually review their PQS to ensure that standards of quality are maintained. Should circumstances arise where this is no longer the case, the Chief Pharmacist should take a risk management approach, which may include implementing contingency plans, to ensure that patient safety and continuity of care are not compromised (see Chapter 3: Minimising risk with injectable medicines).

5.2.6 There should be a culture of continuous, quality improvement in the department. Sharing best practice and learning from errors (both internal and external to the department) to optimise patient care associated with aseptically-prepared medicines should be accepted practice.

5.2.7 The Accountable Pharmacist should authorise documented procedures for product preparation and these procedures should be readily available. These procedures should be based on evaluated data but if no data are available the decision to prepare the product should be made in the context of the clinical needs of the patient and the potential risks.

5.2.8 If a product is requested outside the PQS, i.e. a non-catalogue request, it is the responsibility of the Authorised Pharmacist to consider the risk/benefit for the patient in the context of their clinical needs. Appropriate risk management arrangement should be in place.

5.2.9 If, under exceptional circumstances, an Authorised Pharmacist decides, using the criteria in Chapter 3, to prepare a product for which there are no documented procedures, he/she should take full responsibility for the quality of that product and the procedures used for preparation should be fully documented, along with the rationale for preparation. The Authorised Pharmacist should inform the Accountable Pharmacist of this at the earliest opportunity.

5.3 Audit

5.3.1 It is the responsibility of the Chief Pharmacist to ensure that internal audits of aseptic preparation are carried out on a regular basis. Any faults or deficiencies, however identified, should be promptly rectified. (See Chapter 16: Internal and external audit.)

5.3.2 It is the joint responsibility of the Chief Pharmacist and the Regional Quality Assurance Specialists to ensure that external audits are carried out in accordance with current NHS requirements (NHS Executive 1997).

5.3.3 The Chief Pharmacist is responsible for ensuring that an action plan to address the deficiencies is sent to the external auditor in a timely manner and that actions are completed within the agreed timescale. The Chief Pharmacist is also responsible for communicating to the external auditor any major changes to facilities, key personnel etc., or slippage of the action plan.

5.3.4 It is the responsibility of the Chief Pharmacist to ensure that quality assurance systems are regularly reviewed and that any off-site testing is regularly audited.

5.3.5 The Chief Pharmacist is responsible for regulatory compliance. For example, in accordance with *The Medicines for Human Use (Clinical Trials) Regulations 2004*, manufacture of an investigation medicinal product requires an MIA (IMP) (see Part B – 6).

5.4 Contingency planning

5.4.1 There should be a detailed contingency plan to cover any unforeseen event, e.g. unavailability of key personnel etc. that could lead to shutdown of the unit, or temporary unavailability of the service. The contingency plan should include the details of who to contact in the event of failure. The contingency plan should include business continuity, e.g. the use of alternative aseptic facilities, outsourcing etc. Risk reduction measures, such as review of shelf life and storage conditions, may be necessary.

5.5 Capacity planning

5.5.1 The Chief Pharmacist should ensure that the department has a current and effectively implemented capacity plan (see Part B – 5).

5.5.2 The Chief Pharmacist is responsible for ensuring that the capacity plan is approved by senior hospital management external to pharmacy, for example at board level, to enable it to be effective at managing pharmacy workload in the context of the organisation's injectable medicines policy.

5.5.3 Workload figures should be regularly reviewed (suggested monthly) against this plan and action taken where appropriate. Significant variations should be authorised by senior managers within the organisation, under change control.

5.5.4 The capacity plan should have the following attributes:

- It should ensure adequate resourcing for the expected demand
- There should be a thorough understanding of demand and preparation constraints, and appropriate strategies to highlight imbalances in a timely manner to effect appropriate action
- It should address the entire scope of work undertaken in the aseptic unit, including essential underpinning tasks such as maintenance of the PQS
- If aseptic services staff are involved with dispensing outsourced aseptic products, this should be included in the capacity plan.

5.5.5 The capacity plan should be reviewed at least annually or when there are significant changes to supply and demand. Any changes should be managed via the change control system.

References

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The Medicines for Human Use (Clinical Trials) Regulations 2004. SI 2004 No.1031. London: The Stationery Office.

CHAPTER 6 FORMULATION, STABILITY AND SHELF LIFE

Expiry periods (shelf lives) given to products should be evaluated in accordance with the local conditions and formulations. Data obtained from the literature or from the starting material manufacturer should be carefully assessed to ensure their appropriateness to the local situation.

Under no circumstances should an expiry period of seven days be exceeded for products prepared in unlicensed aseptic units (see Chapter 3: Minimising risk with injectable medicines). As a general principle, the shortest expiry period consistent with the intended usage pattern of the product should be used. Use of the shortest possible shelf life does not obviate the need to comply fully with the standards described in this text.

The overall aim should be to minimise the time between preparation of the product and its administration so that the opportunity for any live microorganisms inadvertently introduced into the product to multiply is restricted and levels of degradation are also minimised.

The range of formulations encountered during aseptic preparation is broad and ranges from fairly simple two-constituent systems to complex mixtures with in excess of 50 starting materials, e.g. parenteral nutrition (PN) regimens, and from simple, well-understood small molecules to complex biopharmaceuticals.

Product shelf life should be assigned to ensure the quality of the product is suitable for the patient at the time of administration. The assignment of a shelf life can be a complex process even for small molecules and is extremely complex for parenteral nutrition and for biopharmaceuticals.

6.1 Stability testing

6.1.1 Where stability studies are to be carried out in-house or specifically commissioned then the standards outlined in *A Standard Protocol for Deriving and Assessment of Stability Part 1 – Aseptic Preparations (small molecules)* (PQAC 2015a), *Part 2 – Aseptic Preparations (Biopharmaceuticals)* (PQAC 2015b), or *Part 4 – Parenteral Nutrition* (PQAC 2016) should be followed.

6.1.2 It should be borne in mind that even if a full in-house stability study is not possible, ongoing information in support of a shelf life assigned can be

obtained by testing products at the end of their shelf life by stability-indicating methods. This should be used to provide additional information to published studies or, in extreme circumstances, to provide assurance of an extrapolation that has been carried out.

6.2 Sources of information

6.2.1 Many sources of stability information exist, some more reliable than others. It is the responsibility of the Authorised Pharmacist to ensure that the information used is scientifically valid and relevant to the local circumstances. Further guidance is given below.

6.2.2 A number of texts are available through quality control and medicines information, including textbooks, product data sheets and published research papers. The manufacturer's SmPC is a prime source of information as this has been reviewed as part of the product licensing process. Often, however, the data is quite limited and aseptic units may need to rely on published or peer-reviewed studies for extended data. General reference sources, such as textbooks, should be used with care and the applicability of the data to the actual brands of products used should be carefully assessed.

6.2.3 For PN, the prime source of information should be the supplier of the major starting materials (amino acid and lipid solutions). A matrix approach should be taken with PN, where all starting materials need to be within pre-defined limits in order to assure stability. It would generally be expected to use the major starting materials, such as amino acids and lipids, from the same manufacturer.

6.2.4 Where a computerised system is used to perform stability calculations (for example, while compounding PN) appropriate validation (see Part B – 2.6) commensurate with the level of risk should be performed on the system, ideally using known stability problems to ensure that the output of the calculations is correct. The use of a computerised system should supplement, and not replace, the professional judgement of a member of staff skilled in formulation and stability assessment.

6.2.5 Suitable data should be sought and evaluated before products are prepared. This data should be retained on file, together with the record of its assessment.

6.2.6 If no data is available, the decision to prepare should be made in the context of the clinical needs of the patient and this risk assessment should be fully documented. This should only occur in exceptional circumstances.

6.2.7 If a product made under the circumstances described above is to continue being prepared in the aseptic unit, then appropriate stability data should be obtained or generated to support the shelf life assigned.

6.3 Data interpretation

6.3.1 Data from information sources needs to be interpreted for the local situation; in general data should only be used for the specific brands, concentrations, diluents and containers that are quoted in the reference. Studies should be checked for compliance with standards (PQAC 2015a and PQAC 2015b).

6.3.2 Generally data can be safely interpolated, for example to any concentrations between the low and high concentrations which have given suitable stability profiles, however care should be taken with biopharmaceuticals (see below).

6.3.3 Extrapolation should only be done where there is a good understanding of the product stability and degradation profile and, for example, the characteristics of various container systems that may be required. Stability of biopharmaceuticals can be influenced by how they are handled and other factors such as the final container, the amount of air present in the final container and the amount of silicone oil in syringes. There should therefore be no extrapolation of data for biopharmaceuticals.

6.3.4 For biopharmaceuticals, units using published or peer-reviewed studies to support an expiry period beyond that stated in the SmPC should ensure that they are using identical practices to those in the study for preparation, storage and transportation with identical starting materials, consumables and storage containers.

6.3.5 The levels, nature and potential toxicity of any degradation products should be considered as part of shelf life assessment.

6.4 Factors affecting stability

Factors which may have an impact on product stability are discussed further below.

6.4.1 Chemical degradation

The main mechanisms of chemical degradation for small molecules are hydrolysis, oxidation and photolysis. Other degradation pathways, e.g. polymerisation and isomerisation, can also occur. For biopharmaceuticals, the situation is highly complex and can include chemical changes, conformational changes, aggregation, fragmentation and interactions with containers and excipients.

6.4.2 Concentration of active components

Concentration can either enhance or reduce stability. For example, Ampicillin degrades more quickly in high concentrations. Oxidation and photodegradation reactions generally follow zero order kinetics and so medicines degraded in this way often have a shorter shelf life at lower concentrations.

6.4.3 pH

The rates of degradation of many drugs are pH dependent. Buffering, or the lack of buffering ability, may have a significant impact on stability.

6.4.4 Diluent / vehicle

Some drugs can be diluted in various diluents but stability is often significantly different in each, for example Cisplatin needs the presence of chloride ions to remain stable.

6.4.5 Catalysis

Some ingredients in formulations can act as catalysts for the breakdown of other ingredients. For example copper ions from trace metal additions in PN preparations catalyse the oxidation of Ascorbic Acid; buffer ions may catalyse the hydrolysis of penicillins.

6.4.6 Ionic strength

The reaction rate may be influenced by the ionic strength of the medium, but this is usually a less important factor than the other factors given above.

6.4.7 Preparation process

The method of preparation can be critical to stability. The correct order of mixing of materials in PN compounding is essential to avoid high concentrations of electrolytes, which affect lipid particle size, and also to avoid high concentrations of divalent metal ions mixing with phosphate, which could cause precipitation.

Biopharmaceuticals are susceptible to changes in handling, which include the level of shaking, contact with components, needle sizes, filtering etc.

6.4.8 Photosensitivity

There can be significant photodegradation of some drugs, e.g. Carmustine. It is important that this is understood and the impact of any light protective wraps is also assessed.

6.4.9 Filters

Filters used in preparation processes can cause problems such as adsorption onto the filter medium that will reduce the potency of some injections. Hence, care should be taken to assess the impact of the use of filters in preparation and also in administration.

6.4.10 Containers

The nature of the container can contribute to stability of the product in a number of ways including:

- by releasing leachable chemicals (e.g. plasticisers and lubricants from rubber stoppers)
- by interacting with the product, for example lubricants may interact with monoclonal antibodies
- by sorption of ingredients from the solution into or onto the container.

There may also be differences in container permeability, allowing gaseous diffusion into the container (important for products which are susceptible to oxidation) and increased water loss leading to concentration of solutions.

6.5 Storage

In accordance with advice in other parts of this handbook (see Chapter 15: Storage and distribution), products should be stored in a refrigerator where this does not impact on quality. In general, low storage temperatures slow down chemical degradation, sorption, etc. However, it should be remembered that low-temperature storage can result in physical instability, e.g. precipitation, such as in Aciclovir infusions. The converse can also be true though: phosphates are less soluble at room or body temperature, which has led to precipitation in PN solution once it is removed from the refrigerator.

6.6 Microbiological and container integrity issues

6.6.1 Aseptic preparation facilities should enable the preparation of injections in controlled environments with a high level of sterility assurance. The integrity of the final container should have been assessed up to the shelf life that individual products are assigned. For single component systems, such as infusion bags, this can take the form of a check for leaks but for multiple component systems, such as capped syringes, there needs to be an assessment of container integrity.

6.6.2 Ideally, this should take the form of in-house integrity testing in accordance with *Protocols for the Integrity Testing of Syringes* (PQAC 2013).

As a minimum, nationally collated data should be reviewed and its applicability to the specific syringe/closure combinations/fill volumes in use should be assessed alongside in-house broth transfer test data.

6.6.3 In order to maintain microbiological integrity, infusion bags should not be spiked ahead of the time of their use in clinical areas.

6.7 Expiry period

6.7.1 The expiry period of the product should be based on all of the information available. Specific pieces of information should not be ignored and should form part of the assessment; this includes physico-chemical stability and microbiological contamination risks.

6.7.2 For biopharmaceuticals, it is particularly important that other investigators' findings are considered alongside any in-house data, specifically where these findings may ask questions of the validity of the data from the in-house study.

6.7.3 The expiry period should be reviewed and reassessed if new data becomes available relevant to the product.

6.7.4 The expiry period should not exceed seven days in any circumstances in an unlicensed aseptic unit.

6.8 Control of procurement contract changes for starting materials and components

Changes to starting materials and key components should be fully assessed using a formal change control procedure before they are introduced (see Chapter 8: Pharmaceutical Quality System). Stability information is often specific to a particular manufacturer of starting material and, hence, a new shelf life assessment will be required when this changes; this re-assessment should be recorded. The document *Assessment of shelf life following a change in supplier of starting material* (R and D 2012) provides further guidance and examples.

6.9 Stability file

6.9.1 Stability data, including copies of studies used and in-house assessments, should be maintained by a controlled system in a stability file (paper-based or electronic folder) for ease of reference.

6.9.2 Worksheets should have stability references which cross-reference to the data and assessments held in the stability file.

6.10 Pharmacovigilance

Any problems with products or patient adverse drug reactions should be investigated thoroughly. This investigation should lead to a review of the assigned formulation, storage conditions and shelf life where appropriate. Reporting of such issues should be encouraged within the organisation, for example via the Datix system.

References

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NHS Pharmaceutical Quality Assurance Committee (PQAC) (2013). *Protocols for the Integrity Testing of Syringes.* 2nd edn. Microbiology Protocols Group and NHS Pharmaceutical Research and Development Group (R and D).

NHS Pharmaceutical Quality Assurance Committee (PQAC) (2015a). *A Standard Protocol for Deriving and Assessment of Stability Part 1 - Aseptic Preparations (small molecules).* 3rd edn. NHS National Pharmaceutical Research and Development Group.

NHS Pharmaceutical Quality Assurance Committee (PQAC) (2015b). *A Standard Protocol for Deriving and Assessment of Stability Part 2 - Aseptic Preparations (Biopharmaceuticals).* 2nd edn. NHS National Pharmaceutical Research and Development Group.

NHS Pharmaceutical Quality Assurance Committee (PQAC) (2016). *A Standard Protocol for Derivation and Assessment of Stability Part 4 – Parenteral Nutrition.* NHS National Research and Development Group.

CHAPTER 7 FACILITIES AND EQUIPMENT

Facilities and equipment should be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and/or design should aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products (EC 2015).

7.1 Design principles for new or refurbished facilities and equipment

7.1.1 The performance criteria of the new facility or new item of critical equipment (such as, isolators, refrigerators etc.) should be established prior to building or installation by the development of a detailed user requirements specification (URS). The URS should be part of an overarching change control for the project that takes into account knowledge of deviations, errors and malfunctions of the previous existing facilities and processes (EC 2015 Annex 15).

7.1.2 Compliance to this previously defined design specification or URS should be confirmed through a series of validation stages which will include design, installation, operational and performance qualification, (DQ, IQ, OQ, PQ), supporting subsequent process validation (PV). The qualification protocols should be approved by the Accountable Pharmacist, including those drawn up by any external contractor providing validation services.

