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ISOPP
Standards of Practice

Safe Handling of Cytotoxics

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Preface

In 2003, the president of the International Society of Oncology Pharmacy Practitioners (ISOPP) approved a recommendation of the secretariat to establish a new Standards Committee. It was envisaged that this committee would be composed of ISOPP members from a number of different regions of the world. With this in mind, and considering the importance of the work of this committee, three co-chairs were appointed from different ISOPP regions:

- Thomas Connor (USA)
- Robert McLauchlan (Australia)
- Johan Vandenbroucke (Belgium)

The first task for the co-chairs was to establish a working committee of motivated and enthusiastic ISOPP members from around the globe. In March 2003, an individual invitation letter was sent to every ISOPP member seeking expressions of interest in joining the committee. Anyone who had previously expressed an interest in the workings of the committee was also approached. This recruitment resulted in a core team of hardworking committee members without whom this Standard would not be possible.

The co-chairs decided that existing regulations, guidelines, standards or recommendations from around the world should be examined prior to starting work on an ISOPP Safe Handling Standard. In order to keep track of all these documents and to be able to analyse these guidelines in a consistent and logical way, a structured database was established. This is a web-based tool to allow committee members from around the world to enter data and access information over the internet. The database was divided into 29 different sections, covering all possible items related to the safe handling of chemotherapy including good manufacturing practice (GMP) for sterile cytotoxic products, clinical oncology pharmacy, medication error prevention and patient related issues.

A total of 15 documents were entered into the database and analysed. The sources of documents examined included:

- Workers Compensation Board of British Columbia (CAN)
- British Columbia Cancer Agency (CAN)
- German Cytotoxic Workgroup (GER)
- National Board of Occupational Safety and Health (USA)
- Occupational Safety and Health Administration (UK)
- Brazilian Society of Oncology Pharmacy (BRA)
- Society of Hospital Pharmacists of Australia (AUS)
- UK Pharmaceutical Isolator Group (UK)
- Worksafe – Victoria Workcover Authority (AUS)
- Guidelines of University Hospital Gent (BEL)

At the ISOPP IX Symposium in Torino, Italy in 2004, the committee co-chairs presented the results of the analysis of the database to the ISOPP secretariat and it was decided that work could proceed into the next phase of writing an ISOPP Standard for the Safe Handling of Cytotoxic Drugs. From previous experience with the database, it was decided that the ISOPP website would be used for communication between committee members, and to this end the Standard of Practice Discussion Forum was set up by the ISOPP publications committee.

All committee members were invited to participate in the writing process or to become part of a reviewing panel. To ensure coverage of all items examined in the database, writers with different areas of expertise were chosen for different chapters of the Standard.

Ten ISOPP members were actively involved in the writing of the Standard:

- Asunción Albert-Mari, Spain
- Thomas Connor, USA
- Sylvie Crauste-Manciet, France
- Harbans Dhillon, Malaysia
- Dianne Kapty, Canada
- Robert McLauchlan, Australia
- Ioanna Saratsiotou, Greece
- Graziella Sassi, Italy
- N Victor Jimenez Torres, Spain
- Johan Vandenbroucke, Belgium

In the writing of the Standard, a number of other resources were consulted, including:

- EudraLex GMP Guideline
- US NIOSH Alert
- US OSHA Guideline
- GMP Hospital, Netherlands
- GMP Hospital, France

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- Italian Guideline for Safe Handling
- MARC Guidelines (Internet)
- QuapoS (Quality Standard for the Oncology Pharmacy Service) DGOP
- Kwaliteitshandboek Cytostatica, NKI-AVL, Netherlands
- Handling Cytotoxic Drugs – Industrial Medicine Assurance Company, Switzerland
- Professional Organisation for Health and Industrial Medicine, Germany
- ASHP guide for Compounding Sterile Preparations
- Preparation and Administration of Anti Cancer Drugs, France
- CAMROQ Education and Training CD ROM, Risk Control and Quality of Chemotherapy Handling – 5 European Countries (France, Belgium, Spain, Portugal, Poland)
- Quality Standard on Oncology Pharmacy Services (DGOP/ESOP 2nd Polish German annual conference for oncology pharmacy "Therapy for practice")

In addition, the personal experience of the writers played an important role in the creation of this work. Where specific references are used, these are quoted and listed at the end of the appropriate Section.

Drafts of each Section were reviewed and discussed by the writing team and the reviewing group, consisting of members from Mexico, Japan, Singapore, Canada, Belgium, Germany and South Africa. Each reviewer was able to provide comments. These comments were discussed and integrated into the draft document upon agreement of the majority of the committee. Not everyone will agree with every detail given in the final document, but the Standards Committee considers this Standard "Evidence Based" in some parts and "Best Practice" in others.

As discussed during the General Assembly of ISOPP in Torino, Italy, in 2004, the committee is aiming at a high level with this Standard. This means that perhaps many practitioners may not fully comply with the Standard as written today, but the Standard should be seen as something we all can work towards. There is a clear goal for ISOPP members around the world. Whereas some of us will successfully comply within a relatively short period of time, others will struggle to fully comply with this Standard. However, they will have at their disposal, documentation of what is regarded as best practice and will know exactly what should be asked of Pharmacy Directors and Hospital Administrators.

We wish all our ISOPP colleagues good luck in the development of a safe and high quality oncology pharmacy service.

Regards

Thomas Connor
Robert McLauchlan
Johan Vandenbroucke

ISOPP Standards Committee Co-Chairs
April 2006

Section 1 – Introduction

Cancer is the uncontrolled growth and spread of cells that may affect almost any tissue of the body. Worldwide, lung and stomach cancers are the most common cancers for men and breast and cervical cancer are the most common for women. More than 11 million new cases of cancer are diagnosed each year and that number is expected to rise to 16 million by 2020. Cancer is responsible for 7.6 million or 13% of all deaths worldwide.[1]

1.1 Cytotoxic drugs

Cytotoxics (chemotherapy drugs, antineoplastic drugs) have been in clinical use for decades and are of great importance in the treatment of cancer and certain other diseases.[2] With close to 100 cytotoxic drugs now in use and many more under development, chemotherapy has opened up new avenues ranging from improving patients' quality of life to achieving a cure.

Cytotoxic drugs are chemicals that affect cell growth and proliferation, most of which either bind directly to genetic material in the cell nucleus, or affect cellular protein synthesis. Typically, cytotoxic drugs do not distinguish between normal and cancerous cells.

Cytotoxic drugs are often administered to immunocompromised patients, and as most of these drugs are myelosuppressive this may place patients at a high risk of developing severe infections. For this reason, when parenteral cytotoxics are prepared, aseptic procedures must be strictly adhered to in order to prevent microbial contamination. In addition, as most of these agents have a narrow therapeutic index, the accuracy of the preparation must be assured. Pharmacy departments should have rigid checking procedures in place (See Section 11 – Checking Procedures).

1.2 Hazardous drugs

In terms of occupational exposure, a hazardous drug is defined as an agent that due to its inherent toxicity presents a danger to healthcare personnel.

These drugs are identified based on one or more of the four following characteristics; they are carcinogenic; genotoxic; teratogenic; or toxic at low doses in animal models or treated patients.[3–5]

Hazardous drugs include antineoplastic and cytotoxic agents, some hormonal agents, immunosuppressants, antiviral medications, and some monoclonal antibodies.

A list of hazardous drugs that require special handling should be posted in every facility at all relevant working places that provides drug preparation and administration services.

1.3 Impact of hazardous drug exposure

In the 1970s, secondary malignancies were reported in patients who received cytotoxic drugs for other, usually solid, primary malignancies. The most commonly seen secondary malignancies were leukaemia and bladder cancer reported after a latency period of 1–10 years.

Studies carried out by Falck *et al*. in the 1970's indicated that unprotected nurses who worked in environments in which hazardous drugs were prepared and administered had higher levels of mutagenic substances in their urine as compared to non-exposed workers.[6] This study suggested that nursing personnel were being occupationally exposed to cytotoxic drugs, many of which are mutagenic. This study was confirmed by numerous studies examining urine mutagenicity, chromosomal aberrations, sister chromatid exchanges and other endpoints in pharmacists and nurses who handle cytotoxic drugs.[7–9]

In addition, workers experienced other adverse health effects. A review of 14 studies described an association between exposure to antineoplastic drugs and adverse reproductive effects, and 9 studies showed some positive association.[10] The most common reproductive effects found in these studies were increased fetal loss,[11,12] congenital malformations,[13] low birth weight and congenital abnormalities,[14] and infertility.[15]

Because these measures were indirect, and a direct cause-and-effect relationship could not be determined, more direct methods of determining exposure have been developed. These methods include urinalysis to determine the presence of parent drugs or metabolites of hazardous drugs handled by healthcare workers, and environmental air and surface sampling techniques.

1.4 Occupational exposure

Occupational exposure to hazardous drugs and the potential health risk to healthcare workers first became a recognized safety concern in the 1970s.

Published data related to the issue of occupational exposure prompted the US Occupational Safety and Health Administration (OSHA) to issue guidelines in 1986 for the handling of antineoplastic and other hazardous agents by healthcare personnel which were updated in 1995.[4]

A number of other organizations in the US also published reports related to the safe handling of hazardous drugs, including the National Institutes of Health (NIH),[16] the National Study Commission on Cytotoxic Exposure (NSCCE),[17] the American Medical Association's (AMA) Council on Scientific Affairs[18] and, most recently, the National Institute for Occupational Safety and Health (NIOSH).[5]

These guidelines are the work of government institutions, but additional safe handling guidelines have been developed by professional organizations of hospital pharmacists and nursing associations (Australia,[19] New Zealand,[20] USA,[3] Canada,[21]). Some recent updates of guidelines include the Society of Hospital Pharmacists of Australia,[22] Quality Standard for the Oncology Pharmacy Practice,[23] the DGOP/ESOP (2005) 2nd Polish–German annual conference for oncology pharmacy "Therapy for practice",[24] Kwaliteitshandboek Cytostatica,[25] the Oncology Nursing Society[26] in the US and the American Society of Health-System Pharmacists.[3] In Europe, most countries have published guidelines concerning the safe handling of cytotoxic drugs or for protection against carcinogenic agents in general.

Some of these publications have the status of national law and are enforceable, other are European directives (to be translated into national laws). Some are pure guidelines (non-enforceable but recommended as "best practice") and some are even from insurance companies, refusing an assurance for the hospital if their standard is not followed.

Sources of exposure of health care providers to cytotoxic drugs are varied and the routes of exposure are typically inhalation, dermal or oral.

One route of exposure is inhalation via droplets, particulates and vapours. Many procedures can result in aerosol generation. For example; drug injection into an IV line, removal of air from the syringe or infusion line, and leakage at the tubing, syringe, or stopcock connection, clipping used needles and crushing used syringes. Drug particles can become airborne after drying of contaminated areas.

Vaporization of antineoplastic agents has been recorded with various drugs such as carmustine, ifosfamide, thiotepa and cyclophosphamide.[27–28]

Dermal contamination can arise from cytotoxic drug contamination on the outside of vials.[29-35] Thus, the environment of operators may be contaminated even before cytotoxic reconstitution has begun. Researchers have detected measurable air levels of cytotoxic drugs inside and outside biological safety cabinets from wipe samples of cytotoxic drugs on surfaces of workstations and at points distant from places of preparation and administration of drugs.

Studies have demonstrated that most work surfaces in areas where cytotoxic drugs are handled are contaminated with the drugs.[9,28,29,36–48] The working surfaces of biological safety cabinets, counter tops, floors, equipment and most other surface have been shown to be contaminated in studies from several countries around the world.

Inadvertent ingestion is also problematical. When food or beverages are prepared, stored, or consumed in work areas, they may easily become contaminated with airborne particles of cytotoxic drugs.

Similarly, hands, cigarettes, cosmetics and chewing gum, can be contaminated.

The greatest risk is direct skin contact with the drug in the event of a spill or leakage where contamination or personnel and the environment may occur.

1.5 Conclusions

Working with or near hazardous drugs in health care settings may cause skin rashes, has been associated with infertility, miscarriage and birth defects, and raises concerns about the possible development of leukaemia or other cancers. To provide workers with the greatest protection, **employers** should:

(a) Implement necessary administrative and engineering controls and
(b) Assure that workers use sound procedures for handling hazardous drugs.

In addition, **employees**, by their work practices influence their own occupational exposure and that of those around them. Employees can help minimise their potential exposure to these agents by:

(a) Staying current on the knowledge of the occupational risk posed by these agents and
(b) Ensuring that their work practices follow the best current recommendations.

These standards represent an international consensus on steps to prevent occupational exposure to hazardous drugs in healthcare settings.

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Section 2 – Transport of cytotoxics

All cytotoxic drugs should be packaged, stored and transported in such a way as to prevent damage and subsequent contamination of the environment, the drug itself, and all personnel involved in the routine handling and transportation of these drugs.

Transportation must be in accordance with all local, state, provincial or federal legislation concerning the transport of hazardous agents. The transport of cytotoxics may be considered in terms of the external transport from drug suppliers, the internal transport of commercial product within the institution, and finally the transport within the institution of the compounded admixture.

For transportation of cytotoxic waste, see Section 15.

2.1 External transport from supplier

2.1.1 Primary containers

Primary containers and shelf cartons should be designed to minimise the risk of breakage by using break resistant materials. This includes vials manufactured from an unbreakable plastic material, glass vials provided in specially designed outer plastic containers, or glass vials over-wrapped in plastic to prevent contamination in the event of breakage of the glass. Pharmacy departments should preferentially purchase products manufactured in this way.

2.1.2 Packaging

To prevent damage to the primary containers, all products for transportation from the manufacturer or wholesaler should preferably be protected with high impact resistant moulded foam, or other suitable packaging material. The packaging must also ensure containment of cytotoxic material in the event of spillage. The product should then be placed in corrugated cardboard shippers for example, which have strong insulating properties, to protect the contents from inadvertent rough handling during transport.

For refrigerated products, the use of ice bricks or ice packs is recommended to maintain the temperature within an acceptable range. All refrigerated shipments should ideally have a temperature monitor inside, usually a digital temperature gauge, which constantly monitors internal temperatures within the shipper during shipment. Packaging should also contain enough foam to ensure the products do not move in transit. In addition, the load should be arranged so that cartons will not move excessively in transit.

2.1.3 Labelling

Cytotoxic drugs must be easily identifiable by all personnel involved in their handling. The outer packaging of containers should display clear warning labels stating the goods are cytotoxic in nature. Most countries have a recognised symbol representing cytotoxic agents. This will vary, but in many cases is purple in colour, and will often contain a diagrammatic representation of a cell in telophase. In some countries this may be a yellow label with a crab-like symbol. It may say "Danger/Caution Cytotoxics" or could contain an exclamation mark. Whatever warning sign is attached it should be clear and instantly recognisable.

Appropriate temperature and light conditions must be clearly labelled on the outer packaging. The shipper itself must have full instructions on the nature of the contents and what to do in case of an emergency, especially in a spill or breakage. It must be clearly stated that the driver avoid contact with any apparent leaked material. There should be clear contact details to source advice should this be required.

2.1.4 Cytotoxic spill management

All personnel involved in the storage and transport of cytotoxic drugs should receive appropriate instruction concerning the potential hazards, correct handling, and procedures to deal with breakages and spills. Either a cytotoxic spill kit should be available in the delivery vehicle, or delivery personnel should have a mobile telephone and a contact number to call for immediate advice in the event of a spill.

2.1.5 Receiving and inventory control

The results of several European and American studies show that surface contamination exists on commercially supplied vials and primary packaging of cytotoxic drugs supplied by manufacturers to pharmacies. Persons involved in receiving and inventory control should be informed of the possibility of surface contamination on cytotoxic drug vials.

Staff should wear single use chemotherapy gloves when handling cytotoxic drug vials.

Packages with visual signs of damage should be quarantined immediately and the supplier should be contacted. It is not advisable to return damaged cytotoxic vials to the supplier but should instead be disposed of appropriately. Staff should wash their hands after handling cytotoxic drug vials. Gloves are not a substitute for hand washing.

Potentially contaminated items such as gloves should be disposed of as hazardous waste. Employers are encouraged to make sure the storage area has sufficient general exhaust ventilation to dilute and remove any airborne contaminants. Depending on the physical nature and quantity of the stored drugs, consideration should be given to installing a dedicated emergency exhaust fan. The fan should be large enough to quickly purge airborne contaminants from the room in the event of a spill and prevent contamination in adjacent areas. (See Sections 1 and 6).

Whenever available, drugs supplied in unbreakable packs are preferred to cytotoxic drugs packaged in glass containers.

2.1.6 Responsibilities of drug manufacturers

It is the responsibility of drug manufacturers to supply cytotoxics in containers which are guaranteed **to be free of contamination**. It is highly desirable that manufacturers provide some form of **certification** that vials and primary packaging are not contaminated with cytotoxics. This analysis should preferably be carried out by an independent laboratory. Hospitals and buying groups should preferentially purchase products which are verified to be free from external contamination.

Manufacturers must provide Material Safety Data Sheets (MSDS) on all of their cytotoxic products with explicit details on decontamination, and protection measures to be followed in the case of a spill or other accident. Each institution should retain a compilation of these Material Safety Data Sheets, should ensure that they are current and reflect the actual products used within the institution, and should update the list whenever purchased products change. These MSDS should be readily available in all areas where hazardous drugs are stored or used (see Section 21.9). The manufacturer must also provide details on physical and chemical stability, recommended storage conditions and requirements for light protection.

2.2 Internal transport of commercial product

The transport of commercial cytotoxic products and the safety measures required will depend on the quantity of drugs being transported.

2.2.1 Packaging

If large quantities of cytotoxic vials need to be transported, it is advisable to use a wheel driven vehicle and the products must be in their original packaging. The outer boxes containing drugs must be wrapped with protective plastic in order to avoid accidents through shock, and they should also be fastened with belts on the wheel driven vehicle to prevent accidents.