Current standards need to be knowledgeably interpreted, and future developments considered before the URS is finalised. Of particular importance is due consideration of current and future capacity and workforce requirements. Sufficient resources (time, funding, personnel and expertise) should be allocated for validation activities (Beaney 2010).

7.1.3 The approach to validation should be detailed as part of the comprehensive Validation Master Plan (VMP). This should also be subject to the deviation and change control systems. (See Chapter 8: Pharmaceutical Quality System).

7.1.4 Each stage of the validation process should be defined in a validation protocol which should be approved and authorised by the appropriate personnel as defined in the VMP. The continued maintenance of the facility or equipment should be considered as part of the VMP (EC 2015 Annex 15).

(Qualifications documents may be combined in some cases e.g. IQ and OQ for small projects.)

7.1.5 It should be clear at which point final handover into use is accepted and this should be documented and signed by the contractor performing the qualification and the personnel defined in the VMP, including the Accountable Pharmacist.

7.1.6 Any planned changes to the facilities, equipment or utilities which may affect the quality of the product should be formally assessed via the change control system.

7.1.7 Facilities and equipment should be designed to allow preparation to take place in areas connected in a logical order. Consideration needs to be given to the workflow of materials, finished products, personnel and waste.

7.1.8 Health and safety should also be considered in the design of a new facility, for example the provision of adequate extraction for disinfectants.

7.1.9 All clean rooms and clean air devices should be independently qualified by the purchaser or by a contractor acting on their behalf. They should subsequently be monitored at regular intervals (see Chapter 11: Monitoring).

7.1.10 All aseptic operations should be performed in a critical zone environment conforming to EU GMP Grade A (EC 2015). This should be located in a clean room, conforming to the correct standard, as defined in section 7.3. All classified rooms in the aseptic suite should conform to EU GMP (EC 2015, BSI 1999).

The critical zone environment may be provided by a clean air device such as:

- a unidirectional air flow workstation (UDAF)
- a pharmaceutical isolator.

There are various design types that will provide these conditions, e.g. horizontal or vertical laminar air flow cabinets, Class II safety cabinets, cytotoxic cabinets, negative and positive pressure isolators.

A well designed and maintained air handling unit (AHU/HVAC) is fundamental to the satisfactory operation of the facility and the AHU should comply with current NHS standards (DH 2007).

7.1.11 All areas used for preparation and storage should allow the orderly and logical positioning of equipment and materials.

Adequate segregation is required to minimise the risk of confusion between different products or components in order to avoid cross contamination and mix-up.

7.1.12 The facility walls, floors and ceilings of the classified environment should be smooth, impervious to fluids, resistant to sanitisation agents, and free from cracks and open joints. There should be an absence of exposed wood throughout the unit. Surfaces should not shed particulate matter and should permit easy, effective sanitisation. The joints between ceilings, walls and floor should be coved (EC 2015, BSI 1999).

7.1.13 Vision panels, switches, lights, intercoms, etc. should be flush fitting and easily cleanable. (The use of stainless steel is more expensive but more durable.)

Electrical trunking should be flush where possible, or at least have a sloping upper surface that aids easy cleaning and prevents accumulation of dust.

The replacement of light fittings (e.g. light bulbs and tubes) should be achievable without breaching the integrity of the clean room suite.

7.1.14 Clean rooms and support rooms should have a filtered air supply that maintains a positive pressure and air flow relative to surrounding areas of a lower grade and should flush the area effectively. In routine use, classified adjacent rooms should achieve a minimum differential pressure of 10 Pascals, and a minimum of 15 Pascals to an unclassified area (see Chapter 11: Monitoring).

It is advised that the design specification is at least 50% more than the minimum pressure differential.

7.1.15 Pressure differential readings between clean rooms and support rooms and from the clean room facility to external areas should be constantly indicated.

7.1.16 Pressure differentials should be constantly indicated across at least one typical HEPA filter supplying the clean rooms.

7.1.17 Air flow patterns should not create any dead spots or standing vortices. Determination of air flow patterns should be carried out on commissioning and after any significant modification to the room or cabinet. For EU Grade B (EC 2015) rooms and all types of clean air device, air flow pattern tests should be carried out annually as part of recommissioning (see Chapter 11: Monitoring).

7.1.18 The AHU should be designed to provide continuous compliance with the requirement for a minimum of 20 air changes per hour in all EU GMP Grade C and D (EC 2015) rooms and 30 air changes per hour in EU GMP Grade B (EC 2015) rooms (see Chapter 11: Monitoring).

This will typically allow the short clean-up period of less than 15 to 20 minutes (EC 2015).

7.1.19 There should be visible and audible alarms to indicate malfunction or failure of the air handling plant. The indicator board should be located at the entrance to the facility to ensure staff are aware of plant failure before entering (Beaney 2010).

The alarm system should also indicate malfunction or failure of the aseptic suite that occurred out of normal working hours and should require manual resetting.

7.1.20 Dispersed oil particulate (DOP) challenge access points should be carefully considered at the design stage. The injection points should be sufficient distance upstream from the terminal HEPA filters to allow uniform challenge (at least 15 duct widths from the filters) and should be located outside the clean areas. Upstream DOP concentration test points should also be provided.

7.1.21 Sinks and hand wash-stations should not be present in the clean room suite, except in exceptional circumstances. A formal hand wash prior to entry to the clean room suite is required. It is desirable to locate the hand wash facility adjacent to the entrance to the clean room suite.

7.1.22 Where it is considered necessary, after risk assessment, to site a sink within the aseptic facility e.g. radiopharmacy units, the location and use of the sink should be carefully considered in view of the potential to cause microbiological contamination. Regular monitoring and disinfection of the sink should be carried out (see Chapter 11: Monitoring).

7.1.23 Wall-mounted dispensers should be avoided in change rooms as they could result in damage to walls if changed and/or difficulty in cleaning.

7.2 General considerations

7.2.1 Clean rooms and clean air devices should run continuously, except during certain cleaning and maintenance activities. Requalification may be required after the activity. Aseptic manipulation should not be carried out until a satisfactory environment has been re-established, as verified by appropriate validation studies.

It is not desirable to operate a clean room with variable air change rates (in particular, operational setback as an energy saving measure is not acceptable) because it is necessary to maintain the operational status of the clean rooms to prevent accidental ingress of external contamination. If variable conditions are to be considered, these should ensure that the minimum operational standards are maintained; i.e. room overpressures remain above minimum standards and cleanup rates are similarly preserved. This should be subject to continuous monitoring (see Chapter 11: Monitoring).

7.2.2 All clean rooms and clean air devices should be cleaned regularly and frequently in accordance with an agreed written procedure. The procedure should require written confirmation that cleaning has been carried out and which cleaning agent was used (see Chapter 12: Cleaning, sanitisation and biodecontamination).

7.2.3 Critical equipment, including air-handling systems, isolators, cabinets, filling pumps, automated compounding systems, radiopharmaceutical calibrators, QC equipment etc. should be operated in accordance with SOPs and should be subject to commissioning and have a documented, planned preventative maintenance (PPM) and calibration schedule.

7.2.4 When monitoring indicates a loss of environmental control, or trend towards this, an impact assessment, root cause analysis and corrective and/or preventative actions (CAPA) should be undertaken (see Chapter 8: Pharmaceutical Quality System).

7.2.5 The operational characteristics (the normal operating parameters) of the facilities and equipment should be confirmed following any planned or unplanned maintenance, i.e. the systems match the parameters established during initial validation.

7.2.6 Reports from service and maintenance visits should be reviewed and accepted by the Accountable Pharmacist in a timely manner, ideally upon receipt, to ensure that the correct level of testing has been applied in accordance with the relevant standards and that the unit complies with these standards. Checks should be documented.

7.2.7 Access to the facility and plant rooms housing the AHU/HVAC systems should be controlled and restricted to authorised personnel. A permit to work system should be in place and strictly enforced. Maintenance or recalibration of systems or equipment should not be undertaken without the documented approval of the Accountable Pharmacist.

7.2.8 The permit to work should detail all work to be undertaken and should be signed again by a senior member of the aseptic team on completion of the work. There should be formal acceptance back into operation after any necessary cleaning of the facility has been undertaken (see Chapter 12: Cleaning, sanitisation and biodecontamination).

7.3 Clean rooms and support rooms

The support room should be appropriately designed and provide adequate space. It is essential that the flow of work, personnel and waste is designed to minimise error, unnecessary crossover and to make efficient use of the space.

Siting equipment in rooms of the appropriate classification

Clean rooms housing clean air devices should be dedicated to aseptic preparation and all other activity should be forbidden.

7.3.1 Unidirectional air flow workstations (cabinets) should be located in a room classified to EU GMP Grade B (EC 2015) and accessed via an appropriate 3-stage change process. The air flow should be considered carefully and workstations positioned to ensure that contra flows do not occur.

7.3.2 Pharmaceutical isolators should be located in a room classified to a minimum of EU GMP Grade D (EC 2015) and accessed via an appropriate 2-stage change process.

7.3.3 Clean rooms should be entered through a changing room, the doors to which should be interlocked. The change room should be flushed effectively with directly filtered air supplied by a ceiling mounted HEPA filter on the clean side of the room.

7.3.4 The changing rooms should be divided by a suitable barrier, or equivalent, separating the space into a clean side and a 'dirty' side.

7.3.5 The final stage of the change area should, in the 'at rest' state, be the same grade as the area into which it leads (EC 2015).

7.3.6 Goods and materials should enter via a separate route to personnel.

7.3.7 The EU GMP Grade B (EC 2015) clean room should have an associated support room classified to a minimum of EU GMP Grade D (EC 2015) which is accessed via an appropriate 2-stage change process.

This area may be used for the storage and assembly of starting materials and components ready for transfer into the clean room.

7.3.8 The EU GMP Grade D (EC 2015) clean room should have an associated support room.

The support room should maintain a minimum of EU GMP Grade D (EC 2015) at rest.

This area may be used for the short-term storage and assembly of starting materials and components ready for transfer into the clean room.

7.3.9 Materials transferred into the support room should be subjected to a decarding and sanitisation process (see Chapter 12: Cleaning, sanitisation and biodecontamination). Transfer of materials should be through a dedicated hatch or hatches.

7.3.10 Ideally there should be dedicated in and out hatches. Alternatively segregation of products in and out can be managed by physical separation such as shelves.

7.3.11 All hatches should be fitted with interlocking doors and flushed with air flow sufficient to enable drying of disinfectants and the removal of particles (see Chapter 12: Cleaning, sanitisation and biodecontamination).

7.4 Clean rooms for specialist applications

7.4.1 Additional considerations should be taken into account for some clean rooms, including those used to prepare Advanced Therapy Medicinal Products (ATMPs). For example, gene therapy medicines require preparation in facilities designed to provide physical, chemical and biological barriers or any combination of these to limit contact with, and to provide a high level of protection for, personnel and the environment, depending on their classification. The most appropriate facilities and their location should be determined by risk assessment. (See Part B – 6, EC 2015 Annex 2).

7.4.2 Consideration should be given, in the risk assessment, to the necessity for a dedicated negative pressure isolator in a minimum EU GMP Grade D (EC 2015) background or Class II safety cabinet in a EU GMP Grade B (EC 2015) background. Dedicated equipment may be required depending on the specific nature of the materials being handled.

7.4.3 In certain circumstances it may be permissible for products of this nature, and other products intended for short term use, (shelf life restricted to 24 hours) to be prepared in isolators located in background environments that do not meet the required standard indicated in Part B – 6.

This should only be in response to an exceptional circumstance, and never routine practice. This should be accompanied by a formal, documented risk assessment (see Part B – 4).

7.4.4 There should be separate facilities for blood labelling in radiopharmacy (MHRA 2015, DH 2013, UKRG 2009).

7.4.4.1 Facilities designed for radiopharmaceutical preparations should comply with the standards contained within *Quality Assurance of Radiopharmaceuticals* (UKRG 2012).

7.4.5 Facilities for PET/Cyclotrons require specialist expertise. More information is available in *Sampson's Textbook of Radiopharmacy* (Theobald 2011) and from the Institute of Physics and Engineering (IPEM) and the European Association of Nuclear Medicine (EANM).

7.5 Quality control facilities

7.5.1 Facilities used for processing samples should be physically separated from aseptic preparation but under the managerial control of the Chief Pharmacist or Quality Controller, or through a contract laboratory via a service and technical agreement (see Part B – 3 and Chapter 5: Management).

7.6 Equipment

The type of clean air device chosen should take into account the nature of the materials to be handled, considering both product and operator protection.

7.6.1 Unidirectional air flow cabinets

As indicated in 7.3.1 above, the position of the cabinet within the room is crucial to the cabinet's correct function. Consideration should be given to the air flow within the clean room to minimise any interference in cabinet air flow, such as can be found if located too close to a door, for example.

7.6.1.1 Air flows within the cabinets and clean room should not create any dead spots or standing vortices. The air flow patterns should be determined on commissioning and after any significant modifications. (See 7.1.17).

7.6.1.2 All materials and components required for preparation should be transferred into the cabinet, in accordance with the transfer sanitisation procedures, prior to aseptic processing.

Sufficient space should be allowed around the working frontage to allow personnel to move in the room without disrupting the air flow in the cabinet. Typically this would be at least one metre. The movement of the operatives in the cabinet should be controlled to minimise the disturbance of air flow patterns.

7.6.1.3 Items should be placed in such a manner as to ensure minimal disruption to the air flow (see Chapter 10: Aseptic processing).

7.6.2 Pharmaceutical isolators

7.6.2.1 The design of the isolator should follow the principles laid down in *Isolators for Pharmaceutical Applications*. Guidance on the operating pressure in isolators for pharmaceutical use is provided (Midcalf et al 2014).

Consideration should always be given to installing a system of isolators which are gaseously biodecontaminated, in order to provide a high level of assurance of elimination of microbial contamination.

7.6.2.2 The critical zones of isolators that are used for the preparation of hazardous pharmaceuticals, e.g. cytotoxic drugs and radiopharmaceuticals, should operate at a negative pressure with respect to the background environment or be designed in such a way as to maximise operator protection as well as maintaining an appropriate level of product protection (HSE and MHRA 2015). 100Pa ± 20Pa is commonly used for positive and negative pressure isolators for pharmaceutical use.

7.6.2.3 Isolators used for handling hazardous pharmaceuticals should be totally exhausted to the outside environment, with appropriate safeguards (HSE and MHRA 2015).

The use of isolators compared to Class II Microbiological Safety Cabinets is preferable to maximise both operator and product protection.

7.6.2.4 Particular emphasis should be placed on ensuring that the glove/sleeve assembly or gauntlet maintains the integrity of the isolator during each and every session (see Chapter 11: Monitoring). Visual inspection of gloves and gauntlets forms an important part of the assessment of integrity but should not be relied upon alone. A pressure measuring device is often used, however its sensitivity should be determined during commissioning by applying different

sized holes to a glove. Cabinet leak tests are a better indicator of the integrity of gloves.

7.6.2.5 The specified leak rate by pressure decay is a critical parameter that allows the user to assess whether its integrity has been compromised. Leak rates of 0.25% for negative isolators and 1% for positive isolators have been advocated (Coles 2012, Bässler 2013). This represents a drop of 25Pa in 6 minutes and 1.5 minutes respectively. A low leak rate is especially important for turbulent flow isolators. Ideally, the inner chamber should be leak tested separately from the whole carcass.

7.6.2.6 Transfer devices are designed so that they do not compromise the EU GMP Grade A (EC 2015) working zone during the transfer of materials and components. An input hatch door release timer should be specified with a minimum of 2 minutes to ensure adequate disinfection time and evaporation.

The transfer of materials and components into and out of the critical zone represents a significant challenge to the integrity of the isolator.