If the need arises to unpack and transport smaller quantities, unbreakable and leak tight boxes should be used. For extra safety, the internal part of these boxes should be made of moulded foam or a sponge-like material, so that the drugs are securely positioned. Such foam should be customised to the size of drugs being transported. The risk of damage may be minimised by manufacturers providing vials contained in shock absorbing plastic containers which are designed to position the vials they contain.

2.2.2 Labelling

In the case of transporting large quantities, the labelling should very clearly indicate that the contents are cytotoxic. If smaller quantities of drug need to be transported after unsealing the primary packaging, then this label should be attached to the transport box.

There should be another label attached stating that the inner contents are sealed and considered safe for transport. This label should also mention whom to inform in case of a spill or other accident.

2.2.3 Spills

Persons transporting commercial product within the institution should have a spill kit available. The contents and use of a spill kit are described in detail in Section 14. In case of an accident, the appropriate staff member should be contacted. Until the relevant staff member arrives, the people transporting the drugs should don their protective clothing (contained within the spill kit) and, in order to deter people from stepping into the contaminated area, clearly mark the area of danger using a warning sign (contained within the spill kit) or special coloured chalk.

2.3 Internal transport of compounded admixture

This section describes the guidelines for the transportation of prepared cytotoxic drugs from pharmacy departments to wards and day care centres within the hospital for in-house use.

All cytotoxic drugs should be packaged, stored and transported in such a way as to prevent damage and subsequent contamination of the environment, the drug itself and all personnel involved in routine handling and transportation of these drugs. Cytotoxic drugs must be transported so as to provide adequate physical and chemical protection for the drug and the drug handler. During transport, if drugs are spilled or become separated from other contents being transported, handler protection is of paramount concern and must be appropriately anticipated and planned for.

2.3.1 Packaging

Cytotoxic admixtures should be packaged in a labelled, sealed, leak-proof container, with outer bags heat sealed whenever possible. This ensures that the container offers protection from light where required, protects the drugs from breakage in transit and, contains leakage if breakage occurs.

2.3.2 Drug transport

Delivery of cytotoxic products must be made directly to the wards and day care centres within the hospital by the personnel transporting these drugs. No detours should be allowed when transporting these drugs. All personnel involved in the transport of cytotoxic drugs should receive appropriate instruction concerning the potential hazards, correct handling, and procedures to deal with breakages and spills.

Containers used for transporting prepared cytotoxic drugs should be hard-walled and robust, made from moulded foam or other suitable packaging material capable of protecting the product from a shock equivalent to a drop of one metre onto a concrete surface.

Wherever possible, disposable containers should be used (for example, sealed plastic bags). For safety reasons, the transport containers may be lined with absorbent material in case there is a spillage of the drug from its container.

The containers should be dedicated for the transportation of cytotoxic drugs only.

The use of pneumatic tubes to transport cytotoxic drugs is NOT RECOMMENDED. Practice standards from some countries, for example Australia, Canada and the United States explicitly prohibit their use. If this transport system is to be used for cytotoxics, it must first be checked and validated using containers filled with a NON cytotoxic product of the same size, weight and volume. All preparations transported in this way must be heat sealed in plastic bags and must be shown not to leak or break under stress. Containers used in pneumatic tubes which carry cytotoxics must be clearly labelled as cytotoxic and reserved for the transport of cytotoxic agents only. There should also be written procedures for dealing with a spillage or other incident involving cytotoxics in pneumatic tubes.

2.3.3 Labelling

As previously described, cytotoxic drugs should be easily identifiable by all personnel involved in their handling. Any opaque outer packaging of containers should clearly display warning labels stating the contents are “cytotoxic” in nature. Such labels should carry an identifying symbol for cytotoxic drugs. Appropriate temperature and light conditions, as well as expiry dates must be clearly labelled on the outer packaging.

2.3.4 Cytotoxic spill management

Cytotoxic drug spill kits must be readily available to personnel involved in the transport of cytotoxic drugs.

All personnel involved in the storage and transport of cytotoxic drugs should receive appropriate instruction concerning the potential hazards, correct handling, and procedures to deal with breakages and spills. All training must be documented and records kept. Re-training must be carried out an annual basis and these records kept. (See also Sections 4 and 21).

2.3.5 Documentation of cytotoxic drugs transportation

Records may be maintained of transportation of prepared cytotoxic drugs from the pharmacy to the various units where these drugs are used. (See also Section 21).

Section 3 – Personnel

3.1 Education and training

This section relates specifically to institutions where cytotoxic agents are prepared in-house. If cytotoxic agents are outsourced (purchased from a commercial supplier), then some of the following may not apply. For example, it may not be pharmacy personnel preparing the cytotoxic agents.

All personnel involved in the preparation and administration of cytotoxic drugs should posses a recognised qualification or should have received certified training in accordance with local regulations.

An assessment of practice should be undertaken on a regular basis for all personnel preparing and administering chemotherapy.

All personnel involved in the handling of cytotoxic drugs, including transportation, storage, and cleaning of facilities, should be trained in the use of personal protective equipment (PPE) and safe handling procedures. These staff members should be evaluated on a regular basis in order to verify compliance with procedures.

Cytotoxic drugs should be handled and stored within the pharmacy by trained employees.

The preparation of parenteral cytotoxic drugs should be undertaken only by pharmacy personnel

Transportation of cytotoxic drugs may be a task of auxiliary personnel.

Administration of chemotherapy should be performed only by certified/qualified health care personnel (See also Sections 4 and 12).

3.2 Health considerations

All personnel involved in any aspect of the handling of cytotoxic drugs should be informed about the risks of occupational exposure to hazardous drugs.

3.2.1 Exclusions from working in cytotoxic preparation

Illness

Whenever possible, personnel with upper respiratory infections or cutaneous infections must be excluded from preparing cytotoxics. Personnel on immunosuppressive therapy should also be excluded.

Family planning

Personnel who are pregnant or breastfeeding and personnel planning imminent parenthood should be permitted to avoid working with cytotoxic drugs. Such staff should be given alternative tasks or rostered to another area of the pharmacy if so requested. Institutions should develop a written policy on how to deal with this issue.

Abnormal pathology results

Personnel with abnormal pathology results should not prepare cytotoxic drugs until the abnormality has been investigated.

3.2.2 Medical examinations

There are no direct measurements to indicate total exposure to cytotoxic drugs. Non-specific measurements have been used as baseline and routine indicators. Staff whose responsibilities involve parenteral cytotoxic drug manipulation should receive a baseline examination that includes assessment of indices such as full blood examination, liver function tests, urea, creatinine and electrolytes.

These measurements may then be used to compare any subsequent measures taken either routinely or following accidental exposures. Regular monitoring, which includes a full blood examination and differential, should be offered at a minimum of six-month intervals. Institutions should have a written policy for baseline and regular monitoring of staff involved in the preparation of cytotoxic drugs. (See also Section 19).

3.3 Facilities

The facility should be designed to allow easy and adequate access for personnel, equipment, and cleaning. The cleanroom area should be designed with ergonomic considerations in mind for the comfort of staff working in the area for prolonged periods. For the safety of personnel working in the cleanroom, there must be adequate visibility into the area for people working in isolation.

Access to the cytotoxic preparation suite must be restricted to individuals working within the area.

A sign restricting the access of unauthorised personnel should be prominently displayed.

Due consideration should be given to the availability of an emergency shower in close proximity to the cytotoxic preparation suite. Emergency eye washing facilities should also be available. (See also Section 6).

3.4 Hygiene

Strict hygiene procedures must be developed and followed in the cytotoxic preparation suite. Eating, drinking, chewing gum and the application of cosmetics must be strictly prohibited. In addition, personnel in the preparation facility should not wear rings, earrings, bracelets or other jewellery.

3.5 Staffing levels

Policies and procedures should be developed and implemented that consider the following:

3.5.1 Number of staff members

A sufficient number of staff members must be available to provide for the expected workload. Staffing should allow for the workload during the busiest period and should take into account the complexity of products manufactured.

3.5.2 Work breaks

The staff allocation must be sufficient to allow for adequate breaks for those working in the cytotoxic cleanroom. It is recommended that no more than two hours be spent working at the cabinet or isolator without a break. Often staff work in isolation, and sufficient breaks must be provided to maintain concentration.

3.5.3 Documentation

Records of the work shifts of personnel working in cytotoxic reconstitution should be established and maintained. The information stored may include the duration of shifts worked, the location (if more than one isolator or biological safety cabinet exists), the number of manipulations, and the total amount of drug handled. Some other measure of complexity or risk may be incorporated; such as whether the drug is in powder form or solution, and whether the agent is supplied in a vial or ampoule. (See also Section 21).

Section 4 – Education and training

4.1 Education on cytotoxic risks and safe handling

In order to understand the risks involved and to ensure the safe handling of these agents, all staff who will be involved in the handling of cytotoxic drugs must be provided with adequate education. All staff who handle, or are likely to handle, cytotoxic drugs should receive appropriate education prior to exposure to risk. This will include pharmacy staff, nursing and medical staff, and other support staff including porters, and cleaners who may transport cytotoxic agents or may clean a potentially contaminated area. When available, specific educational courses should be attended.