7.6.2.7 A service contract should be in place for all critical equipment (see Chapter 11: Monitoring).

7.6.3 Other equipment

7.6.3.1 The impact of other equipment, such as compounders, automated filling systems, radiopharmacy HPLC, dose calibrators etc. on disturbance of air flow in clean environments should be risk assessed (MHRA 2015).

7.7 Gowning

The operator is an essential part of the aseptic preparation process in hospitals. To minimise the risk of contaminating products with microorganisms and particles originating from the operators, it is essential to wear clean room clothing the quality of which should be appropriate for the process and the EU GMP grade of the working area (EC 2015).

7.7.1 A defined hand wash employing a biocidal agent should be used immediately before entering the aseptic suite. This should be followed by the routine application of a disinfectant hand rub/gel at the point of gloving.

Alcoholic gels and rubs are not appropriate for use on gloves as the emollients may damage glove materials; therefore alcohol 70% should be used.

7.7.2 The changing process should be defined and documented, and should include details of the appropriate clothing to be worn in each area.

7.7.3 The minimum requirement for clothing for each grade of environment is given in Table 7.1:

Table 7.1
Minimum clothing requirements

GRADE OF ENVIRONMENT	MINIMUM CLOTHING REQUIREMENTS
D	■ Hair, and where relevant, facial hair, beards and moustaches including stubble should be completely covered, for example with a beard snood ■ A non-shedding protective coat or suit ■ Dedicated shoes or overshoes.
C	■ Hair, and where relevant, facial hair, beards and moustaches including stubble should be completely covered, for example with a beard snood ■ A single- or two-piece trouser suit (which sheds virtually no fibres or particulate matter), gathered at the wrists and with a high neck ■ Dedicated shoes or overshoes.
B	■ Headgear should totally enclose hair, and where relevant, facial hair, beards and moustaches including stubble; it should be tucked into the neck of the suit ■ A sterile face mask ■ Non-powdered sterile gloves ■ A single piece clean room coverall, gathered at the wrists and with a high neck ■ Trouser legs should be tucked inside the footwear and garment sleeves into the gloves ■ Dedicated footwear, e.g. clean room slippers ■ All clothing should shed virtually no fibres or particulate matter and should be sterilised*.

7.7.4 The changing procedures should be appropriate for the grade of room specified and the processes undertaken.

7.7.5 On entering the clean room suite, unnecessary outdoor clothing and accessories should be removed and footwear should be changed or overshoes used.

7.7.6 Typical changing processes are indicated in Table 7.2:

Table 7.2
Typical changing processes

STAGE	GRADE D	GRADE C	GRADE B
1	Remove outdoor clothing and accessories	Remove outdoor clothing and accessories	Remove outdoor clothing and accessories
2	**Either** Don dedicated coat, hat and footwear (bare feet in clogs are not permitted) **or** Remove outer clothing down to underwear ■ tights and socks are acceptable – Don a dedicated ■ one or two piece suit ■ footwear (bare feet in clogs are not permitted – disposable clean room socks are preferred) ■ head covering ■ gloves Facial hair should be completely covered	Remove outer clothing down to underwear ■ tights and socks are acceptable – Don a dedicated ■ one or two piece suit ■ footwear (bare feet in clogs are not permitted – disposable clean room socks are preferred) ■ head covering ■ gloves Facial hair should be completely covered	Remove outer clothing down to underwear ■ tights and socks are acceptable – **Don a dedicated ■ one or two piece suit ■ footwear (bare feet in clogs are not permitted – disposable clean room socks are preferred) ■ head covering ■ gloves Facial hair should be completely covered
3			■ Don sterile* coverall, hood, mask, boots and gloves, over stage 2 clothing

* *Sterilised clean room clothing should be worn by all staff entering the EU GMP Grade B (EC 2015) room. Alternative methods that guarantee the clothing is initially free from viable organisms may be used, e.g. a validated biocidal wash. Levels of particulate contamination should also be controlled.*

** *Specialised clean room undergarments are an acceptable alternative.*

7.7.7 If the movement is from an EU GMP Grade D (EC 2015) support room to an EU GMP Grade D (EC 2015) isolator room, there should be a minimum of a change of gloves and footwear.

Best practice would be a change of footwear (or additional overshoes) and replacement of a coat. If a two piece suit is worn, an additional coat should be worn in the cleaner area.

7.7.8 There should be a periodic review of the garments and their fit to specifications (recommended annually).

The garment should be subject to validated laundering and, where appropriate, sterilisation processes. These processes should be subject to a regular audit.

7.7.9 There should be procedures in place detailing the use of garments and identifying the length of time they may be worn and how they are stored whilst not in use. Sterile garments for use in EU GMP Grade B (EC 2015) rooms should be worn for one session only.

7.7.10 The changing frequency for clean room coats for EU GMP Grade D (EC 2015) should not be less frequently than weekly, however changing frequency should be increased if the garment is worn for most of the working day.

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CHAPTER 8 PHARMACEUTICAL QUALITY SYSTEM

Developments in EU Good Manufacturing Practice (GMP) (EC 2015) have highlighted the need for a robust Pharmaceutical Quality System (PQS) (ICH 2008). Anyone preparing medicines should embrace the concept of Quality Management, that covers all matters, which individually or collectively influence the quality of the product.

Quality Management (previously Quality Assurance) is 'the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use'. Quality Management therefore incorporates GMP (EC 2015).

In accordance with EU GMP (EC 2015), senior managers have overall responsibility for the PQS and associated quality indicators (see Chapter 5: Management). It is, however, everyone's responsibility to comply with the quality system.

8.1 Pharmaceutical Quality System – general principles

8.1.1 A robust PQS should be in place incorporating EU GMP (EC 2015) and Quality Risk Management (ICH 2005).

8.1.2 The PQS should be fully documented, for example in a quality manual, and its effectiveness monitored.

8.1.3 Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the PQS and continually improve its effectiveness. They should ensure that resources are appropriately applied to a specific product, process or site. (See Chapter 5: Management.)

8.1.4 There should be defined Quality Management (previously Quality Assurance) duties specifically enshrined in job descriptions.

8.2 Design of the PQS

The design of the PQS should reflect the size and complexity of the preparation activities and should incorporate risk management principles (ICH 2005). It should, as a minimum, include the following:

8.2.1 Quality aspects throughout the product lifecycle

8.2.1.1 That is, product initiation, regular preparation, discontinuation (ICH 2008). There should be procedures in place for:

- Product initiation: This should consider, for example, risk assessments (see Chapter 3: Minimising risk with injectable medicines), formulation and stability (see Chapter 6: Formulation, stability and shelf life), change control
- Regular preparation: This should consider the impact on capacity of any increased frequency of preparation, review of trends etc.
- Product discontinuation: There should be a procedure to assess the impact of the discontinuation on patients, to consider alternative treatments, if appropriate, and to manage the discontinuation process.

8.2.2 Documentation control systems

8.2.2.1 In addition to the requirements in 8.3 below, there should be an overarching procedure that defines responsibility for writing, verifying and approving, and archiving, all types of documentation (SOPs, worksheets, specifications, logs etc).

8.2.3 Standard operating procedures

See section 8.4

8.2.4 Validation Master Plans

8.2.4.1 This includes computerised systems (see Part B – 2.6).

8.2.4.2 There should be a comprehensive and current Validation Master Plan (VMP) that summarises all validation activities carried out in the unit. Additionally, there may be individual VMPs for specific equipment or activities (PQAC 2009).

8.2.5 Deviation Management, planned and unplanned, e.g. deviations, microbiological non-conformances, error reporting, accident reporting, minor defect reporting systems

Note: Planned deviations may be more appropriately managed as temporary change controls.

8.2.5.1 There should be a suitable system, or series of systems, for management and trending of all types of deviations and sufficient resource to implement this in a timely manner.

8.2.5.2 Investigations of deviations should include an appropriate level of root cause analysis. Corrective and/or preventative actions (CAPAs) should be identified as a result of these investigations and their effectiveness should be monitored and assessed. Where human error is suspected as the cause, care should be taken to ensure that any process, procedural or system-based errors or problems have not been overlooked.

8.2.6 Change control

8.2.6.1 There should be a robust system for documenting and approving all planned changes (both temporary or permanent). All changes should be evaluated for their potential impact on product quality, and a decision made on whether or not to implement them.

8.2.6.2 Implementation of all changes should be tracked and they should be reviewed after a suitable period to ascertain whether they have worked as intended and to establish whether they have had any unanticipated detrimental impact on product quality.

8.2.7 Quality Review

8.2.7.1 There should be periodic management review, with the involvement of senior management, of the operation of the PQS to identify opportunities for continual improvement of products, processes and the system itself (see Chapter 5: Management).

8.2.8 Personnel and training policies (see Chapter 9: Personnel, training and competency assessment)

8.2.8.1 An approved and current training programme should be available. Completion of training should be documented in individual training records.

8.2.8.2 A system for the evaluation of the training programme, paying particular attention to practical skills, should be implemented (see Part B – 2.4).

8.2.9 Management of outsourced activities (see Chapter 5: Management)

8.2.9.1 Suitable technical agreements should be in place that define responsibilities for any outsourced activities and products. (A specimen technical agreement is given in Part B – 3).

8.2.9.2 Sufficient resource should be available to define and monitor technical agreements (see Chapter 3: Minimising risk with injectable medicines).

8.2.10 Internal audit (see Chapter 16: Internal and external audit)

8.2.10.1 A comprehensive programme of internal audits should be undertaken with the awareness and support of senior management, to review the continued effectiveness and further development of the PQS.

8.2.11 Complaints (see Chapter 15: Storage and distribution)

8.2.11.1 A system should be in place to record, investigate and identify the reason for any complaints.

8.2.11.2 Complaints should be closed out in a timely manner and reviewed regularly for trends as part of quality management meetings (see Chapter 5: Management).

8.2.12 Product recall (see Chapter 15: Storage and distribution)

8.2.12.1 There should be robust procedures for recall that are tested for efficiency and timeliness on an annual basis if an actual recall has not been undertaken.

8.3 Documentation – general issues

8.3.1 A comprehensive documentation system with clear detail should be in place. The Accountable Pharmacist has responsibility for the approval of all systems of work and documentation used in the unit. All documents should be independently approved.

8.3.2 Appropriate document controls should be in place i.e. unique identification, author, approved signatory, approval date, issue date and date for review, reference for superseded version.

8.3.3 In any one unit, worksheets and labels should have a standardised style and presentation within product type.

8.3.4 All documents should be regularly reviewed at defined intervals. Superseded documents should be clearly identified as such and should be retained for a sufficient period to satisfy legislative requirements. (East Anglia Medicines Information Service 2015).

8.3.5 Any draft documents should be identified and carefully controlled so that there is no risk that an incorrect version could be inadvertently approved for use.

8.4 Standard operating procedures

Standard operating procedures should be written in clear, numbered steps in the imperative tense and should include the following:

- control of documentation systems
- deviation management
- change control
- receipt of orders, including prescription verification and transcription
- purchasing, receipt and storage of components
- cleaning, disinfection and sanitation processes
- entering and exiting from clean areas, including the correct use of protective clothing
- environmental monitoring (both physical and microbiological) of the clean rooms and clean air devices
- use of any equipment required for preparation, including cleaning and calibration instructions where appropriate
- generation of worksheets and labels
- product preparation, checking and release
- process validation, including media fills
- staff training, including operator validation using broth transfer trials and formal skills assessment
- actions to be taken when failures are identified by the monitoring systems, e.g. process simulations or operator validation tests, environmental monitoring and sterility tests
- storage and distribution
- product complaints and recalls, and handling of defective products (including, where appropriate, a defect log)
- product returns.

8.5 Worksheets

8.5.1 Individual worksheets reproduced from a suitably approved master format should be used, including electronic formats.

8.5.2 The worksheet should be sufficiently detailed to allow the traceability of starting materials and components, where appropriate, to establish an audit trail for the product (see Chapter 13: Starting materials, components and consumables).

8.5.3 Completed worksheets should be retained for a sufficient period to satisfy legislative requirements. (East Anglia Medicines Information Service 2015).

8.5.4 Worksheets will vary for each unit and should be designed to promote good workflow and to minimise the possibility of transcription errors. They should include:

- the name and/or formula of the product
- a unique identifier for the product
- a written protocol for routinely-prepared products
- manufacturers and batch numbers of medicinal ingredients, listed in order of the compounding process where the order of mixing is important e.g. manual additions to parenteral nutrition solutions
- manufacturers and batch numbers of sterile components used to prepare the product, where appropriate (see Chapter 13: Starting materials, components and consumables)
- date of preparation
- expiry date and time (if applicable) of product
- the signature or initials of staff carrying out preparation and checking procedures
- details of any calculation and the signature or initials of staff carrying out and independently checking such calculations
- the signature or initials of the Authorised Pharmacist or Accredited Product Approver releasing the product, and the date of approval
- a label reconciliation procedure for all labels
- a record of the label on the product
- the patient's name (or other identifier)
- the patient's age for paediatric patients (aged under 16) to the nearest year or nearest month if under 1 year, where systems allow for this (Toft 2012)
- a comments section for recording any unusual occurrences, deviations, or observations.

8.5.5 There should be clear differentiation of paediatric worksheets. The use of colour should be considered (Toft 2012).

8.6 Other documentation

8.6.1 Operation, cleaning, maintenance and fault logs should be kept for all facilities and equipment. All planned preventative maintenance and breakdown maintenance should be recorded for key equipment and facilities.

8.6.2 A planned deviation (temporary change control) form should be available for all products made outside the standard operational procedures. Where deviations from specifications occur, measures taken to ensure that the final product is satisfactory should be documented.

8.6.3 A record should be maintained of errors and near-misses and of investigations undertaken. Trending should be carried out.

8.6.4 Units should participate in the Pharmaceutical Aseptic Services Group (PASG), national aseptic error monitoring scheme, or the UK Radiopharmacy Group error reporting scheme (if appropriate).

8.6.5 Risk analysis, trending and corrective and/or preventative actions (CAPA) should be carried out to an appropriate level depending upon severity.

8.6.6 There should be a record of the Authorised Pharmacist supervising each preparation session.

8.7 Computerised systems (see also Part B – 2.6)

8.7.1 Where computerised systems are in use, access should be restricted, by use of passwords or similar, to staff trained to use the system, with records being retained of any such training.

8.7.2 If a computerised system is used for document control, the system should be fully validated using a risk-based approach to decide the level of validation required. In such cases, the computerised system should demonstrate a level of accuracy and traceability which is at least as good as any paper-based system it replaces.

8.7.3 If document masters are held electronically, there should be a demonstrable system of backups of the master copies. In addition, there should be a failsafe or fallback system in place to allow timely provision of up-to-date documents in the event of computerised system failure.

8.7.4 Where an electronic prescribing system is linked to the generation of an electronic worksheet, patient details, doses etc. should be verified initially and checked manually at the product approval stage against the prescription (see Chapter 4: Prescribing, clinical pharmacy and aseptic services verification, and Chapter 14: Product approval).

8.7.5 Planned updates or alterations to a validated computerised system should be handled via a formal change control process employing a risk-based impact assessment of the proposed changes to hardware or software.

8.7.6 Periodic rolling re-validation is recommended for critical computerised systems at regular intervals (suggested every three years) to ensure maintenance of a validated state. If this is not the case, a written justification should be on file.

8.7.7 Records held solely in electronic form should remain accessible for the life of the document. Where this period exceeds the working life of the system, provision should be made for retaining access to records in a timely fashion.

8.7.8 Where a computerised system fulfills a critical function in the aseptic process, there should be a robust back-up system in place, which allows continued use of the system in the event of hardware, software or network failure. The procedure for switching to the back-up should be documented and periodically tested.

8.8 Labels

8.8.1 Labels should comply with all statutory and professional requirements including the *British Pharmacopoeia* monograph on Unlicensed Medicines. (BP Commission Secretariat, current edition).

8.8.2 Labels should be clear, unambiguous, with no overtyping of content during generation.

8.8.3 They should include the following information:

- approved name of medicine (brand name for biologicals)
- quantity and strength
- vehicle containing the drug when used as a diluent
- final volume
- route of administration
- expiry date and time (if applicable)

- batch number (or other unique identifier)
- appropriate cautionary notices
- storage requirements
- name of patient (or other identifier)
- name and address of pharmacy.

The following may also be included:

- preparation date
- patient's location
- rate of administration, e.g. for parenteral nutrition
- patient's hospital number
- Controlled Drug (if applicable).

Note: POM should not be stated on the label for an unlicensed medicine.

8.8.4 For parenteral nutrition, the maximum concentration of Glucose or osmolarity that can be infused peripherally should be agreed locally and any solutions containing in excess of this concentration should be labelled 'To be given by central line only' (DH 2011).

8.8.5 Vinca alkaloids should be labelled 'Fatal if given by any other route' (NPSA 2008).

8.8.6 Intrathecal products should be labelled 'For intrathecal use only' (DH 2008).

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CHAPTER 9 PERSONNEL, TRAINING AND COMPETENCY ASSESSMENT

It is essential for individuals to demonstrate their competence and for organisations to accurately and appropriately record training and competence of staff for the role or task they are undertaking.

Use should be made of appropriate resources such as those on the NHS TSET, GPhC, RPS and Skills for Health websites to support individuals and organisations meet these operational standards and also provide support for more advanced roles.

9.1 Personnel

9.1.1 Any aseptic preparation service should be managed by an Accountable Pharmacist who has current practical and theoretical experience in aseptic preparation and/or manufacture. (At least two years' experience in an aseptic unit would normally be expected.) A pharmacist working in a locum capacity is not normally acceptable to perform an Accountable Pharmacist role. The Accountable Pharmacist should be knowledgeable in all aspects of aseptic preparation, including the following areas:

- Good Manufacturing Practice (GMP) as defined by EU GMP (EC 2015)
- formulation
- validation
- aseptic processing
- pharmaceutical quality systems (PQS)
- quality control
- radiopharmacy and radiation protection (where applicable).

9.1.2 The Accountable Pharmacist should have this title and associated responsibilities clearly stated in their job description.

9.1.3 The Accountable Pharmacist should be assured that the facilities and systems in place are capable, on a day-to-day basis, of providing an adequate quality service able to meet the needs of patients.

9.1.4 Any Authorised Pharmacist called on to deputise for the Accountable Pharmacist should have the necessary level of training and knowledge, and be clear about the limits of his/her authority and responsibility in this deputising role. These limits should be agreed with the Accountable Pharmacist.

9.1.5 Specific aspects of the service can be delegated to an Accredited Product Approver provided that they are given clear and precise training in both his/her duties and the limits of authority and responsibility are defined.

9.1.6 Before undertaking radiopharmacy preparation, staff are required to achieve 'adequate training' as defined (IR(ME)R 2000).

9.1.7 Anyone entering the unit that is not involved in the aseptic preparation process, e.g. staff, service engineers and visitors, should observe the rules on clothing applicable for the area. (A simplified training procedure on the elements of GMP for personnel entering the clean room facility, e.g. engineers and cleaning staff, should also be available and they should be observed where possible.)

9.2 Staff hygiene

9.2.1 Standards of hygiene are of critical importance in aseptic processing and staff should maintain high standards of personal hygiene. This should be detailed locally in a standard operating procedure.

9.2.2 Staff should be required to report skin lesions, known infections or potential symptoms of infections to the Authorised Pharmacist supervising at the time. A decision should be made as to whether staff carry out the full range of duties under these circumstances.

9.2.3 Within an aseptic unit, GMP overrides religious practices for patient safety reasons. Suitably designed clean room clothing may be acceptable from both GMP and religious perspectives and should be sought, if appropriate.

9.2.4 Tattoos and piercings should be managed in the same way as skin lesions in the Occupational Health policy. This will normally mean that personnel will be excluded from clean areas until any tattoo or piercing has healed.

9.2.5 Wrist watches and jewellery should not be worn. Piercings, if not removed, should be covered.

9.2.6 Cosmetics, nail varnish, false nails, false eyelashes etc., should not be worn in clean areas.

9.3 Training

9.3.1 All staff should receive training and be assessed as competent for the range of activities they will perform in their role, as outlined in recognised competency frameworks such as those from NHS TSET, RPS, Skills for Health etc. Training should provide staff with at least:

- an appropriate knowledge of current EU GMP (EC 2015)
- a knowledge of local practices, including health and safety
- a knowledge of pharmaceutical microbiology
- a working knowledge of the department, products and services provided.

9.3.2 An approved and current training programme should be available. Completion of training should be documented in individual training records. A system for the evaluation of the training programme, paying particular attention to practical skills, should be implemented (see Part B – 2.4).

9.3.3 An individual training record should be available for each member of staff. This should include the following:

- current job description
- initial training (may include hospital specific mandatory requirements, e.g. infection control)
- operator validation
- external training courses
- in-house GMP training
- additional training, e.g. competency assessment/logs etc.

9.4 Competency assessment

9.4.1 Initial training should involve competency assessment and sign off at appropriate levels.

9.4.2 Regular reassessment of the competency of each member of staff should be undertaken, and revision or retraining provided where necessary.

9.4.3 The effectiveness of any additional training or retraining needed as a result of a deficiency should be checked after delivery and after a further time interval to ensure that the additional training has been effective and is retained.

9.4.4 A key element of operator competency is regular assessment of aseptic technique using broth. (The recommended procedure is referred to in Part B – 2.2.) This should be complemented by regular observation of aseptic technique to ensure that the operator can prepare dosage units precisely and safely.

9.4.5 Initial competence of operators should be established by the successful completion of three consecutive Universal Operator Broth Transfer Validation Tests. Regular re-assessment (at least six-monthly) should be undertaken. In the event of failure, an investigation should be undertaken and three consecutive operator broth transfer validation tests should be successfully undertaken.

9.4.6 Another key element is the demonstration of competency to perform calculations correctly for the tasks being undertaken (Toft B 2012).

9.4.7 Any staff undertaking checking should have evidence that they are competent to do so. Use should be made of national competency frameworks (ASAWG 2014).

9.4.8 Where a suitably trained member of staff has been absent from the aseptic operation for more than 6 months, the Accountable Pharmacist should assure him/herself as to the competence of that member of staff before allowing him/her to resume aseptic preparation.

9.4.9 There should be a commitment to a programme of development for all staff. Use should be made of the Technical Professional Development Portal (**www.tpdportal.org.uk**) when appropriate.

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CHAPTER 10 ASEPTIC PROCESSING

When sterile products are manipulated aseptically there is always a risk that microbial contamination may occur. A high level of sterility assurance can be achieved by:

- good clean room design (see Chapter 7: Facilities and equipment)
- good process design
- comprehensive validation of the facility, equipment, and the preparation processes
- control of starting materials and components (see Chapter 13: Starting materials, components and consumables)
- control of the aseptic processes e.g. by use of standard operating procedures, monitoring, training, competency assessment, supervision, etc.

10.1 Process design

In designing the process, consideration should be given to risks from microbial contamination (see Chapter 3: Minimising risk with injectable medicines), risks of errors in preparation (e.g. wrong drug or wrong volume, cross contamination of products, particulate contamination) and risks to the staff involved in the preparation (e.g. exposure to hazardous substances, injuries from sharps or repetitive strain injuries). There may also be additional considerations for gaseous biodecontamination isolators and for radiopharmacy for radiation protection.

10.1.1 Entry and exit of personnel, gowning and gloving

10.1.1.1 Changing and washing procedures should be designed to minimise contamination of clean area clothing or carry through of contaminants to the clean areas.

10.1.1.2 Clean room clothing should be appropriate to the grade of the working area and changed at appropriate frequency (see Chapter 7: Facilities and equipment).

10.1.1.3 Wrist watches, cosmetics and jewellery should not be worn in clean areas (see Chapter 9: Personnel, training and competency assessment).

10.1.1.4 Exit procedures should ensure safe and appropriate disposal of waste (DH 2013) removal and disposal/segregation of gloves and clean room clothing and hand washing to prevent cross contamination or inadvertent exposure to hazardous substances (COSHH 2002).

10.1.2 Choice of equipment and materials

10.1.2.1 The clean air device to be used for aseptic preparation should be selected based on product type, equipment availability and relative risks of microbial contamination and risks to operators (e.g. potential exposure to hazardous substances or ergonomic issues).

10.1.2.2 Triple- or double-wrapped, sterile disposable equipment should be used where available to avoid or reduce the need for disinfection of the outer surface during transfer.

10.1.2.3 Vials should be used, where possible, in preference to ampoules, as this better enables the maintenance of a 'closed procedure' for aseptic compounding.

10.1.2.4 Aseptic preparation processes should be designed to minimise the use of sharps. (*The Health and Safety (Sharp Instruments in Healthcare) Regulations 2013*). Only if non-sharp or safer-sharp devices are not available or reasonably practical should exposed sharps be used. Re-sheathing of needles by hand after use is not permitted. If re-sheathing is undertaken (e.g. for radiation protection reasons in radiopharmacy) this should be documented in a risk assessment and safe working practices implemented to reduce risk of injury (UKRG 2013, PASG 2014).

10.1.3 Good aseptic practice principles

10.1.3.1 Aseptic preparation processes should be designed to minimise the number of aseptic connections/manipulations. A summary table covering all the products prepared (grouping of similar products is acceptable) and the typical maximum number of aseptic connections/manipulations with any relevant comments should be available on file.

10.1.3.2 Closed procedures should be used (as this is one of the conditions for aseptic preparation in an unlicensed unit).

10.1.3.3 All materials transferred into the clean room and critical zone should be sanitised prior to transfer (see Chapter 12: Cleaning, sanitisation and biodecontamination).

10.1.3.4 Syringes or needles packed in strips should be separated before transfer into the critical zone to reduce the potential for particle dispersion.

10.1.3.5 Starting materials transferred into the critical zone should be allowed to dry before proceeding with the preparation.

10.1.3.6 The critical zone should be kept free and uncluttered with any materials positioned in the critical zone so that there is unobstructed air flow over and around them. Materials should not be stored in the critical zone.

10.1.3.7 Operators should avoid reaching over the product to access equipment or dispose of waste.

10.1.3.8 Aseptic processing techniques used during manipulation of the product should ensure 'no-touch' of critical surfaces to avoid any contact with any surface which will be in contact with the sterile fluid path.

10.1.3.9 Over-wrapped items should be peeled open in the air stream from the HEPA filter in a manner that will minimise shedding of particles. Paper-backed items should not be torn open.

10.1.3.10 If re-sheathing of needles is required for containment or asepsis, a re-sheathing aid such as a needle block should be used (see 10.1.2.4).

10.1.3.11 The surfaces of bungs that will be penetrated and the necks of ampoules to be opened should be wiped with a fresh sterile 70% alcohol impregnated wipe and allowed to dry before proceeding.

10.1.3.12 Ampoules should be opened in the air stream from the HEPA filter.

10.1.3.13 When withdrawing from glass ampoules, a sterile filter straw or filter needle should be used to remove glass particles. The filter straw or needle should be replaced with a fresh sterile needle before adding the solution to another container. Alternatively the solution from an ampoule should be passed through a suitable filter into the final container so that any particles generated from the opening of the ampoule and extraction of liquid are removed.

10.1.3.14 Ampoules should only ever be used for a single withdrawal immediately after opening and then discarded (see Chapter 2 definition of closed procedure). If multiple ampoules are used, the withdrawal should be made before opening the next ampoule.

10.1.3.15 When using vials, pressure equalisation techniques using the syringe or venting devices should be employed to avoid aerosols.
Note: This may not be applicable in radiopharmacy.

10.1.3.16 When making additions to infusion bags, the additive port should be positioned so it is in the HEPA filtered air stream rather than on the work surface.

Best practice is to ensure that, wherever possible, manipulations are undertaken in mid-air, well away from work surfaces or other objects. Air flows more slowly close to surfaces increasing the chance of deposition of particles.

10.1.3.17 An appropriate gauge of needle should be used that will minimise damage to rubber bungs whilst still maintaining an acceptable flow rate.

10.1.3.18 Needles should be inserted through the centre of the additive port, keeping the needle straight to avoid puncturing the bag.

10.1.3.19 All tubing should be clear of fluid and securely clamped before removal from the critical zone.

10.1.3.20 The work surface and gloves should be sanitised between products or contacts during preparation activity. Time to allow drying after sanitisation is required.

10.1.3.21 Any spillage of product should be wiped up immediately. Gloves should be changed and the work surface cleaned and sanitised before continuing work. Consideration should be given to performing an additional set of finger dabs before changing gloves.

10.1.4 Product segregation and in-process checks

10.1.4.1 Processes should be designed with appropriate segregation of products and flow of materials to ensure there is no inadvertent cross contamination or mix-up of products.

10.1.4.2 Appropriate pre- and in-process checks required should be defined for each product type and suitably recorded (see Chapter 8: Pharmaceutical Quality System).

10.1.4.3 If vials are used for more than one patient (vial sharing) then it should be carried out on a campaign basis and there should be measures in place to ensure that there is a robust in-process checking system carried out by accredited in-process checkers (see Chapter 9: Personnel, training and competency assessment) including the drug, concentration and volume measured, unless all measurements can be checked retrospectively, i.e. the product is a liquid medicine solely drawn up into syringes which can then be volume checked at the product approval stage (PQAC 2014).

10.1.4.4 If auto-compounders are used (e.g. for parenteral nutrition preparation) checks on the correctness of set-up should include (MHRA 2015):

- The correct starting material is connected to the correct line. This check should be independent of set-up, and may be either a second operator or automated verification (e.g. barcode linking). Replenishment of starting solutions throughout the process should be similarly verified
- Volume delivery checks
- Independent check on the required volume for each solution
- Reconciliation of starting solutions at the end of the session
- Details of remaining manual additions.

10.1.4.5 Waste disposal procedures should be designed to prevent cross contamination and risks to personnel from hazardous substances or sharps and be in accordance with healthcare waste standards (DH 2013).

10.2 Validation

Validation of the aseptic process can be spilt into three distinct areas:

- Facility and equipment validation (see Chapter 7: Facilities and equipment)
- Process validation (see Part B – 2.1)
- Operator validation (see Part B – 2.2).

Validation should be performed when an aseptic unit is commissioned and when any new equipment, process, technique or member of staff is introduced into the process and at defined intervals. The purpose is to show that under simulated conditions aseptic products can be consistently prepared to the required quality using the defined process.

Any subsequent changes should be assessed in the same manner to ensure that they do not compromise that quality (see Chapter 8: Pharmaceutical Quality System).

Validation methods are described in more detail in Part B – 2 but it should be remembered that they only represent the capabilities of the aseptic processing system as tested. To ensure the reproducibility of quality of the product, strict adherence to the validated standard operating procedures is essential.

10.2.1 Process validations should be designed to cover the range of processes used within the unit and should reflect worst case (see 10.1.3.1).

10.2.2 Operator validations should be up to date and should cover the range of aseptic techniques and clean air devices which an operator will use.

10.3 Control of the aseptic process

10.3.1 All key elements and manipulative steps in the aseptic process, from the starting material to the finished product, should be controlled by comprehensive standard operating procedures to ensure that the process consistently produces a product of the requisite quality.

10.3.2 Aseptic processing should be carried out by validated staff (see 10.2).

10.3.3 Staff should be fully conversant with all the relevant standard operating procedures (as determined by their role) before being deemed competent to work in the aseptic preparation unit.

10.3.4 Regular updating of staff on the procedures should be undertaken, documented and the extent of knowledge assessed.

10.3.5 Pre- and in-process checking should be performed by appropriately accredited staff (see Chapter 9: Personnel, training and competency assessment).