In addition, patients and carers who are involved in the delivery of chemotherapy in the home should receive some basic education and training in the principles of safe handling, and dealing with spills, waste disposal and patients' excreta. Written instructions should be given to the patient or carer, including information on the use of oral chemotherapeutic agents.

4.1.1 Content of educational courses

An education program on the risks of exposure to cytotoxic agents and the measures required for safe handling should be developed and implemented. This program should be structured and may contain the following elements:

(a) The potential risks of exposure to cytotoxic agents
(b) Basic pharmacology of cytotoxic agents
(c) Theory of aseptic technique
(d) Use of personal protective equipment (PPE)
(e) Theory of containment devices and barriers
(f) Theory of hierarchy of protection measures
(g) Handling of cytotoxic waste
(h) Cytotoxic spills and accidental exposure
(i) Prescribing of cytotoxic agents
(j) Validation of cytotoxic prescriptions
(k) Hospital policies and procedures on cytotoxic management
(l) Cytotoxic drug use processes (drug selection, prescription validation, preparation, dispensing, drug administration and drug use evaluation)

The education provided should be tailored to the needs of the individual after consideration of the job description, previous level of education, and their specific responsibilities relating to cytotoxic drugs. This education should be ongoing with attendance at in-house or external courses, seminars and symposia strongly encouraged. Consideration should be given to the re-education of staff members who have had a prolonged break from working in the area.

4.1.2 Education providers

Education should be provided by appropriate academic, clinical, or technical specialists. This requirement will vary depending on the specific education required. If an accredited course is available, then staff should attend such a course. A specified number of hours to be completed should be determined by the course provider.

4.1.3 Documentation

Education sessions or attendance at courses should be documented and records retained indefinitely in the staff members' human resources file.

4.1.4 Certification

Educational courses offered by professional bodies should preferably have received some form of accreditation and an allocation of continuing education hours.

4.1.5 Evaluation

Feedback on educational courses attended should be an integral part of any program. The effectiveness of the educational process should be assessed and reviewed on a regular basis. This may be achieved by the administration of a competency test or examination at the end of the education program.

4.1.6 Re-education

It is recommended that the education program be repeated every 2–3 years to cover the introduction of new drugs into practice or any other technical innovations. Education should be repeated whenever any major change in practice occurs.

4.2 Training in the manipulation and safe handling of cytotoxic drugs

Before being permitted to work in the cytotoxic preparation facility, all staff must be trained in the safe handling of cytotoxic drugs and related waste. This training may be provided for pharmacists, pre-registration pharmacy graduates and pharmacy technicians. Other pharmacy staff and support personnel may also need to be trained in dealing with cytotoxic spills, transporting cytotoxics, and the correct storage of cytotoxic agents.

The training of nurses should concentrate on safe handling during cytotoxic administration, waste handling, management of extravasation and spill management.

This training may be offered in-house or by an external training provider. If internal training is provided adequate resources must be available.

Staff members handling cytotoxic drugs should be supplied with appropriate up-to-date information on all aspects of the safe handling of cytotoxic drugs as well as the reported hazards of low level exposure to these agents.

4.2.1 Content of training courses

A training program in cytotoxic reconstitution should be developed and implemented. This program should be structured and may contain the following elements:

(a) The potential risks of exposure to cytotoxic agents
(b) Use of safety cabinet/isolator
(c) Working in a cleanroom
(d) Aseptic technique
(e) Use of personal protective equipment
(f) Use of containment devices
(g) Use of specialised equipment
(h) Handling of cytotoxic waste
(i) Dealing with cytotoxic spills
(j) Emergency procedures
(k) Documentation
(l) Labelling and packaging
(m) Transport of cytotoxics
(n) Environmental monitoring
(o) Cleaning procedures
(p) Health monitoring
(q) Validation processes

After consideration of the job description and related risk, training should be tailored to the specific needs of the individual. Training should be ongoing with regular updates for any new procedures or products, and should include periodic tests of staff competency. Whenever a new hazardous drug is introduced into the workplace, staff should receive adequate information about the risks of potential exposure to the agent.

Each institution should develop and maintain a procedure manual which details the policies and procedures for the appropriate manufacture and administration of cytotoxic agents. This should include a description of aseptic technique, standard operating procedures for cytotoxic reconstitution and administration, cleaning procedures, information on dealing with spills, transporting cytotoxics, and information on health monitoring. It should contain a full description of all personal protective equipment and special containment devices to be used in the preparation of cytotoxics. This manual should be regularly updated and should be available to staff at all times.

4.2.2 Trainers

Training of staff in the manipulation of parenteral cytotoxic drugs should be undertaken by an experienced operator. If an accredited training course is available it is recommended that personnel attend. Standard operating procedures for training should be developed and maintained. Each type of procedure to be undertaken should have a specific and detailed standard operating procedure. Before personnel attempt to prepare or administer an item for a patient they must be trained in that particular standard operating procedure.

4.2.3 Documentation

The training of staff in cytotoxic reconstitution must be structured and all stages should be documented. Records of training received should be retained indefinitely in the staff members' human resources file.

4.2.4 Validation

Validation of processes

The objective is to demonstrate that the processes used during the aseptic preparation and the staff undertaking the aseptic manipulation are capable of maintaining the sterility of the product. The *media fill test (or Broth test)* is intended to simulate routine aseptic operations, but uses microbiological media to produce units that can be tested for contamination.

The test must be representative of the routine activity in terms of the number of simulated preparations produced and must be performed using the same devices and same transfer methods as the routine procedure. Tryptone soya culture media is normally used for the test. The sterility of the culture media must be checked before performing the *media fill test* to ensure that the installation does not interact with the sterility. For example, when sterilized isolators are used, the sterilization method can inhibit the microbiological growth and give false negative results when performing the *media fill test*. The test must be performed at least 3 times, and filled units should be incubated at the designed temperature for 14 days. The expected results are that not one positive unit is found. In the case of a positive result, the cause of the failure must be investigated and focus on whether the facility, process or operator is the root cause. Revalidation of the process should be performed when this root cause of the failure is identified. In addition, revalidation of the process should be performed when any change is made to either the process or the facilities.

Validation of the operator

One objective is to demonstrate that the aseptic technique of the operator undertaking the aseptic manipulation is capable of maintaining the sterility of the product. All aseptic manipulation should be broken into a number of key steps (i.e. withdrawing solution from a vial, addition of a solution to an infusion bag) and each key step may be investigated using a *media fill test*. The operator should also be able to demonstrate an understanding of the safe handling techniques required to prevent exposure to hazardous drugs.

A second objective is to ensure that the operator can carry out these aseptic manipulations without contaminating herself/himself or the environment. The use of a fluorescein dye detected with ultraviolet light is most commonly employed.

Validation of training

The objective is to confirm that all staff have a satisfactory level of knowledge and competency for the duties they are required to undertake. The training program should be validated and should include the critical steps especially aseptic process and chemical contamination risks. The impact of training on the trainee should be validated by performing competency checks.

Re-validation should occur on a regular basis. The frequency of this re-validation will depend on a number of factors including the staff turnover in the area, and the duration of rosters in the area. As a minimum, staff regularly reconstituting cytotoxics should undergo a validation test annually.

4.2.5 Evaluation

Ongoing feedback on the training provided should be an integral part of the program. The effectiveness of the training should be assessed and reviewed on a regular basis.

4.2.6 Re-training

To cover the introduction of new drugs into practice or any other technical innovations, it is recommended that the training program be repeated every 2–3 years.

Training should be repeated whenever any major change in practice occurs.

Section 5 – Hierarchic order in protection measures

It is very common in the setting of standards for industrial hygiene to include an obligation to follow a hierarchic order of level of protection for employees at their workplace.

An example of this obligation can be found in Directive 2004/37/EC of the European Parliament and the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work,[1] or in most of the national regulations or laws on industrial health and safety.

According to the provisions of these laws and regulations, the employer must perform a risk analysis comprising the following steps:

- Definition of the work areas to be evaluated (e.g. cytotoxic preparation facility, reception of goods, transport, administration, etc.)
- Ascertainment of hazards and burdens (e.g. classification of substances)
- Evaluation of these hazards and burdens
- Specification of the necessary measures
- Testing and evaluation of the effectiveness of the measures (to ensure the protective measures have achieved the intended aim or whether they have possibly resulted in the generation of new hazards)
- Documentation

It is not logical to install a level of protection far higher or to accept a level far lower for cytotoxic drugs compared to the measures taken for other toxic or carcinogenic products.

However, it is imperative that the sequence of protection levels starts with level 1 and ends at level 4 = TOP → BOTTOM

In other words, one is not free to choose the measures in protection to exposure of cytotoxic drugs.

The levels of protection measures are in descending order of importance:

5.1 Level 1: Elimination, substitution, replacement

Change the product to another product which is non-toxic or less toxic

Currently, this is rarely possible in the treatment of cancer patients, but this level could become very important as more targeted therapies become available.

If level 1 is impossible or is insufficient, then the next level is applied

5.2 Level 2: Isolation of the hazard/source containment

Contain the toxic product in its container or at source

By containing the product at its source, the contamination of persons or materials is prevented.