10.3.6 All staff working in aseptic processing should be made fully aware of the potential consequences of any deviation from the validated procedure, both to the integrity of the product and to the intended recipient. Regular reminders of the critical nature of the process should be provided. Staff should report any unusual or unexpected occurrence and any errors they have, or might have, made to the Authorised Pharmacist supervising at the time (even if they have been immediately corrected). Any deviation should be fully documented and managed (see Chapter 8: Pharmaceutical Quality System).

10.3.7 There should be a formal system for the assessment of any proposed change which may affect product quality (see Chapter 8: Pharmaceutical Quality System).

10.3.8 Staff involved in aseptic processing should be taught to recognise upper limb disorders (repetitive strain injuries) and to use techniques to minimise these conditions wherever possible (PASG 1998).

10.3.9 Standard operating procedures should be written and implemented for all equipment used for aseptic processing (see Chapter 8: Pharmaceutical Quality System).

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CHAPTER 11 MONITORING

It is essential to ensure facilities and conditions are maintained and processes are followed in a consistent manner by all staff. This is ensured by regular monitoring and testing of the environment, process and finished product and forms an essential part of the quality assurance of all aseptically-prepared products. Standards and guidelines are available for many of the physical and microbiological aspects (Farwell 1995, EC 2015, BSI 1999b, BSI 2015, Midcalf et al 2004, PHSS 2002, PDA 1980, Needle and Sizer 1998, BSI 2000, UKRG 2012). The Accountable Pharmacist, Authorised Pharmacists and senior staff should refer to, and have an understanding of, these documents, with particular emphasis on the sections relating to aseptic processing.

Particular importance should be attached to obtaining meaningful results, monitoring trends, setting 'in-house' standards and action limits, investigating out-of-specification results and deviations and undertaking corrective and/or preventative actions (CAPA). Information should be actively and knowledgeably assessed and not merely filed for record purposes.

The monitoring programme forms an important part of the Pharmaceutical Quality System and comprises a programme of environmental monitoring carried out by the staff undertaking aseptic preparation and a series of planned preventative maintenance (PPM) and environmental tests undertaken by suitably trained personnel or contracted out to an appropriate organisation with an appropriate service level agreement and technical agreement (see Part B – 3).

11.1 Programme of monitoring and testing

11.1.1 Each unit should have a sessional, daily, weekly, monthly monitoring programme and a quarterly and annual testing programme. All results should be documented and retained for inspection.

A recommended frequency is shown for guidance in Tables 11.1 and 11.2. This should be considered to be a minimum requirement. The optimum frequency of testing will be a function of the individual unit and the activity within the unit. The programme should be such that it confirms that control of the environment within standards is maintained. It is not a substitute for the continual vigilance of operators in ensuring the correct functioning of all equipment. Rapid gaseous biodecontamination isolators are available for aseptic preparation and the frequency of testing could be reduced to the minimum frequency as in Table 11.1 if full confidence is established (Hiom et al 2004). However, any microbiological growth found should be considered as requiring a full investigation. (PICS 2007).

Table 11.1
Microbiological monitoring programme (minimum frequency)

TEST	LIQUID SANITISATION CRITICAL ZONE *	GASEOUS BIODECONTAMINATION CRITICAL ZONE **	CLEAN ROOM SUITE
Finger dabs	Sessional	Weekly	Not applicable
Settle plates	Sessional	Weekly	Weekly
Surface contact plates	Weekly	Weekly	Weekly
Active air samples	3 Monthly	3 Monthly	3 Monthly
Surface swabs ***	3 Monthly	3 Monthly	3 Monthly

** Liquid sanitisation includes wipe and spray into conventional isolators and cabinets.*
*** Gaseous biodecontamination includes VHP isolators.*
**** Tests on equipment, uneven surfaces and crevices etc.*

Table 11.2.1
Physical monitoring programme of a clean room

ASEPTIC FACILITY TEST	MINIMUM FREQUENCY
Pressure differential between rooms	Monitor continuously, record daily
Pressure differential across HEPAs	Monitor continuously, record weekly
Particle counts	3 Monthly in use, annual 'at rest' – (MHRA 2015)
Air changes/hour	3 Monthly
Filter integrity/Installation leak test	Annual
Air flow pattern	Annual – EU GMP Grade B (EC 2015) or after significant work on the Air Handling Unit
Temperature of fridges	Monitor continuously, record daily
Temperature in critical storage rooms	Monitor continuously, record daily
Relative humidity *	Annual
Noise	Annual
Light	Annual
Clean up rate	After in use test

* *Relative humidity is a useful indicator of potential moisture condensation that could promote the growth of microbes and therefore 3 monthly measurement is advised.*

Table 11.2.2
Physical monitoring programme for a unidirectional air flow cabinet

UNIDIRECTIONAL AIR FLOW CABINET TEST	MINIMUM FREQUENCY
Pressure differential across HEPA	Monitor continuously, record daily
Particle counts	3 Monthly in use, annual 'at rest' – (MHRA 2015)
Air velocity	3 Monthly
Uniformity of air flow +/- 20%	3 Monthly
Filter integrity/Installation leak test	Annual*
Air flow pattern	Annual or after moving the cabinet
Noise	Annual
Light	Annual

** The MHRA (MHRA 2015) state a minimum of annually but early detection of a problem will reduce the risk of compromising the work area and a more frequent test schedule may be considered appropriate.*

Table 11.2.3
Physical monitoring programme for a class 2 safety cabinet

CLASS 2 SAFETY CABINET TEST (BSI 2000)	MINIMUM FREQUENCY
Pressure differential of extract	Monitor continuously, record daily
Pressure differential across downflow HEPA	Monitor continuously, record daily
Particle counts	3 Monthly in use, annual 'at rest' – (MHRA 2015)
Air velocity	3 Monthly
Air uniformity +/- 20%	3 Monthly
Filter integrity/Installation leak test	Annual*
Product protection test**	Annual
Operator protection test***	Annual
Air flow pattern	Annual
Alarm function	Weekly
Noise	Annual
Light	Annual

** The MHRA (MHRA 2015) state a minimum of annually but early detection of a problem will reduce the risk of compromising the work area and a more frequent test schedule may be considered appropriate.*

*** The product protection test is considered to be desirable using appropriate methodology e.g. smoke and particle counts, external KI discus test (BSI 2000). Air inflow tests are not considered adequate.*

**** This test is not essential in radiopharmacy as other operator protection testing is used, e.g. film badges.*

Table 11.2.4
Physical monitoring programme for isolators

ISOLATOR TEST	MINIMUM CHAMBER FREQUENCY	MINIMUM HATCH FREQUENCY
Pressure differential from chamber to external room	Monitor continuously if possible, record daily	Record weekly if possible
Pressure differential across HEPAs	Monitor continuously if possible, record daily	Record weekly if possible
Air changes per hour	Monitor continuously, record daily if measured	Record weekly if measured
Particle counts	3 Monthly in use, annual 'at rest' – (MHRA 2015)	Annual 'at rest'
Air velocity	3 Monthly	3 Monthly
Air uniformity – unless turbulent	3 Monthly	Not applicable
Filter integrity/Installation leak test	Annual*	Annual*
Glove/sleeve and gauntlet integrity	Sessional	Not applicable
Isolator leak test	-ve pressure weekly, +ve pressure monthly	-ve pressure weekly, +ve pressure monthly
Air flow pattern	Annual	Not applicable
Alarm function	Weekly	Not applicable
Door/hatch timer	Not applicable	Annual
Noise	Annual	Not applicable
Light	Annual	Not applicable

** The MHRA (MHRA 2015) state a minimum of annually but early detection of a problem will reduce the risk of compromising the work area and a more frequent test schedule may be considered appropriate.*

11.1.2 Action and alert levels should be set to indicate when corrective action and investigation respectively should be carried out.

A monthly and annual review of trends and types of microorganisms should be made.

Trend data should be carried out for each workstation, operator, person carrying out the liquid sanitisation of items taken into the work area and for each clean room. (Species level identification of organisms can be of assistance when reviewing the effect of personnel on the clean room environment). (See Part B – 1).

The annual review should be used to re-evaluate the alert levels and, if necessary, modify them.

11.2 Equipment used for monitoring

11.2.1 Equipment used in monitoring should be calibrated at least annually by comparing with a traceable standard. A system should be in place to check all test certificates before signing the equipment back into use. Thermometers should be within 0.5°C (MHRA 2015), room pressure devices within 2Pa and HEPA filter pressure devices within 10% of the test device.

There is a requirement to monitor the storage temperature of microbial growth media, such as agar plates, aseptic manipulation kits and similar.

Pressure monitoring devices should be zeroed and calibrated to ensure warning and action levels are not breached.

11.2.2 Evidence should be available to demonstrate that environmental monitoring media are fit for purpose at the point of use.

The microbiological media used should be proven to be capable of supporting a broad spectrum of bacterial and fungal growth at the time of use.

This can be achieved by exposing a weekly positive control plate in an uncontrolled environment for sufficient time to provide a count of 5 or more after incubation.

11.2.3 Steps should be taken to ensure that surface sampling materials do not leave media residues; e.g. use of a sterile IMS wipe after sampling.

Microorganisms require water to reproduce and grow, and therefore leaving a surface wet after sampling with a moistened swab or contact plate could result in a proliferation of microbial contamination.

11.2.4 Plates should be labelled, wrapped in cling film or appropriately bagged as soon as possible after exposure and sent for incubation.

This is to ensure they do not become contaminated post exposure during transport to the laboratory and during incubation. The use of a plastic bag should be avoided if condensation becomes a problem as droplets of water falling on the agar surface during transportation could increase the count.

11.2.5 A negative control plate should be included on a weekly basis to check the plates are sterile and the post exposure handling, transport and incubation process does not introduce contamination.

11.2.6 Incubation should commence within seven days of exposure.

11.2.7 Liquid media such as Tryptone Soya Broth (TSB) used in aseptic validation kits should be assessed for fertility after use as described in Part B – 1.

11.3 Monitoring the aseptic preparation process

11.3.1 It is important that all staff, on commencing aseptic preparation, assure themselves that all equipment is functioning satisfactorily. Potential problems should be reported to senior staff.

A record should be made to demonstrate all checks have been completed as defined in local procedures.

11.3.2 When the unit is in use the critical zone of the controlled workspace should be monitored on a sessional basis. Settle plate exposure should seek to assess the worst case conditions – that is, capture microorganisms generated from the activity, for example, as close to the process in a EU GMP Grade A (EC 2015) environment as practical. For this to be successful, the way the plate is exposed is important and should form part of the standard operating procedure.

This may be achieved by the exposure of settle plates and undertaking a finger dab at the end of the work session.

Two settle plates should be used in two- or three- glove isolators or cabinets below 1.5 metres internal width and four plates should be exposed in four-glove isolators or cabinets 1.5 metres and above in width.

11.3.3 Passive air sampling using settle plates should be carried out for the full duration of the session. If sessions are longer than 4 hours, a second set of plates should be exposed.

11.3.4 When monitoring the clean room according to Table 11.1, one plate should be exposed in every aseptic preparation room and an additional plate per 12m^2 floor area. Each room and each isolator transfer hatch should be monitored weekly.

Care should be taken in input hatches not to wet the agar with alcohol spray as it will affect the performance of the agar, inhibit growth and therefore could mask a problem. Care should also be taken to ensure maximum exposure of the agar by careful placement of the lid of the settle plate (See Part B –1).

11.3.5 Process validation using broth to simulate the aseptic procedure should be performed initially (three times is normal) and subsequently, at least on a 6 monthly basis. New processes or changes to existing processes, including the scale of activity, should be assessed to ensure previous validations remain valid (MHRA 2015).

A programme using different operators should be prepared. Process validation can form part of the periodic review of aseptic technique to supplement information from operator manipulation kits.

Comment: There is limited value in performing continuous particle monitoring for a manual closed process (MHRA 2015).

Automated processes require urgent intervention if the operation goes wrong and a continuous particle system can provide an alert for staff to check and, if necessary, stop the process. Manual operations such as opening syringe or needle packets, using low linting wipes or spraying disinfectant will generate particles sufficient to momentarily create a localised environment outside EU GMP Grade A (EC 2015). Quarterly occupied testing will allow an assessment of the particle generation inherent in the process as described in 11.6 for each workstation (MHRA 2015). The report should be risk assessed with reference to the aseptic procedures.

11.4 Environmental monitoring results

11.4.1 Alert limits for rooms should be established during commissioning. (Normally at least five sets of results should be obtained for each plate position.) The ideal methodology is to take the mean + 2 x standard deviation (95% value) or half the action limit, whichever is the smaller. Trending should be carried out to ensure the room remains in control. The alert limits should be reassessed during an annual review.

11.4.2 For pharmaceutical applications, the major criterion on which the aseptic facilities are assessed should be the risk of microbiological contamination of the product. Guideline action limits for microbiological data are given in Table 11.3. These limits are based on EU GMP (EC 2015) requirements.

Table 11.3
Environmental monitoring of controlled areas and clean air devices: Action limits for microbiological tests in operation

GRADE	FINGER DABS CFU/HAND	SETTLE PLATES (90MM) CFU	CONTACT PLATE CFU/55MM DIAMETER	ACTIVE AIR SAMPLE CFU/M^3
A (device)	< 1	< 1	< 1	< 1
B	Not applicable	5	5	10
C	Not applicable	50	25	100
D	Not applicable	100	50	200

Notes:
- Validated surface swabbing may be used as an alternative to contact plates. The same limits should be used for swabbing a 10 x 10cm area.
- Maximum exposure time for a settle plate is 4 hours.

11.4.3 If a plate exceeds the limits, the laboratory should assess the validity of the result and, if necessary, an out-of-specification review should be raised to determine whether the observation can be attributed to the test method or an artefact.

For example, if a finger dab plate is overgrown with colonies, it is unlikely to be associated with a finger but should nevertheless be investigated. A photograph of the plate may assist with the investigation.

11.4.4 Plates exposed in a gaseous biodecontamination isolator are expected to be clear after incubation. Any growth should be prioritised and identified to species level where possible.

Investigation by the aseptic unit staff should be carried out immediately. Guidance is given in Part B – 1.

11.4.5 Cabinets and isolators relying on liquid sanitisation of components will occasionally produce high counts due to the variability of bioburden and the efficiency of the process (Cockcroft 2001). If action levels are exceeded, growth should be identified to genus and preferably species level where possible.

Trending of results should be undertaken (see Part B – 1).

11.5 Testing the clean room environment and clean air devices

11.5.1 Equipment used in testing should be serviced and calibrated at least annually.

The test certificate is often presented as a set of results and the assessor should decide whether the equipment is fit for purpose before taking the equipment back into use.

11.5.2 In-use testing is important to provide assurance that procedures do not challenge aseptic manipulations with potentially viable particles. The assessment of airborne viable contamination should be carried out using an active air sampler (Part B – 1).

Use of an active air sampler will result in disturbance of air flow and could therefore impact on a product if being made at the time. It is therefore safer and often cost effective to carry out routine broth manipulation kits during quarterly environmental testing. Therefore, the choice of broth manipulation kit is important and all operators should be rostered in rotation to complete the kits. Sufficient kits to allow manipulations to occupy at least 20 minutes should be selected. Completing process validation manipulation kits has the greatest value (Part B – 2.1), however the Universal Operator Broth Transfer Validation Test (UOBTVT) includes a range of aseptic techniques and takes the required time to complete (Part B – 2.2).

A particle counter should be used to assess the total viable and non-viable particles.

Both the sampling devices should be positioned in the work area as close to the site of critical manipulations as possible without being knocked during operation. The active air sampler should be set to sample 1m^3 of air and the particle counter should be set to repeatedly sample 10L of air. The tester needs to position themselves to allow the preparation process to be observed along with the particle count. If the particle counter display only monitors a single result it should be set to read 5µ. If the counter registers a 5µ count, the activity undertaken just before the count is recorded should be noted. The report should be analysed with reference to the SOPs for similar preparations. If particle counts are recorded whilst critical

operations are being conducted, such as assembly of a syringe and needle or the puncture of a septum, the procedure may need to be changed to allow particles to disperse before the activity is conducted. This assessment is essential when turbulent flow has been identified e.g. using a smoke pencil.

11.5.3 The Filter integrity/Installation leak test (dispersed oil particulate (DOP) test) should be carried out on all supply HEPA filters.

The NHS specification for filters is given in table 11.5. DOP testing is often contracted out (see Part B – 3). The test forms the basis of acceptable viable and non-viable particle test results in the **'at rest'** state and therefore should be carried out by competent personnel. A protocol is available for guidance to ensure testing is carried out to NHS standards (PQAC 2010).

11.6 Environmental test results

11.6.1 Senior personnel concerned with aseptic preparation should have an understanding of clean room 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 workstation, isolator design, etc. and the procedures carried out.

For pharmaceutical applications, the major criterion on which the aseptic facilities are assessed should be the risk of microbiological contamination of the product. However, because of the imprecision and variability of the microbiological test methods it is sometimes more practical to demonstrate environmental control using physical data. Guideline limits for physical and microbiological data in operation are given in Tables 11.3 and 11.4. These limits are based on EU GMP (EC 2015) requirements and BS EN ISO 14644 (BSI 1999b).

Note: For the annual retest using 'at rest' conditions, no preparation activity is carried out and the isolator or cabinet should be cleared of all items other than dedicated items such as cleaning materials. Therefore the test results should be used to determine whether there has been any deterioration since the previous test.

11.6.2 All areas associated with the aseptic preparation process should be assessed by the Accountable Pharmacist for compliance with the appropriate standards on commissioning, following maintenance procedures and routinely at an agreed frequency.

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.

'At rest' particle counts should be established during Operational Qualification and alert and action limits set.

For example, an isolator will typically not produce any particles > 0.5µ and therefore particle counts observed in the 'at rest' test could be a sign of fabric deterioration e.g. rust formation, particle build up due to inadequate cleaning or gaskets crumbling.

Table 11.4
Environmental monitoring of controlled areas and clean air devices: Limits for physical tests

GRADE	PARTICLE COUNTS (MAXIMUM PARTICLES/M³)				AIR CHANGES (NUMBER PER HOUR)	PRESSURE DIFFERENTIAL PASCALS (PA) TO ADJACENT LOW CLASS AREA
	AT REST		IN OPERATION			
	0.5µm	5.0µm	0.5µm	5.0µm		
A (device)	3 520 *	20 *	3 520	20	Not applicable	Isolator >15 ****
B	3 520	29	352 000	2 900	> 30 ***	> 10
C	352 000	2 900	3 520 000	29 000	> 20	> 10
D	3 520 000	29 000	35 200 000	290 000 **	> 20	>15

** It is recommended that tighter limits than EU GMP (EC 2015) 'at rest' are adopted for NHS aseptic units, for example based on commissioning data or calculated according to BS EN ISO 14644-1 (BSI 1999b). EU GMP Annex 1 (EC 2015) indicates that the 'in operation' and 'at rest' states should be defined for each room or suite of rooms.*

*** EU GMP (EC 2015) does not define the particle limits for 'in operation' for a EU GMP Grade D (EC 2015) room. It is recommended that the room is tested and BS EN ISO Class 9 (BSI 2015) is adopted.*

**** The number of air changes per hour can be less than the values stated in table 11.4 provided it can be demonstrated that the room will return to the 'at rest' conditions within 20 minutes. (This is referred to as the recovery or 'clean up' rate). These figures are the usual minimum specification for new facilities, however under all conditions a minimum of 20 air changes per hour should be achieved.*

***** Minimum recommendation for isolators used to manipulate cytotoxic drug substances (HSE and MHRA 2015).*

It is important that the required clean up time of 20 minutes is achieved (EC 2015).

Table 11.5
HEPA filter classification and testing for aseptic preparation

EU GMP GRADE (EC 2015) OF ENVIRONMENT	MINIMUM CLASSIFICATION OF FILTER (BSI 2009)	DOP TEST MINIMUM (PQAC 2010)
A and B	H14	≤0.001%
C and D	H13	≤0.01%

Note:
Any deviation from these limits should be fully documented and justified by the Accountable Pharmacist.

11.7 Sterility testing and/or end of session broth tests

11.7.1 A documented sterility test programme should be in place, which includes consideration of all process variables. The minimum expectation is one sterility test per operational work station per week. Variables such as product and operators should be cyclically covered on a rolling basis. This sterility testing frequency only applies where there is sufficient data to demonstrate that the areas are adequately controlled and therefore would not initially apply for new facilities where there is no history. Any sterility test failures should be identified to species (and preferably strain) level and thoroughly investigated.

11.7.2 The use of a suitably designed 'end of session media fill simulation' may be considered as an alternative to sterility testing of the finished product as part of an on-going monitoring programme.

End of session broth tests (EOS) can be developed (MHRA 2015) using TSB (Part B – 1). The EOS test should be designed to incorporate similar components and processes used in the preparation of aseptic products. Broth can be used to fill items used in a preparation, however, residues of product should not impede the ability of the medium to support microorganism growth. This does not completely remove the requirement to carry out sterility tests, but could justify reducing the frequency to monthly.

It is not recommended that an EOS kit is used for radiopharmaceutical preparation using a ^{99m}Tc generator as it is important to assure the sterility of the generator throughout its use (Society of Nuclear Medicine 2006) and this cannot be achieved through use of an EOS.

11.7.3 If an end of session broth test fails, an investigation should be undertaken. If there is no satisfactory explanation, the result should be treated as operator broth transfer validation test failure (see Chapter 9: Personnel, training and competency assessment) and corrective and/or preventative action (CAPA) undertaken.

11.8 Monitoring of finished products

11.8.1 There should be a planned programme of physical, chemical and microbiological analysis of the finished product, as appropriate.

11.8.2 Samples may be obtained from:

- unused products
- additional specially-prepared samples
- an in-process sample taken at the end of the compounding procedure before the final seals are in place and before removal from the critical zone.

11.8.3 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.

11.8.4 The testing laboratory should be fully conversant with the technical background and requirements in aseptic preparation, together with the validated methodology for analysing the products and samples. The Accountable Pharmacist should ensure that the testing laboratory has a comprehensive knowledge of pharmaceutical microbiology.

11.8.5 A technical agreement should be in place with the providers of any external testing services and this should be monitored. (An example of a technical agreement is given in Part B – 3).

11.9 Sink and drain monitoring

All sinks, wash-stations and drains associated with the clean room suite, as well as social hand washing sinks, should be monitored.

Hot and cold tap water supplies should be tested on commissioning and monitored on a quarterly basis by total viable count (TVC) to ensure the water is not heavily contaminated (see Part B – 1). A limit of 100cfu/ml has historically been adopted for potable water. Drains should be similarly monitored (WHO 2003).

If the limit is exceeded, identification of the genus of the organisms present is advised.

Organisms that form biofilms (such as pseudomonads) and other Gram negative organisms should trigger treatment. The water system should be flushed for a minimum of 2 minutes and the water retested. If the supply continues to fail the TVC due to pseudomonads or other Gram negative organisms, the estates department should be asked to look at the supply as described in HTM 04 01 (DH 2006).

Drains: if the limit is exceeded, then the drains should be flushed with water for a minimum of 2 minutes and subjected to either the designated heated trap exposure or suitable chemical disinfection and retested.

Note: *For water sampling from sinks and drains conditions see Part B – 1, BSI 1999a.*

11.10 Planned preventative maintenance

It is important not to confuse PPM with testing. The aim of PPM is to prevent a process from failing due to a defective piece of equipment. There should be a PPM plan in place for all critical pieces of equipment.

11.10.1 A technical agreement should be in place for PPM of all critical pieces of equipment detailing frequency, permits to work, responsibilities, expected tasks and actions and reporting mechanism (see Part B – 3).

For isolators, the PPM schedule should concentrate on the integrity of the carcass by paying particular attention to changing seals and gaskets, and tightening bolts and screws. Indicator light operation, door timer checks and gauge calibration are often overlooked. The leak test should be recorded before and after PPM activity and the results used to determine whether the unit is deteriorating between visits.

An assessment of the performance of the fans for all cabinets and air handling systems will provide an early warning if a fan requires replacing and prevent a failure of the equipment.

11.10.2 All reports should be assessed by the Accountable Pharmacist against the technical agreement to ensure all work has been carried out and the outcome is satisfactory. If not, appropriate action should be taken to remedy any deficiencies.

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CHAPTER 12 CLEANING, SANITISATION AND BIODECONTAMINATION

Clean air devices, in combination with the design, structure and use of clean rooms, are intended to provide a clean environment in which to prepare sterile medicines. Therefore the sanitisation of clean areas is particularly important (EC 2015). There are a number of ways to reduce contamination, including cleaning, sanitisation, disinfection and biodecontamination.

It is important to remember that surfaces in clean rooms, and clean air devices, together with the surfaces of starting materials, components and consumables, can become contaminated with microorganisms over time, even if the area is not occupied.

These surfaces of starting materials, components and consumables present a considerable risk because of the potential to transfer the contamination into the critical zone.

Therefore, the appropriate use of cleaning and disinfecting agents (that is, sanitisation) are important parts of the contamination control programme.

12.1 General principles

12.1.1 All sanitisation processes should be undertaken regularly in accordance with a written programme and subject to standard operating procedures.

12.1.2 All cleaning and disinfecting agents employed in the clean room facility should be subject to a formal, documented assessment and approval process.

12.1.3 Where disinfectants are used, more than one type should be employed to reduce the risk of the development of resistance in microorganisms.

Environmental monitoring data should be regularly reviewed to highlight trends that might suggest the presence of resistant organisms or spores (see Chapter 11: Monitoring).

12.1.4 Cleaning and disinfecting agents should be free from viable microorganisms. Those used in Grade A and B areas should be sterile prior to use (EC 2015).

It is advisable that all controlled areas including EU GMP Grades C and D (EC 2015) should use sterile water as a diluent when needed.

12.1.5 Wherever possible, sterile ready-to-use agents should be used. If not, in-use dilutions should be freshly prepared for each cleaning session. Samples from freshly-prepared dilutions should be monitored for microbiological contamination at least once every six months.

12.1.6 Wet or damp cleaning with effective detergents should be the method of choice. (Disinfectants only work when wet.) Dry dusting alone is not recommended but dedicated vacuum cleaners with the appropriate control (that is, HEPA filtered) may be used to remove any dust and debris.

12.1.7 The following factors should be considered when choosing a sanitisation process:

- efficacy of the sanitisation agent to achieve sufficient coverage to achieve microbial kill
- contact time, evaporation rate, air flow over the surface and air change rate
- organic and inorganic load present in the unit, including drug residues
- type and level of microbial contamination (bioburden)
- physical nature of the object (e.g. crevices, folds, hinges, and lumens)
- presence of biofilms
- other factors such as relative humidity involved in biodecontamination
- other factors such as health and safety and presentation etc.

12.1.8 The use of sanitisation agents should be controlled according to a documented procedure/policy and this should include:

- a statement of the in-use shelf life, which should be justified and documented. Information from manufacturers may be acceptable, subject to critical appraisal
- an indication on any container of sanitisation agent as to the date of opening. (Processes in place should ensure that these are not used beyond the specified in-use shelf life)
- a requirement that storage of in-house diluted sanitisation agents is not permitted. These should be prepared in previously cleaned containers with sterile water and used immediately
- steps to limit operator variability in-use e.g. a defined training programme, detailed procedures for preparation and application etc.

- for purchased items, an assurance from the manufacturer regarding the quality and effectiveness of the supplied item and confirmation that the product is sterile if specified
- for items sterilised by irradiation, evidence that this process has been completed satisfactorily (e.g. proof of activity/absence of degradation)
- during use, processes to ensure that the external surfaces of any container of the sanitisation agent itself are sanitised such that it does not present a risk of contamination during use.

12.1.9 Sterile water, and where appropriate, sterile non-foaming detergents, should be used periodically to ensure the removal of residues, e.g. of medicines and disinfectants, biofilms, dirt and grease.

12.1.10 Logs should be kept of the areas cleaned indicating the agents used. These should be checked for compliance before use of the facility and reviewed periodically.

12.1.11 All staff performing any cleaning duties should have received documented training, including the relevant elements of EU GMP (EC 2015) and specific information relating to the agents and methods employed. Cleaners should be assessed to be competent before being allowed to work unsupervised.

12.1.12 There should be continuity of cleaning staff with the provision of adequate suitably trained cover. Any contract cleaners should be subject to a technical (quality) agreement which is closely monitored (see Part B – 3).

12.1.13 The effectiveness of cleaning should be routinely demonstrated by review of the surface monitoring programme employed; both microbiological and chemical (see Chapter 11: Monitoring).

12.1.14 Surface monitoring results should be trended. If these show an increase in microbiological contamination, change in microbial flora, or the presence of objectionable organisms, the prompt use of additional cleaning and/or the use of alternative disinfectants should be considered.

12.1.15 Surface monitoring for residues (in particular, hazardous materials such as cytotoxic agents) should be routinely undertaken (minimum annually) and trending carried out. The sites chosen for residue monitoring should reflect the perceived highest risk areas.

Cleaning regimens should be demonstrated to effectively remove chemical contamination. If residues persist, prompt use of additional cleaning and/or the use of alternative products should be considered. The chemistry and solubility of the residues should be considered to ensure effective removal.

12.2 Cleaning the facility

The correct level of cleanliness should be achieved by a well-designed facility which is maintained in a clean and dry status (see Chapter 7: Facilities and equipment).

Note: Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places or in the situation of gross contamination. Such processes, if used, should be validated and documented.

12.2.1 Controlled areas should be regularly cleaned according to a written, approved procedure and, when necessary, disinfected using validated and approved agents. Cleaning of outer areas of the facility is equally important to minimise the entry of contamination into the controlled areas.

Table 12.1
Minimum recommended cleaning frequencies

	CEILING	WALLS	FLOORS	HANDLES AND SWITCHES	BENCHES AND TROLLEYS (UNDERSIDES)	MISCELLANEOUS EQUIPMENT, E.G. EXTERNAL SURFACES OF CLEAN AIR DEVICES, FRIDGES ETC.
Grade B	3M	M	D	D	D (3M)	W
Grade C	6M	3M	D	D	D (3M)	W
Grade D	A	3M	W	D	D (3M)	M
Unclassified e.g Outer support areas		A	W	W	W	M
Stores			W	W	W	M
Sinks and hand wash stations	As a minimum, sinks and hand wash-stations should be cleaned daily including taps and other fitments. Drains and traps should be disinfected regularly (minimum weekly). Taps should be flushed for 2 minutes before use on a daily basis (DH 2012).					

A - annually, M - monthly, W - weekly, D - daily

Note:
The above frequencies are based on regular daily usage of the environment concerned. Where rooms or equipment are used intermittently, cleaning and monitoring regimens may need to be amended following an appropriate and documented risk assessment.

12.2.2 Dedicated clean room cleaning equipment should be used appropriate to the grade of room, e.g. sterile in EU GMP Grade B (EC 2015).

12.2.3 Clean room cleaning equipment should be stored separately from all other cleaning materials and securely so that it is not used in the incorrect areas, and to minimise microbiological contamination.

12.2.4 The facility should be cleaned in a defined order.

This normally means that the cleaning process starts in the cleanest grade area and progresses outwards to the areas with the lowest grade of cleanliness. It is usual to begin at high level and finish at low level and to work from the point furthest from the door to the point nearest the door.

Best practice is to apply cleaning agents with separate, overlapping stroke techniques in defined directions.