If possible, source containment should be continuous throughout the entire process of production and administration of the product.

If levels 1 and 2 are impossible or insufficient, then the next level is applied

5.3 Level 3: Engineering controls/ventilation

Apply local and general ventilation or extraction in order to dilute the toxic product

Any form of dilution will reduce the concentration of the contamination. Any form of extraction will reduce the amount of contamination. (e.g. opening a window and/or door to a patient's room to allow ventilation)

Biological safety cabinets and isolators should be considered as level 3 measures. These ventilation tools offer additional protection features; for biological safety cabinets this would include such things as controlled airflow, protection shields, and HEPA filters.

For isolators this would include such things as hatches, glove ports, HEPA filters, and a physical barrier between the product and operator.

None of these features will prevent contamination within the biological safety cabinet or isolator from occurring. Once contamination has occurred, it will inevitably enter the environment.

Some laws and regulations use a 5th level of hierarchic order. In this case there is an additional level between levels 3 and 4 – Level 3B

5.3.1 Level 3 B: Administrative controls/ organization measures

Organise the work in such a way that the duration of exposure is reduced. Organise the work in such a way that the number of employees exposed is reduced. If levels 1, 2, and 3 are impossible or insufficient, then the next level is applied.

5.4 Level 4: Personal protective equipment

Individual protection by using personal tools

Gloves, masks, gowns, goggles or face shields, and other equipment create a temporary barrier between the contamination and the operator.

It is important to use "proven" resistant material; tested for these specific products and conditions.

Terminology such as "cytotoxic glove" is not sufficient to ensure adequate protection unless accompanied by test results.

For such tests, the specific conditions should be taken into account. e.g:

(a) HYPEC procedure (direct contact with cytotoxic drug for 30 minutes at temperatures of 42°C)
(b) temperature of glove after only 3 minutes on the hand reaches 34°C
(c) continuous stretching of the glove during preparatory or administration activities versus static test conditions.

Safe work practices should be incorporated into Standard Operating Procedures (SOP) and these procedures should be reviewed and updated on a regular basis. All staff should be educated and trained in accordance with these procedures and performance should be reviewed periodically.

REFERENCE

1 Directive 2004/37/EC of the European Parliament and the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC 2004). Available at: http://europa.eu/scadplus/leg/en/cha/c11137.htm Accessed February 2007.

Section 6 – Facilities for sterile cytotoxic reconstitution and personal protective equipment

Facilities for the sterile reconstitution of cytotoxic agents need to ensure both the protection of the product and the protection of the drug handlers.

Aseptic drug manipulation must take place in a controlled environment to ensure the sterility of the end product. Additional protective measures are required to guarantee the safety of the operators.

6.1 Centralised preparation

Centralised preparation of parenteral cytotoxic drugs should be implemented to protect the final product against microbiological and particulate contamination and to protect handlers against exposure to hazardous drugs. Taking into account the pharmaceutical analysis and the quality control implemented, centralised preparation improves the entire quality of the preparation and thus the safety of patients is enhanced. Centralisation of services also provides economic benefits.

Centralisation is commonly located in the pharmacy department. Many institutions site the preparation facility within an oncology outpatient department or close to the inpatient ward where chemotherapy is most commonly administered (that is, a satellite pharmacy). This offers advantages in terms of ease of transport of cytotoxics as well as enhanced communication between pharmacy, medical, and nursing staff.

The satellite pharmacy must be under the control of a pharmacist.

Under no circumstances should nursing staff be permitted to prepare/reconstitute cytotoxic agents on the ward.

6.2 Facilities

Due to the risk of contamination, cytotoxic reconstitution must be performed in a room dedicated solely to that task with similarly dedicated equipment.

Access to the room where cytotoxic preparation is performed must be restricted to trained and validated pharmacy personnel. A warning sign must clearly identify that the access is controlled and limited to authorised personnel only. The use of standard symbols and colours to depict cytotoxic agents is recommended. This sign should contain wording such as:

"Cytotoxic Preparation Area. Access Restricted to Authorised Personnel Only"

The cytotoxic facility should be designed to allow easy and adequate access for personnel, equipment, and cleaning. The room surfaces should be designed to minimise particle shedding and to prevent the build-up of particulate matter. The design must facilitate effective cleaning. Walls must be lined with a smooth, durable surface, lighting recessed into the ceiling, and the room should contain as few projecting ledges or shelves as possible. Floors should be poured and seamless if possible. Vinyl tiles have been shown to trap and hold drugs.

In the event of contamination of the eye with hazardous material, there should be emergency eye wash facilities available for use by staff. Eyes that become contaminated should undergo sustained irrigation with either a commercial eye irrigation solution or sodium chloride (0.9%). Due to the potential for water pressure damage to the eye, it is not recommended to irrigate the eye directly with running water from a tap. Consideration should also be given to the installation of an emergency shower.

6.2.1 Class of cleanroom

General classification of the cleanroom ("Class") is given by the ISO 14644-1 international standard.[1] This classification is based on the maximum level of particulate contamination. For sterile medicinal products, classification of the room must be referred to the classification ("Grade") given by the EudraLex Good Manufacturing Practices Annex 1, Volume 4, Manufacture of Sterile Medicinal Products,[2] and by the draft PIC/S Guidelines.[3] EudraLax applies to the pharmaceutical industry while the draft of the PIC/S

Guidelines are meant for the pharmaceutical inspection services controlling (hospital) pharmacies.

This classification takes into account both particulate and microbiological contamination. The room shall be designed to facilitate asepsis in the handling and preparation of cytotoxic drugs, and shall also be designed to provide containment of cytotoxic drugs, particularly in the event of the failure of the biological safety cabinet/isolator or spillage outside the cabinet/isolator. The requirements for "Class" or "Grade" environments will depend upon both the type of preparation and the equipment used.

(a) Type of Preparation

Preparation of sterile cytotoxic drugs can be defined as an aseptic preparation.

(b) Environmental Setting

Sterile cytotoxic preparation using aseptic technique must be performed in a Grade A environment. Characteristics of a Grade A environment are shown in Table 1 (particulate contamination) and Table 2 (microbial contamination). Table 3 summarises the relationship between the ISO classification[1] the EudraLex[2] classification, and the US federal standard 209E with regard to particulate contamination.

Note: Federal standard 209E has been replaced with ISO Standard 14644-1. Taking into account that some suppliers and users may not yet have switched over, this data is provided for information only.

The Grade A environment corresponds approximately to the ISO Class 5.

Both laminar airflow hoods and isolators are able to guarantee a Grade A environment. The main difference between these two approaches is related to the requirements for the immediate environment of the equipment used.

According to the PIC/S draft Guidelines,[3] when a laminar airflow hood (biological safety cabinet) is used for aseptic manipulations, the recommended grade of background environment is:

Aseptic preparation of products with shelf life <24 hours: at least Grade **D**

Aseptic preparation of products with shelf life >24 hours: at least Grade **B***

* If aseptic procedures are extensively documented, grade C could be accepted for existing facilities. In that case, grade B clothing should be worn.

If an isolator is used (permanently closed – see Section 8), the recommended grade of background environment is:

Aseptic preparation of products with shelf life <24 hours: at least Grade **D**

Aseptic preparation of products with shelf life >24 hours: at least Grade **D**

For terminally sterilised products, the background environment for filling these products is at least Grade C.

Note that an anteroom leading to a positive pressure room may be ISO Class 8 (see Table 3) but an **anteroom leading to a negative pressure room shall meet at least ISO Class 7** (see Table 3) criteria

Table 1. Airborne particulate classification[2]

	At rest	In operation		
Grade	Maximum permitted number of particles/m^3 equal to or above			
	0.5 μm	5 μm	0.5 μm	5 μm
A	3500	1	3500	1
B	3500	1	350 000	2000
C	350 000	2000	3 500 000	20 000
D	3 500 000	20 000	Not defined	Not defined

Table 2. Recommended limits for microbial contamination[2]

Grade	Air sample cfu/m^3	Settle plates (diameter 90mm) cfu/4 hours	Contact plates (diameter 55 mm) cfu/plate	Glove print 5 finger cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

Table 3. Relationship between ISO classification,[1] EudraLex Classification,[2] and US federal standard No. 209 E (US FS 209E)

Grade/Class	Maximum permitted number of particles/m^3 equal to or above				
	0.1 μm	0.2 μm	0.3 μm	0.5 μm	5 μm
Class ISO 5 (US FS 100)	100 000	23 700	10 200	3520	29
Grade A and B (at rest)	/	/	/	3500	1
Class ISO 7 (US FS 10,000)	/	/	/	352 000	2930
Grade C				350 000	2000
Class ISO 8 (US FS 100,000)	/	/	/	3 520 000	29 300
Grade D	/	/	/	3 500 000	20 000

*Note: US FS 209 E has been replaced with ISO Standard 14644-1.

so that air drawn into the negative pressure environment is of the same ISO Class 7 (see Table 3) quality.

A pressure indicator shall be installed that can be readily monitored for correct room pressurization.

The BSC and Compounding Aseptic Isolator shall be 100% vented to the outside air through HEPA filtration.