12.2.5 For EU GMP Grade B (EC 2015) areas mopheads should be sterile, low-linting, disposable and intended for single use only, or they may be resterilised after each cleaning session. This sterilisation process should be validated and subject to regular review.

12.2.6 All methods of application, including preloaded mops, should deliver enough of the product to achieve effective cleaning and/or disinfection for the full period of contact to the defined area.

Pooling of excess amounts of cleaning or disinfecting agents should be avoided. Ideally surfaces should become dry within 1 hour of application. Conversely, sufficient product should remain to achieve the required efficacy throughout the recommended contact time i.e. disinfectants should not be spread too thinly.

12.2.7 Adhesive flooring designed to remove soiling from footwear and the wheels of equipment should be incorporated into cleaning schedules.

Those contamination control floor coverings intended for reuse should be cleaned and regenerated regularly with manufacturer's approved agents. When using tacky mats, the normal minimum expectation is that each foot should impact with the mat twice. Wheeled vehicles should travel in straight lines and not turn on the surface of the mat as this can cause permanent damage.

Those intended for removal should be replaced as soon as soiling is seen to be unacceptable. Such removal or cleaning should be performed to minimise the liberation of particles. Every effort should be made to remove any adhesive residues resulting from placement of these mats.

12.3 Clean air devices

12.3.1 Clean air devices should be cleaned and disinfected before and after each working session with approved sterile agents (typically 70% alcohol).

12.3.2 Internal work surfaces of clean air devices should have a periodic sporicidal clean (minimum monthly, or where monitoring results dictate, or following an incident, e.g. a spillage, sleeve replacement etc.).

All traces of sporicide should be removed after an appropriate contact time, e.g. with 70% sterile alcohol wipes.

For gaseous biodecontamination isolators, a clean of the internal surfaces with a non-ionic sterile detergent should be carried out before vapourised hydrogen peroxide (VHP) gassing (**Note:** IMS wipes can cause interference with hydrogen peroxide sensors and are therefore not recommended).

12.3.3 Periodically all clean room surfaces, particularly the external surfaces of clean air devices, should be cleaned with an agent that will remove chemical residues (at a minimum quarterly frequency).

These might include sterile agents, such as neutral detergent, water, or acidified water and a weak alkali wash, depending on the nature of the materials handled.

12.3.4 All surfaces, both internal and external, should be cleaned in accordance with a written schedule with attention given to difficult-to-access nooks and crannies. Installed equipment should follow a similar regime.

12.4 Gaseous biodecontamination

12.4.1 The ability to decontaminate isolators with a sporicidal gaseous agent should be considered at the time of purchase of a new isolator.

Gaseous agents such as VHP or ionised hydrogen peroxide (IHP) have good profiles as bactericides, and fungicides and importantly as sporicides. They can be utilised for the decontamination of the internal surfaces of an isolator as well as for the transfer disinfection process.

The use of spray and wipe techniques remain acceptable as a method of transfer disinfection. However, if a new unit or isolator is required, the use of gassing technology should be taken into consideration and a risk assessment performed (MHRA 2015).

12.4.2 Biodecontamination should be performed in a controlled manner, that is, the process should be reproducible, with a defined microbiological kill profile, load profile and an independent processing record. The cycle should be automatic, recorded on a printout, and reviewed (including any alarms) to confirm acceptability.

12.4.3 Physical cleaning of isolators employing biodecontamination is required in addition to the decontamination process, however.

12.5 Transfer disinfection processes

Surface disinfection of components prior to the transfer is vital in preventing the ingress of contamination into critical areas.

The design of the transfer disinfection process is of utmost importance. As an alternative to liquid sanitisation, the use of irradiated triple-wrapped products should be considered as it can improve the sterility assurance of the process. The use of multi-packs or user specific preparation kits can be beneficial.

Note: Further guidance and advice is available (PQAC 2015).

12.5.1 The process should have a written standard operating procedure and should be validated.

12.5.2 Sterile agents should be used in EU GMP Grade A and B (EC 2015) zones and during the last sanitisation stages of the transfer disinfection process (MHRA 2015).

Best practice is that sterile agents are used throughout the transfer disinfection process to reduce the risk of selecting the incorrect agent.

Note: Although 70% alcohol solutions are widely used, these are not sporicidal (Cockcroft et al 2001). Spores should be removed both by a physical wiping stage in the surface sanitisation procedure and by the application of a sporicidal agent such as hydrogen peroxide or chlorine-based agents (MHRA 2015).

12.5.3 The contact time should be clearly stated, validated and maintained in practice. The minimum period for contact with a disinfectant in the transfer process is 2 minutes. Evidence should be available to substantiate the effectiveness of this contact time.

It is assumed that starting materials and components used for aseptic preparation such as needles, luer connections etc. are transferred into a support room, stored, with subsequent transfer through airlocks into the clean room and then into a clean air device.

12.5.4 The storage of paper and cardboard in the support room should also be minimised, whilst at the same time ensuring that the product is protected, e.g. from light, and secure and key information, e.g. the Summary of Product Characteristics (SmPC), is still available to allow correct use of the product.

12.5.5 Before transfer to the clean room, a sanitisation step using a wipe and spray technique including a sporicidal agent designed to inactivate bacterial and fungal spores should be carried out. (Step 1)

12.5.6 Before transfer to the working zone a second sanitisation step using a spray and wipe technique including a disinfectant should be carried out. (Step 2)

12.5.7 The minimum expectation is therefore two discrete decontamination steps, with a spray and wipe performed at both steps and the first decontamination step should use a sporicidal agent.

Spraying should take place as the product is transferred into the transfer hatch. This activity should not be remote from the hatch.

12.5.8 The only exemption from using a sporicidal agent in step 1, at the current time, is for radiopharmaceuticals and biologically-derived medicines, but only where evidence is available that the product performance may be affected by sporicidal residues (MHRA 2015). Evidence for radiopharmaceuticals is available (Dadda et al 2014, Fisher et al 1977, Murray et al 1986, Stringer et al 1997, Verbruggen et al 1985). Justification may be possible in other circumstances, however documentation to support the approach taken should be available. In these situations, a four-stage disinfection process with alcohol is required. Serious consideration should also be given to other methods of transfer to minimise the risk of bacterial and fungal spores entering the critical zone, e.g. use of irradiated double- and triple-wrapped components.

12.5.9 During sanitisation, particular attention should be paid to the rubber septa of vials and break lines of ampoules, which should be subjected to all stages of the sanitisation treatment. Over-seals (e.g. flip-off caps) should therefore be removed at the first sanitisation stage.

It is important to ensure that the disinfectant gets into all difficult to access areas such as under the crimp seal of vials.

12.5.10 An effective contact time for the sanitising agent should be used. Third party supplier data may be used, provided that this is reviewed to demonstrate its relevance to the intended use. Where contact time differs from the manufacturer's recommendations, this should be supported by scientifically valid microbiological studies.

Consideration should also be given to the air classification of the support room and a risk assessment should be performed where this room is unclassified to consider if any additional controls are required.

12.5.11 The following factors should be considered in development of a surface sanitisation strategy:

- The bioburden challenge presented by the type of item being sanitised, i.e. number of surfaces and ease of cleaning
- The minimum residence period post sanitisation (2 minutes is usually applied as a guidance value for a disinfectant effect. Longer times may be required for a sporicidal effect)
- Periodic verification of sanitisation effectiveness. (This should be carried out with frequency based on a risk assessment)
- Any extended storage time for sanitised components. (This is considered to be a risk factor, and subsequent sanitisation steps prior to use should address this risk)
- Minimising the exposure time of items supplied as sterile prior to entering the EU GMP Grade A (EC 2015) critical zone to reduce the risk of contamination
- The requirement for any folds on the surface of sealed packages to be sanitised
- The effective shelf life of products in use.

12.5.12 Consideration should also be given to other methods (e.g. irradiated double- and triple-wrapped components) to minimise the transfer of bacterial and fungal spores.

12.6 Additional requirements concerning transfer disinfection processes

12.6.1 Clothing requirements: As a minimum requirement, gloves should be worn for all transfer disinfection processes. These should be sterile or disinfected before use.

Best practice is that a non-shedding protective coat or suit, face mask, clean room shoes and suitable headwear are worn to protect the product and operator during transfer disinfection processes (see Chapter 7: Facilities and equipment).

12.6.2 Operator technique: It is essential that a high degree of diligence and attention to detail is applied. The standard operating procedure should define the process and be followed. Routine supervision of this activity is required.

12.6.3 Wiping technique: Impregnated wipes should be used in preference to dry wipes (the latter being wetted in situ).

Evidence indicates that dry wipes are rarely wetted enough to readily release sufficient liquid onto the surface. In addition, the undulating and micro-structures of surfaces being disinfected do not facilitate the effective delivery of disinfectant by the wipe process (Panousi et al 2009).

12.6.4 Wipes used should be low linting and be sterile when used at the last step of transfer for aseptic products.

Although natural fibre wipes may potentially shed more particulates, they have the advantage of increased wickability over most synthetic materials, holding more liquid and therefore releasing more disinfectant to kill surface-borne organisms. They also entrap particles and absorb residues more readily.

The roles and uses of the wipes are:

- *To physically remove the bioburden from the surface*
- *To ensure the presence of sufficient disinfectant for long enough to kill vegetative and, where needed, spore-forming organisms*
- *To facilitate the destruction and removal of contaminants by the application of pressure against microbial cell walls during the wiping process.*

12.6.5 For non-sporicidal wipes, a fresh surface of each wipe is required to prevent the transfer of dirt and bioburden from the wipe to other surfaces.

This can be achieved by systematically folding the wipe. Care should be taken to ensure that surfaces are not reused.

12.6.6 Wiping technique should follow defined wipe patterns, with additional care taken for cleaning in folds, the rubber septa of vials, and the break lines of ampoules.

12.6.7 The initial bioburden of container surfaces should be well-controlled and regularly monitored (minimum annually). Starting materials, components and consumables should be stored to minimise bioburden.

12.6.8 Health and safety aspects should be considered for relevant disinfecting and biodecontamination agents, in particular sporicidal agents, and also for dealing with spillages of chemicals and products, e.g. cytotoxics.

This may be demonstrated by contemporary COSHH (The Control of Substances Hazardous to Health Regulations 2002) records and risk assessments.

12.7 Tray cleaning

12.7.1 In addition to routine spraying and wiping with liquid disinfectant, trays used for the transfer of components into clean rooms and clean air devices should be designed to be easily cleanable. They should be washed and decontaminated periodically. The frequency should be justified and defined by local practice and needs.

12.7.2 Tray cleaning should not take place in the clean or controlled support area. Tray cleaning should be in a suitable location.

Sinks, hand wash-stations and basins used for hand washing should be avoided for health and safety reasons (e.g. the exposure to cytotoxics).

12.7.3 Following washing, trays should be dried, disinfected, and returned into the aseptic suite. Trays should not be left to 'drain'.

12.7.4 Tray cleaning should be periodically validated. Annual revalidation is suggested.

12.8 Hand washing

Hand contamination, whether gloved or ungloved, also poses a considerable risk to the clean environment, as this is probably the greatest potential for transferring microbial contamination.

12.8.1 The use of appropriate hand hygiene techniques, hand disinfectants and gloving technique is a vital part of good contamination control.

12.8.2 The choice of disinfectant for hand sanitisation, as well as the techniques utilised, should be effective against the types of microorganisms likely to be present.

Note: Ordinary hand wash agents (e.g. soap) are not suitable on their own for use in the clean room environment. Antimicrobial agents such as chlorhexidine and iodophors are recommended.

12.8.3 Hand washing effectiveness should be assessed and documented.

12.8.4 Hand washing facilities should be located outside of, and adjacent to, the clean room suite. In a new unit, hand washing facilities should be located next to the main entrance of the clean room suite.

In older facilities, the use of hand basins within the toilet facilities may be permitted providing they are cleaned daily. In addition, hands cleaned in such hand basins should be further treated by the application of an alcoholic hand gel prior to entry to the clean room suite.

12.8.5 Hand washing facilities and the water supplied to them should be regularly monitored for compliance with appropriate limits, e.g. the EU limits for potable water are 100cfu/ml at 25°C and 10cfu/ml at 35°C (see Chapter 11: Monitoring). Taps should be flushed each day that the unit is in use (see Table 12.1).

12.9 Cleaning validation

12.9.1 Periodic verification of sanitisation effectiveness should be carried out, with frequency based on risk assessment. This applies to general cleaning of the environment and specifically to transfer disinfection.

The following are suggested minimum frequencies:

Table 12.2
Suggested minimum sampling frequencies for cleaning validation

	MICROBIOLOGY	CHEMICAL
Hand wash	Annual	Not applicable
Transfer disinfection	6 Monthly	Not applicable
Critical zone	6 Monthly	Annual
Room cleaning	Annual	Annual

Notes:
Cleaning validation should consider the level of contamination before and after cleaning.
Chemical decontamination should consider product residues, and possibly, disinfectant residues.
Tray cleaning should be periodically validated. Annual revalidation is suggested.

12.9.2 Limits should be established locally, and be based upon both microbiological and chemical residue analysis.

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CHAPTER 13 STARTING MATERIALS, COMPONENTS AND CONSUMABLES

There need to be robust systems in place to control the quality of starting materials, components and consumables used in the preparation of medicines. Lack of control can have a direct impact on overall product quality.

Management of change in the supply of materials should be carefully controlled and monitored to ensure no additional risks are introduced.

13.1 Starting materials

This term applies to all materials used in the preparation of a medicinal product, excluding components or consumables but including any re-worked products (see below). These materials may also be termed ingredients.

13.1.1 Starting materials should be sterile products and should preferably have a Marketing Authorisation. Unlicensed starting materials should not be used where there is a licensed equivalent available. (MHRA 2014).

13.1.2 Where unlicensed starting materials are used, it is incumbent on the Accountable Pharmacist to ensure that the product is of the appropriate quality by means of specifications, certificates of analysis or conformity, quality control tests or a combination of these. This assessment should be documented and be in accordance with the organisation's unlicensed medicines policy.

13.1.3 Unlicensed starting materials should always be obtained from a manufacturer with an appropriate manufacturer's licence. Supply of medicines licensed in countries outside of the UK, often via an importer, may be acceptable but should be in accordance with the unlicensed medicines policy.

13.1.4 For licensed starting materials, systems for receipt should also include verification that the Summary of Product Characteristics or technical information supplied has not changed since the previous receipt. Where changes are noted, there should be an impact assessment conducted and if the change requires a modification then change management procedures should be invoked.

13.1.5 For unpreserved starting materials, the in-use shelf life should be restricted to one aseptic work session (not exceeding 4 hours) during which the material remains in the critical zone (PQAC 2014).

13.1.6 Similar starting materials for each product should be sourced from the same manufacturer i.e. no mixed strengths of the same material from different manufacturers.

The formulation from one manufacturer may differ from that of another and has the risk of incompatibility or effect on shelf life (see Chapter 6: Formulation, stability and shelf life).

13.1.7 Non-sterile starting materials should never be used.

13.1.8 Any material that is re-worked should be treated as a new starting material. The re-working of a product transforms it into a starting material. Its suitability for use should be assessed as for any other starting material.

13.1.9 Ampoules should only ever be used for a single withdrawal immediately after opening and then discarded under the description of a closed procedure (PQAC 2014).

13.1.10 The sharing of vials of starting materials between patients is an acceptable process provided that it is carried out on a campaign basis and is subject to robust risk assessment (PQAC 2014).

A campaign basis means that two or more doses may be drawn up from the same vial or the same pool of vials as long as these doses are made sequentially, that no other products are present in the work zone throughout the process, and that the vials stay within the Grade A work zone throughout the process.

13.1.11 Vial sharing for single use vials outside of pharmacy aseptic units is unacceptable (PQAC 2014).

13.2 Components and other consumables

Critical components include:

- Syringes and caps used as final containers
- Connecting sets used for compounding purposes.