Additional comments related to the use of isolators: When isolator technology is used, the requirements for the immediate surroundings will depend upon the pressure type of the isolator, and the type of pass through hatches. Positive air pressure isolators, which are totally and permanently enclosed, may be located in an uncontrolled room or a **D** Grade (ISO 8) environment. Negative air pressure isolators must be located at least in a Grade C (ISO 7) environment.

In the case of preparation of cytotoxic agents, containment is the most important aspect to be considered, and special attention must be paid to the transfer system/pass through hatches used between the isolator and the environment. Type F[4] pass transfer devices are highly recommended to remove waste and end-products. These devices use double interlocking doors to ensure both the containment of any chemical contamination and the sterility of the final product. Type A[4] transfer devices must be avoided because during the transfer, inside isolator air can be directly exhausted into the isolator environment, especially when using a positive air pressure isolator. See Section 8.

According to USP Chapter <797>,[5] where three risk levels are introduced, the requirements of a Class D cleanroom for low-risk operations and a Class C cleanroom for medium and high-risk operations must be achieved. Those risk levels are assigned according to the conditions in which sterile preparations are compounded.

According to USP <797>[5] Hazardous Drugs as CSPs (Compounded Sterile Preparations):

Low-risk conditions

(1) The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 (see Table 1) or better air quality using only sterile ingredients, products, components, and devices.
(2) The compounding involves only transfer, measuring, and mixing manipulations using no more than three commercially manufactured sterile products and entries into one container package (e.g., bag, vial) of sterile product to make the CSP.
(3) Manipulations are limited to aseptically opening ampoules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.

For a low-risk preparation, in the absence of passing a sterility test,[5] the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 48 hours at controlled room temperature, for not more than 14 days at a cold temperature, and for 45 days in solid frozen state at −20°C or colder.[5]

Examples of low-risk compounding:

(1) Single volume transfers of sterile dosage forms from ampoules, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers. The solution content of ampoules should be passed through a sterile filter to remove any particles.
(2) Simple aseptic measuring and transferring with not more than three (3) manufactured products including an infusion or diluent solution to compound drug admixtures and nutritional solutions.

Medium-risk conditions

Medium-risk conditions include multiple individual or small doses of sterile products that are compounded or pooled to prepare a compound sterile product that will be administered either to multiple patients or to one patient on multiple occasions.

Examples of medium risk conditions:

(1) The compounding process includes complex aseptic manipulations other then a single-volume transfer.
(2) The compounding process requires an unusually long duration, such as that required to complete dissolution or homogeneous mixing.
(3) The compounded sterile products do not contain broad-spectrum bacteriostatic substances, and they are administrated over several days.

For medium-risk preparations, in the absence of passing a sterility test the storage periods cannot

exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature, for not more than 7 days at a cold temperature, and for 45 days in solid frozen state at −20°C or colder.

Examples of medium risk compounding:

(1) The compounding of Total Parenteral Nutrition fluids by using manual or automated devices that require multiple injections and detachments and attachments of the nutrient source products to the device or machine to deliver all nutritional components to the final sterile container.
(2) The filling of reservoirs of injection and infusion devices with multiple sterile products and evacuation of air from these reservoirs before the filled device is dispensed.
(3) The filling of reservoirs of injection and infusion devices with volumes of sterile drug solutions that will be administered over several days at ambient temperatures between 25° and 40°C.
(4) The transfer of multiple ampoules or vials into a single, final sterile container or product.

High-risk conditions

High-risk conditions include:

(1) The compounding of non sterile ingredients, including manufactured products for routes of administration other than those listed under c in the introduction of the official Pharmacopeial Forum that are incorporated or a non sterile device that is employed before terminal sterilization.
(2) The compounding of sterile ingredients, components, devices and mixtures exposed to air quality inferior to ISO Class 5; this includes the storage in environments inferior to ISO Class 5 or opened or partially used packages of manufactured sterile products that lack microbial preservatives.
(3) The compounding of non sterile products exposed to air quality inferior to ISO Class 5 for at least 6 hours before sterilization.

For high-risk preparations, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature, for not more than 3 days at a cold temperature, and for 45 days in solid frozen state at −20°C or colder.

Examples of high-risk compounding:

(1) The process of dissolving non sterile bulk drug and nutrient powders to make a solution, which will be terminally sterilized.
(2) The situation when sterile ingredients, components, devices and mixtures are exposed to air quality inferior to ISO Class 5.
(3) The process of measuring and mixing sterile ingredients in non sterile devices before sterilisation is performed.

6.2.2 Pressure differentials

According to USP <797>,[5] there is no option for the pressure of the preparation room which should be negative.

According to the PIC/S draft guidelines[3]:

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

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

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

Therefore, combining both recommendations, BSC's of Grade **A** (ISO 5) are located in a negative air pressure room of Grade **C** (ISO 7). Positive pressure isolators Grade **A** (ISO 5) are located in a negative air pressure room of Grade **D** (ISO 8) or uncontrolled Grade room. Negative air pressure isolators Grade **A** (ISO 5) are located in a negative air pressure room of Grade **C** (ISO 7).

Pressure differentials should be established within the cytotoxic preparation facility with the double objective of protecting the operators and maintaining the sterility of parenteral product. Two possibilities exist: Positive and negative pressure differentials with the surrounding environment.

(a) Positive Pressure Differential

Positive air pressure of the preparation room and negative air pressure of the airlock hatches and the anteroom. In this case, the negative air pressure of the hatches and personnel zone acts as a trap to isolate potentially contaminated air.

(b) Negative Pressure Differential

Negative air pressure of the preparation room and positive air pressure of the airlock hatches and the anteroom. In this case, the positive air pressure of the hatches acts as a barrier.

(c) Pressure Differential Between Adjacent Rooms

EudraLex[2] recommends a 10–15 Pa pressure difference between adjacent rooms of different grade. Note: this does not apply in the case of a negative pressure room.

For example, a typical graduation configuration for a cleanroom used for aseptic preparation is given below:

- 10–15 Pa between Grade A and B
- 8–10 Pa between Grade B and C
- 2–6 Pa between Grade C and D
- 2 Pa between Grade D and surrounding zone

Note that this example of graduation has to be adapted in order to reach the above proposed pressure differential (a) or (b) for aseptic preparation of toxic drugs.

In all cases, it is recommended that the room where cytotoxic agents are stored is under negative pressure to prevent the dissemination of contamination in the event of breakage.

According to USP <797>,[5] Hazardous drugs as CSP's (Compounded Sterile Preparations): The ISO Class 5 (see Table 3) BSC or Compounding Aseptic Isolator (see definition below) shall be placed in an ISO Class 7 (see Table 3) room that is physically separated, i.e., a different room, from other preparation areas, and optimally has no less than **0.01-inch (0.0254 cm) water column [2.4905 Pa] negative pressure** to adjacent positive pressure ISO Class 7, or better, anterooms, thus providing inward airflow to contain any airborne drug.

If a compounding isolator that meets the requirements for asepsis and containment is used outside of a cleanroom, the room must maintain a minimum negative pressure of 0.01 inch **(0.0254 cm)** water column **(2.4905 Pa)** and have a minimum of **12 air changes per hour**.

6.2.3 Air changes

A minimum air change of 20 room volumes per hour is required. Areas known to generate large numbers of particles, for example changing rooms, may have an air change rate of up to 60 volumes per hour.

6.2.4 External exhaust of air from the work area

The air from the workplace must be exhausted to the atmosphere to prevent exposure of personnel. A HEPA exhaust filter should be used to decrease contamination of the air exhausted. However, it is known that some anticancer drugs are vaporised and then pass through HEPA filters. Some countries, for example Australia, may mandate the use of activated carbon filters to trap vapourised cytotoxics. However, it should be noted that these filters may not guarantee complete retention in all cases. See Section 8.

The location of the exhaust point of the duct is usually 2 m above the nearest building.

6.2.5 Temperature and humidity

In order to prevent microbiological contamination and to ensure comfort of the personnel working in the area, the temperature of the preparation rooms must be controlled. A temperature in the range of 18–22°C is acceptable.

The humidity must be controlled in order to prevent corrosion and condensation on any work surfaces and also to provide operator comfort. In addition, for isolators which are sterilized by hydrogen peroxide vapour, the humidity of the surrounding environment must be strictly controlled. The human comfort zone is generally in the range of 30% to 70% relative humidity. For isolators sterilized by hydrogen peroxide a 50% relative humidity level must be reached and controlled between 40% and 60%.

6.2.6 Access of personnel to the cleanroom

Access to the cleanroom should be through an anteroom. An effective airlock must exist between the cytotoxic suite and the external environment. Adequate procedures must be in place to prevent the simultaneous opening of doors and pass-through

hatches. If interlocking doors are used, a safety override switch should be installed for emergency situations. The doors should preferably be fitted with an audible or visual alarm to prevent both doors being opened simultaneously.