Other components include:

- Reconstitution devices
- Venting devices
- Syringes and needles not used as final container
- Parts of filling systems in direct contact with the product.

Consumables include:

- Alcohol sprays
- Wipes (including cleaning tool covers)
- Other cleaning agents and materials
- Sharps bins
- Trays.

13.2.1 Components should be purchased pre-sterilised from the manufacturer. The product should be either a CE marked medical device or have a documented form of approval. It should be packaged in such a way that it can be passed into the aseptic environment without increasing the risk of product or environmental contamination.

13.2.2 Any filters used should be pre-assembled by the manufacturer, CE marked and guaranteed sterile.

13.2.3 There should be a record of batch numbers on the worksheet for critical components (see Chapter 8: Pharmaceutical Quality System).

13.2.4 Batch traceability for other components should be available to enable the audit trail in the event of a recall. A log may be used for this purpose.

13.2.5 Local sterilisation of non-sterile consumables and equipment is acceptable provided that sterility is assured. Such sterilisation processes should be validated, appropriately monitored and meet all current standards. (DH 2013, BSI 2012). Assurance should be given that there is no risk of cross contamination from surgical instruments or other types of non-pharmaceutical activity. An audit trail should be available. A Technical Agreement is required with some evidence of periodic audit of the sterilising site. (See Part B – 3).

13.2.6 Filling systems should not be modified.

13.2.7 Sterile components should be stored so as to minimise any increase in the bioburden on the surface of the primary and secondary packaging. All items should be appropriately stored to prevent damage. No items should ever be stored directly on a floor.

13.2.8 Sterile components should not be used beyond one working session.

13.2.9 Consumables used within the critical environment, EU GMP Grades A and B (EC 2015), should be sterile.

13.2.10 Once transferred into the clean room using the spray and wipe technique, paper-backed components should not be stored in the clean room (see Chapter 12: Cleaning, sanitisation and biodecontamination).

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CHAPTER 14 PRODUCT APPROVAL

Units operate under a professional exemption to the UK *Medicines Act 1968* and incorporated into the *Human Medicines Regulation 2012*. This allows preparation of pharmaceuticals to be undertaken without the need for product and manufacturing licences to be held. Supervision, as applied to Section 10 aseptic preparation activities, has been defined by the NHS (PQAC 2014). This definition cannot be considered in isolation and should be fully supported by the UK national competency framework for product approval (ASAWG 2014) giving assurance of resource, governance and oversight in line with national requirements.

14.1 A formal, recorded decision of product approval (release) should be taken by an Accredited Product Approver before a product is released and after completion of all preparation and checking procedures. (Use of a checklist may be helpful for complex products).

14.2 The Accountable Pharmacist should ensure that robust systems are in place to train, assess and authorise individuals to carry out the product approval process. For non-pharmacists, these systems should comply with the UK national competency framework for product approval (ASAWG 2014) requirements. A current list of Accredited Product Approvers should be available.

14.3 The Accountable Pharmacist should ensure that an effective and comprehensive Pharmaceutical Quality System is in place within the unit (see Chapter 8: Pharmaceutical Quality System).

14.4 There should be an appropriate structure so that all Accredited Product Approvers are accountable directly to the Accountable Pharmacist for this activity and that this is reflected in their job description.

14.5 The Accredited Product Approver should not, other than in exceptional circumstances, be the person who prepared the product.

Note: Out of hours the requirements for supervision still apply.

14.6 There should be written procedures covering final accuracy checking and product approval (release). These processes may, or may not, be undertaken by the same person. Details of the roles and responsibilities of all the staff involved in these processes should be clearly defined.

14.7 The Authorised Pharmacist responsible for supervision should be identifiable and contactable at any point.

14.8 The Accredited Product Approver should ensure that they are authorised to approve the specific product for release, e.g. cytotoxics, parenteral nutrition etc.

Note: Intrathecal chemotherapy should only be approved for release by an Authorised Pharmacist named on the intrathecal chemotherapy register (DH 2008).

14.9 All those involved in the process of product approval should maintain the appropriate levels of competence and act in accordance with the GPhC standards of conduct, ethics and performance (GPhC 2015).

14.10 The Accredited Product Approver should, after completion of the preparation process but before release:

- carry out a visual inspection of the product (for particles, precipitation and integrity)
- ensure that the product complies with the prescription, the clinical trial protocol (if applicable) and the appropriate specification, including labelling
- ensure that the product has been prepared by competent and validated operators according to approved procedures, and be aware of any deviation reports
- be aware of recent microbiological and environmental results for the facilities
- ensure that the daily monitoring records for the unit are satisfactory, e.g. pressure differentials, cleaning
- be aware of the status of the unit and ensure the planned preventative maintenance programme is up to date
- be aware of recent retrospective testing results for products
- consider any prospective testing results, e.g. analytical testing, weight checks
- ensure that all necessary accuracy checks e.g. including in-process checks and reconciliation of empty and part-used containers of starting materials have been carried out
- ensure any planned deviations (temporary change controls) have been approved by an Authorised Pharmacist.

14.11 In the case of any unplanned deviation, any decision to approve the product should be taken by an Authorised Pharmacist.

14.12 All errors detected should be recorded via the Pharmaceutical Aseptic Services Group (PASG) national aseptic error reporting scheme, or the UK Radiopharmacy Group error reporting scheme (if appropriate). They should be trended and investigated to an appropriate level depending upon the severity.

14.13 The Authorised Pharmacist should be aware of, and act on, any errors detected and any interventions made both during the preparative stages and/or at the product approval stage. This is relevant even where the product is able to be released.

14.14 There should be a written procedure for dealing with preparations failing to meet the required standard. The investigation of these events should be fully documented and corrective and/or preventative actions (CAPA) implemented to an appropriate level. Trending of failures should be undertaken regularly and any adverse trends or major failures to comply with standards should be brought to the attention of the Chief Pharmacist (see Chapter 5: Management).

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Note:

At the time of publication there are currently consultations on:

- The GPhC's *Standards of conduct, ethics and performance.* Details are available at: ***https://www.pharmacyregulation.org/news/pharmacy-regulator-launches-major-consultation-new-standards-pharmacy-professionals*** (accessed on 28 April 2016). Consultation closes 27 June 2016.
- Changes to Section 10 of the *Medicines Act 1968*. This includes a proposal for the relevant provisions to appear in the *Human Medicines Regulations 2012*. Department of Health (2016). Pharmacy dispensing models and displaying prices on medicines. Available at: ***https://www.gov.uk/government/consultations/pharmacy-dispensing-models-and-displaying-prices-on-medicines*** (accessed on 28 April 2016). Consultation closes 17 May 2016.

CHAPTER 15 STORAGE AND DISTRIBUTION

With changes to NHS structures and the amalgamation of some hospitals into single entity, multi-sited bodies; storage and distribution of aseptically-prepared products assumes a higher priority than previously. Aseptic units performing any distribution activities are required to comply with the principles of Good Distribution Practice (GDP) (Guidelines on Good Distribution Practice of Medicinal Products for Human Use 2013) (EC 2013).

15.1 General issues

15.1.1 Staff involved with storage and distribution should be aware of their responsibilities with regard to the integrity of the product. Training and assessment should be undertaken as appropriate and the results documented (see Chapter 9: Personnel, training and competency assessment).

15.1.2 A close examination should be made of all stages between product approval and product use to ensure that the quality of the product is not compromised before its expiry.

15.2 Storage

15.2.1 Special attention should be paid to the storage of products with specific handling instructions as specified in national legislation. Special storage conditions (and special authorisations) may be required for such products. Radioactive materials and other hazardous products, as well as products presenting special safety risks of fire or explosion (e.g. combustibles, flammable liquids), should be stored in one or more dedicated areas subject to local legislation and appropriate safety and security measures, e.g. *The Control of Substances Hazardous to Health Regulations 2002, The Ionising Radiations Regulations 1999.*

15.2.2 Products should be stored under refrigeration, normally 2–8°C, unless it would be detrimental to the product to do so. Refrigerators should not be overloaded. For products and starting materials where refrigeration is not appropriate, suitable storage conditions should be maintained to ensure no deterioration occurs.

15.2.3 All refrigerators and other areas used for the storage of aseptic products and starting materials within the pharmacy should be temperature mapped before use and at defined intervals.

15.2.4 Refrigerators and other storage areas should be continually monitored to ensure compliance with the appropriate temperature range; 2–8°C for refrigerators, and not more than 25°C for ambient areas. Temperature monitoring should also take place in the end-user department.

15.2.5 The temperature monitoring procedure should include action to be taken in the event of an out-of-specification reading and appropriate records of actions should be maintained. Trend monitoring should be performed regularly.

15.2.6 Calibration of temperature monitoring equipment should be carried out annually using a two-point check as a minimum. The calibration should be traceable to a national or international measurement standard.

15.2.7 Any automatic temperature monitoring system should be validated initially and also subsequently when appropriate (see Part B – 2.6).

15.2.8 Equipment repair, maintenance and calibration operations should be carried out in such a way that the quality of the medicinal products being stored is not compromised.

15.2.9 Alarm systems should be in place to provide alerts when there are excursions from pre-defined storage conditions. Alarm levels should be appropriately set and alarms should be regularly tested to ensure adequate functionality. The Authorised Pharmacist supervising at the time should be aware of any alarms being activated and take appropriate action.

15.2.10 Should failure of refrigeration or cold chain occur for a limited period, for whatever reason, an informed decision on the continued viability of affected stock should be made from knowledge of the ambient temperature stability or consulting the manufacturer of the starting materials.

15.2.11 Any returned or unused products should be clearly marked and segregated from other products.

15.3 Distribution

15.3.1 Regardless of the method of distribution, products should not be exposed to conditions that may compromise their quality, security and integrity.

15.3.2 Distribution should be controlled and validated as rigorously as storage. Medicinal products should be transported in containers that have no adverse effect on the quality of the products, and that offer adequate protection from external influences, including seasonal variations in temperature, contamination etc.

15.3.3 Transit containers should be of an appropriate defined specification and comply with any appropriate regulations. (*Transport of Dangerous Goods (Safety Advisers) Regulations 1999, Carriage of Dangerous Goods by Road (Driver Training) Regulations 1996, The Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2009* (CDG 2009) and subsequent amendments.) Selection of a container and packaging should be based on the storage and transportation requirements of the medicinal products; the space required for the amount of medicines; the anticipated external temperature extremes; the estimated maximum time for transportation.

15.3.4 Due regard should be given to health and safety considerations relating to potential hazards posed by the products during distribution. All applicable regulations, e.g. *The Control of Substances Hazardous to Health Regulations 2002* and transport regulations (*Transport of Dangerous Goods (Safety Advisers) Regulations 1999, Carriage of Dangerous Goods by Road (Driver Training) Regulations 1996, The Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2009* (CDG 2009) and subsequent amendments), should be complied with. The hospital's safety advisor should be able to provide additional information.

15.3.5 Transit containers should bear labels providing sufficient information on handling and storage requirements and precautions to ensure that the products are properly handled and secured at all times. The containers should enable identification of the contents of the containers and the source.

15.3.6 Labelling on transit containers of potentially hazardous products (e.g. cytotoxics) should include details of contacts and actions to be taken in an emergency. For radiopharmaceuticals separate regulations apply. (*Transport of Dangerous Goods (Safety Advisers) Regulations 1999, Carriage of Dangerous Goods by Road (Driver Training) Regulations 1996, The Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2009* (CDG 2009) and subsequent amendments.)

15.3.7 Consideration should be given to preventing the relative movement of components, such as syringe barrel and plunger, during transport and storage.

15.3.8 Where appropriate, the security of the cold/ambient chain should be assured and periodically revalidated.

15.3.9 Staff involved in storage and distribution should be aware of their responsibilities with regard to the integrity of the product. Training and assessment should be undertaken as appropriate and the results documented.

15.3.10 Records should be maintained of the destination of all products if not recorded elsewhere, e.g. on the prescription. There should be additional recording systems for distribution of Controlled Drugs and radioactive products.

15.3.11 There should be a policy for the handling of returned or unused products, including any outsourced products, which considers environmental factors. Returned or unused products may be useful for testing purposes (see Chapter 11: Monitoring).

15.4 Complaints and recall

15.4.1 Complaints should be recorded with all the original details. A distinction should be made between complaints related to the quality of a medicinal product and those related to service, including distribution.

15.4.2 Any product complaint should be thoroughly investigated to identify the origin of, or reason for, the complaint. A person should be given specific responsibility for handling of complaints and allocated sufficient resource to satisfactorily discharge this responsibility.

15.4.3 If necessary, appropriate follow-up actions (including corrective and/or preventative actions (CAPA)) should be taken after investigation and evaluation of the complaint.

15.4.4 Procedures for recall should be in place, and should be reviewed on a regular basis. These should cover the recall of products made by the aseptic unit in the event of a potential problem with the product itself or a known problem with any components or starting materials used in it, e.g. a Drug Alert issued either by MHRA or company-led, a Field Safety Notice for a component etc.

15.4.5 Recall exercises should be undertaken on an annual basis to ensure the efficiency and timeliness of the process, if an actual recall has not occurred. A report should be produced following assessment of the recall process (either through a simulated or actual recall).

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CHAPTER 16 INTERNAL AND EXTERNAL AUDIT

Systems need constant monitoring to ensure that they continue to meet the requirements and needs of the organisation.

A comprehensive programme of internal audits, undertaken by trained personnel, is essential to the continued effectiveness and further development of the Pharmaceutical Quality System (PQS). Internal audits can be used to identify system deficiencies, areas of non conformance and opportunities for improvement and should be programmed according to importance of the areas or processes being audited.

Internal audits (if undertaken conscientiously) provide those most familiar with the operation of the aseptic unit the opportunity to critique their processes as the auditors should be familiar with any perceived weak points in their operation. Internal audit, undertaken in a diligent manner, is therefore a fundamental part of Quality Management.

Results from both internal and external audits form an essential input into the management review process.

16.1 Audit involving all areas in which aseptic preparation takes place (including any satellites) should be undertaken on a regular planned basis (PQCC 1999) to monitor implementation and compliance with these defined NHS standards and to propose any corrective measures.

16.2 In addition to inspection of premises, equipment and processes, a detailed quality review of the Pharmaceutical Quality System (PQS) is required (see Chapter 8: Pharmaceutical Quality System).

16.3 The audit programme should be determined in advance with the plan documented and adhered to. A number of different techniques may be used. For example, low level regular housekeeping audits, higher level process audits such as horizontal audits or linear audits on a rotating programme and systems/checklist style audits on a less frequent basis (PQCC 1999).

16.4 Audits should include a review of the capacity planning within the unit (see Chapter 5: Management and Part B – 5).

16.5 Internal audit should be conducted in an independent and detailed way by designated and competent staff.

16.6 Observations made during audits should be clearly recorded along with any proposals for corrective actions.

16.7 An action plan should be drawn up detailing timescales and persons responsible for the actions.

16.8 There should be an SOP in place that details the management and review of the action plan, and the effectiveness of these procedures should be verified during audit. (See Chapter 5: Management and Chapter 8: Pharmaceutical Quality System).

16.9 Corrective actions should be reviewed at the next audit or earlier if appropriate.

16.10 The audit report should be submitted to senior management. Any deficiencies should be assessed in terms of risk to the quality of the product, and a decision to cease activity made if necessary. There should be appropriate escalation procedures in place allowing risks to be identified to the hospital management via the Chief Pharmacist.

16.11 An external audit should be carried out by the Regional Quality Assurance Specialist or any other accredited auditor (PQAC 2011) at least every 12 to 18 months (NHS Executive 1997). The unit should respond with a realistic action plan within the timeframe agreed with the auditor. Equivalent external audits are required in other Home Countries of the UK.

16.12 Aseptic units which prepare intrathecal chemotherapy should be subject to audits for compliance with the current *National Guidance on the Safe Administration of Intrathecal Chemotherapy* (DH 2008).

References

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