This anteroom must be the only access to the cytotoxic cleanroom. If possible, this anteroom should not share access to other non-cytotoxic cleanrooms in order to prevent any cross contamination occurring. The anteroom should provide facilities for gowning of personnel entering the cleanroom and should be ventilated through a HEPA filter. A full length mirror should be available in the anteroom so that staff can check that they are appropriately gowned prior to entering the cleanroom. Consideration should be given to the use of sticky mats. Step-over barriers should be used to separate the different stages of change. Attention should be paid to the exit of persons and separate circulation zones should be identified allowing discarding of protective gowns and gloves before exiting the restricted access zone.

The pressure within the anteroom may be positive or negative depending on the concept chosen (see Section 6.2.2)

6.2.7 Pass-through hatches

A pass-through hatch is essential to prevent direct access between the cytotoxic cleanroom and the external environment. There are two possibilities for the location of such hatches. These hatches may either be between the cleanroom and the anteroom or between the cleanroom and the external environment. If the latter option is selected, then interlocking doors must be used and the unit must be HEPA filtered. Hatch doors should preferably be fitted with an audible or visual alarm to prevent doors being opened simultaneously.

For specific hatches used for entry to a pharmaceutical isolator see Section 8.

In order to minimise cross contamination, separate hatches for entry and exit of products are preferable.

6.2.8 Storage room

According to USP <797>,[5] hazardous drugs shall be stored separately from other stock in a manner to prevent contamination and personnel exposure. Such storage is preferably within a containment area such as a negative pressure room. The storage area must have sufficient general exhaust ventilation, e.g. - at least 12 air exchanges per hour to dilute and remove any airborne contaminants. Hazardous drugs shall be handled with caution using appropriate chemotherapy gloves during distribution, receiving, storage, preparing for administration, and disposal.

6.2.9 Monitoring of facilities

An ongoing monitoring program should be established. In controlled workplaces, the parameters to be monitored are microbiological contamination, particulate contamination, HEPA filtration, air velocity, and pressure differentials. Visual inspection of the surfaces and joints should be performed regularly for cracks or other damage. Specifications to be maintained depend on the grade of the room (see Section 6.2.1).

A check list should be used to assess the conformity of the room and equipment before daily use. Pressure differentials must be checked before entry into the cleanroom. Consideration should be given to the installation of manometer alarms, preferably visual, which alert staff to inadequate pressure differentials.

Particulate contamination and air velocity should be assessed on a regular basis.

Microbiological contamination should be checked on a daily basis by sampling surfaces (contact plates). Passive air sampling should be done daily with settle plates (Petri dishes of diameter 90 mm) and active air sampling done on a regular basis. Testing must be carried out more frequently if any abnormality in any test is detected, or if any maintenance or repair work is carried out.

Frequency of monitoring[3]

Table 4. Minimum frequency of physical monitoring

Laminar flow cabinets (LFCs)/Biohazard Safety Cabinets (BSCs):	*Frequency*
Pressure differentials between rooms	Before beginning of work, usually daily
Pressure differentials across HEPA filters (workstation)	Before beginning of work, usually daily
Particle counts	Yearly at rest and in the operational state
Room air changes per hour	Yearly
Air velocities on workstations	Yearly
HEPA filter integrity checks	Yearly
Isolators:	
Isolator glove integrity	Visual checks every session
Pressure differentials across HEPA filters	Before beginning of work, usually daily
Isolator pressure hold test (with gloves attached)	Weekly

Table 5. Minimum frequency for microbiological monitoring

Settle plates	Every working session in the Grade A (ISO 5) zone Once a week in clean room
Surface samples	Weekly
Active air samples	Weekly
Glove finger dabs	At the end of each working session

6.2.10 Microbiological monitoring

Passive air sampling is performed using settle plates which must be placed according to a sampling plan previously defined. This plan may be developed in conjunction with the institution's department of microbiology. Settle plates should be exposed under normal operating conditions for a period of 4 hours. Maximum acceptable levels of microbiological contamination depend on the environment grade[2]:

Grade A environment < 1 cfu/plate
Grade B environment 5 cfu/plate
Grade C environment 50 cfu/plate
Grade D environment 100 cfu/plate

Active air sampling is performed using bio-collectors. The sampling method is based on collecting a known volume of air during a defined period of time. Air is drawn over a nutrient agar surface at such velocity that any particulate contaminants are impacted onto the surface. Active air sampling is a more sensitive method than passive air sampling. Maximum acceptable levels of microbiological contamination depend on the environment grade[2]:

Grade A environment < 1 cfu/plate
Grade B environment 10 cfu/plate
Grade C environment 100 cfu/plate
Grade D environment 200 cfu/plate

Microbiological monitoring of surfaces can be performed either by contact plates (diameter 55 mm) or using swabs. Contact plates provide a higher degree of reproducibility than swabs and are easier to use. However, swabs could be useful for sampling inaccessible places such as corners. In addition, no recommendation of maximum acceptable levels is available for the swabs. For the contact plate method, contact with the surface to be sampled must be applied at a defined pressure for a defined period of time. A standard procedure of a light hand pressure for 2–5 seconds is likely to be satisfactory.

Maximum acceptable levels of microbiological contamination for contact plates depend on the environment grade[2]:

Grade A environment < 1 cfu/plate
Grade B environment 5 cfu/plate
Grade C environment 25 cfu/plate
Grade D environment 50 cfu/plate

6.2.11 Air particle sampling

Air particle sampling is performed to verify that the environment reaches specification. Particle measurement is based on the use of a discrete airborne particle counter to measure the concentration of particles at designated sizes equal or greater than the threshold stated.

Maximum acceptable levels of particulate contamination depend on the environment grade[2] – see Table 1. Maximum permitted levels are given both at rest and under normal operating conditions. The particulate conditions given at rest should be achieved after a short clean up period of 15–20 minutes (guidance value) after completion of operations. For the grade A environment, it is accepted that the "In Operation" specifications may not be achieved under normal operating conditions due to the nature of the work being carried out (for example, over wrapping of sterile medical devices). In this case, particle counts above the specifications can be generated without compromising the quality of the preparation. Consequently, the particle control should be focussed on the "at rest" conditions.

6.2.12 Certification and Quality Assurance

Whenever possible, all equipment and processes used for cytotoxic preparation which affect product sterility or product attributes should be qualified or validated. Any certificates issued shall be reviewed, approved, and signed off by a designated pharmacist, and retained indefinitely. This will vary according to local practice and regulations.

Qualification is required for the room and for the equipment used. This includes the biological safety cabinet, pharmaceutical isolator, and automated filling pump among other equipment. This qualification process consists of four steps:

(1) **Design (Design Qualification [DQ])**: The documented verification that the proposed

design of facilities, systems and equipment is suitable for the intended purpose.

- **Approval of the design and drawing**: This approval must be obtained, in accordance with local regulations, by the body responsible for pharmacy practice, for example a state board of pharmacy, a pharmaceutical society, or licence inspector, and by the pharmacist responsible for the unit.

(2) **Installation (Installation Qualification [IQ]):** The documented verification that the facilities, system and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations. At this stage, the installation is on site but is not operational. The objective at this point is to review the compliance with specifications.

(3) **Operation (Operational Qualification [OQ]):** The documented verification that the facilities, systems, and equipment, as installed or modified, perform as intended throughout all anticipated ranges. The objective is to check that the installation operates effectively under normal working conditions but without activity. Examples of operational certification for rooms are given below:

- HEPA filter integrity test
- Functional check of pressure regulation and alarms
- Air change rate per hours
- Particle count
- Pressure differential
- Noise level
- Light Level

(4) **Performance (Performance Qualification [PQ]):** The documented verification that the facilities, system and equipment taken together, can perform effectively and reproducibly, based on the approved process method and product specification. The objective is to check that the installation operates effectively under normal operating conditions during routine activity. Examples of performance certification are given below:

- Checking procedures of use and monitoring of the installation
- Air distribution studies

6.2.13 Validation

Validation is the documented evidence that the process, operating within established parameters, can perform effectively and reproducibly to produce cytotoxic drugs meeting all predetermined specifications and quality attributes. In terms of sterile facilities, validation that the processes used during the aseptic preparation maintain the sterility of the end product is required.

Validation of the process (see Section 4.10.1)

6.3 Clothing & PPE

The correct selection and use of personal protective equipment (PPE) is required to both ensure the sterility of the end product and protect the operator. PPE must be worn to protect personnel during cytotoxic reconstitution and during other activities where they may come into contact with hazardous drugs. Activities may include opening drug packaging, handling vials or finished product, labelling drug containers, or disposing of waste. PPE includes gloves, gowns or coveralls, boots or overshoes, masks, head coverings, and protective eyewear.

The specific protective equipment required will depend upon the grade of room in which the operator is working. The highest level of protection is for zones A/B where the aseptic manipulations are performed (BSC in a Grade B room). Examples of PPE required are shown in Table 6.

(a) Gowns

The use of disposable coveralls or gowns made of non-linting and non-absorbent polyethylene-coated polypropylene material is recommended.[6] The gown used should have the following characteristics:

- Long and closed at the neck
- Long sleeves with cuffs gripped at the wrist
- Disposable sleeve covers to protect the wrist and lower arm
- Waterproof material for the front and sleeves
- Sterile
- Non-linting

Integrated coveralls which include head and foot coverings are very suitable in terms of both microbiological and chemical contamination.

Table 6. Clothing required for differing grades of environment[2]

Grade of Room	Requirements for PPE
Grade D	Hair/Beard Covering Normal Protective Clothing
Grade C	Hair/Beard Covering Clothes gripped at wrist with raised Collar Clothing must not shed fibres or particles
Grade A/B	Hood or other head covering Mask Sterile, Non-powdered gloves Sterile or disinfected boots or overshoes Sterile clothing which must not shed fibres or particles Sterile clothing must be capable of retaining particles shed by operator

(b) Overshoes should be worn:

- If shoes are worn in the production zone. Dedicated shoes should be used for this purpose.
- In the event of any accidental contamination

(c) Masks

Surgical masks should be used during production in cleanroom. A mask (type P2 or P3 for solids and liquids) is required when changing the pre-filter, in the event of any accidental contamination and for oral preparations. Common surgical masks offer no protection against aerosols.

(d) Protective Goggles

Goggles are recommended when any projection risk is present. In most cases the glass screen of the biological safety cabinet should offer adequate protection against any possible spray of solutions during cytotoxic reconstitution. Goggles must be worn when cleaning a spill. See Section 14.

(e) Gloves

Gloves used must be proven to be resistant to chemotherapy and labelled as chemotherapy gloves. Gloves used should have the following characteristics:

- Sterile, non-powdered
- Latex (consider latex-sensitive workers), nitrile, or neoprene gloves may be used if they have been validated for the specific purpose of cytotoxic reconstitution

A double pair of gloves may be used. The outer glove must extend over the cuff of the the gown. Gloves should be changed at least every 30 minutes or whenever damage or obvious contamination occurs. Gloves should not be decontaminated with alcohol.

(f) Hair Covering

The hair must be covered with a separate head covering or an integrated hood of a coverall. Men with beards may need to wear a separate covering for this purpose

(g) Personal protective equipment for Isolator and BSC III users

The gowning procedure will depend on the grade of the room where the isolator or BSC III is located (see above table 2). In addition, personal protective equipment has to be considered for tasks performed outside the barrier enclosure where the risk of chemical contamination is present (e.g. handling vials).

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Section 7 – Special devices

In the late 1990s, much information became available concerning the possible occupational exposure to cytotoxic drugs and environmental contamination with these agents. These problems may arise during routine handling of the drug vials or ampoules, during an aseptic preparation process, or during the administration of the cytotoxic drug.

These observations have been confirmed objectively by examinations using fluorescein dye and direct analysis of the product by wipe sampling.

Around this time, pharmaceutical companies began to promote special devices for the reconstitution and administration of cytotoxic drugs. The aim of these devices is to prevent or minimize any possible contamination.

These special devices may be considered in 3 categories:

(a) Devices to protect the handler of the vial/ampoule
(b) Devices to protect the operator during preparation
(c) Devices to protect the administrator during administration of the cytotoxic drug to the patient

7.1 Devices to protect the handler of the drug vial or ampoule

In the late 1990s, several studies indicated that vials and ampoules delivered from pharmaceutical companies may be contaminated on the outside with the cytotoxic drug. In some cases contamination was detectable in up to 30 to 50% of the vials examined.

This was the result of contamination during the manufacturing process (for example, foam forming or dust from powder form of drug) and/or inadequate washing of the vials before packaging. Many companies have now focussed more attention on this problem but with different levels of success.

It is strongly recommended that cytotoxic drug vials be enclosed in plastic coating in order to contain any possible contamination on the outside of the vial. This plastic coating should also cover the bottom of the vial. Many manufacturers now supply cytotoxics in plastic shrink wrap for this purpose.

Some manufacturers supply their cytotoxic agents encased in specially designed moulded plastic containers to contain any possible contamination, and also to protect against any shock during transport.

Some manufacturers supply their cytotoxic agents encased in specially designed moulded plastic containers to contain any possible contamination, and also to protect against any shock during transport.

Many manufacturers now supply cytotoxic agents in this way.

Individual packaging in shock absorbent material is required.

Test reports should document the ability of the packaging to adequately contain all contents in the event of a cracked vial or ampoule

It is the responsibility of pharmaceutical manufacturers to guarantee that the external surfaces of drug vials are free of contamination. One objective way to ensure commitment to deliver contamination-free products is to mandate analysis by an independent laboratory, detailing the amounts of product on the outer surface of the first, middle, and last vial/ampoule of the batch prepared. See also Section 2.1.6. Pharmacists should favour manufacturers who take this problem seriously and are prepared to work to ensure contamination-free vials.

7.2 Devices to protect the operator during preparation

Numerous studies have shown that aseptic manipulation using a classic syringe and needle technique almost universally results in contamination. Droplets, leakage from vial stoppers after multiple punctures, and aerosol generation resulting from increased pressure inside drug vials have also been observed. Some measures have been employed to protect operators using this classic technique. This includes the use of Luer connections on needles and syringes to minimise the risk of separation. To reduce the risk of high pressure syringing, wide bore needles (18 G/1.2 mm) are preferable when reconstituting cytotoxic drugs. The maximum recommended bore size for piercing additive ports is 21 G/0.8 mm. The use of

filter needles is best avoided unless the drug has been removed from a glass ampoule or particulate matter is clearly visible.

Techniques which prevent a pressure differential between the inside and outside of cytotoxic drug vials are recommended. Air venting devices fitted with a 0.2 micron hydrophobic filter may be used for this purpose.

In order to comply with the 2° level in the hierarchy of protection measures, various manufacturers have promoted the use of "closed systems" for the preparation of hazardous drugs.

> It is very important that the term "closed system" is clearly defined.
> A clear distinction must be made between a closed system in the context of microbiological contamination and a closed system in the context of chemical contamination and occupational exposure.

7.2.1 The word "closed" in terms of microbiological contamination

Examples of definitions:

(a) Product is not in open communication with the surroundings.
(b) When a product is in a closed container and the activity is just an addition of a fluid. (Netherlands)
(c) A system allowing the removing and transfer of a sterile product to another sterile container in which the seal and the transfer material (sterile needle, tube or set), remains in place during the whole process. (France)
(d) With toxic products, the removal of fluid from an ampoule in a class A environment is to be considered a closed system. (France)
(e) Aseptic transfer of a sterile, non pyrogenic finished pharmaceutical (e.g. from vials or ampoules) obtained from a licensed manufacture into sterile final container. (United States)
(f) One withdraw out of an ampoule or one puncture trough a rubber stopper of a vial and in a class A environment. (United Kingdom)
(g) A system that tends to provide protection against contamination (WHO GMP)

It is clear that these definitions focus only on the microbiological quality of the end product where the concern is purely introducing micro-organisms into a sterile product. In this context, there is no consideration of the sterile product coming out of the vial or ampoule thus contaminating the environment.

7.2.2 The word "closed" in terms of chemical contamination

Examples of definitions:

(a) Semi-closed system (fluid or powder) When an overpressure occurs in the vial, the air can escape through a venting filter into the surrounding air. (Netherlands)
(b) Closed system (powder): When an overpressure occurs in the vial, the air can **NOT** escape into the surrounding air (Netherlands).
(c) A system which can operate without an open connection between the contaminated inner space and the surroundings during the mixing and preparative procedure. (Quality Standards – DGOP & ESOP)
(d) A drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system. (USA)

The terminology semi-closed is misleading and should not be used, either a system is closed or it is not (in comparison, either a device is sterile or it is not).

The USA (NIOSH) definition is the only definition which includes drug vapours. Filters with a diameter of 0.22 μm and HEPA filters DO NOT retain the vapour of cytotoxic products. Filters with active carbon can absorb vapours on a temporary basis only and therefore should be accompanied with studies indicating the maximum loading, working conditions and the minimum and maximum retention time of the filter capacity.

In cytotoxic reconstitution both microbiological contamination and hazardous drug containment are concerns. The NIOSH definition is therefore the most comprehensive and complete.

Closed System Drug Transfer Device

A drug transfer device which mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system

Manufacturers of special preparation devices must clearly indicate:

(a) If the device covers all steps in the preparation process or if it covers only some of the steps in the process. If the latter applies, then

the manufacturer should indicate clearly where the closed properties of the device are NOT retained.

(b) If the device retains its closed characteristics when more than one vial is used for a particular preparation

(c) If studies have shown the device to fulfil the aim of eliminating or reducing the environmental contamination in daily practice and to what degree.

To avoid confusion, it is strongly recommended that if a device claims to prevent chemical contamination the term used should be Containment Device (This is a Leakproof, airtight device).

7.3 Devices to protect the admistrator during drug administration

Preparation is only one part of the process and many more people are working in drug administration than drug preparation.

Administration systems include infusion bags, infusion lines, ambulatory pump systems, and other materials used in administering a drug by another route. Other routes include direct intravenous injection (IV Push), intraperitoneal, intramuscular, intradermal, intravesical (bladder instillation), and local regional perfusion.

The NIOSH definition of a closed system drug transfer device may also be applied to the administration of hazardous drugs:

A contained administration system is a drug administration device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system.

In addition the manufacturer of special administration devices must clearly indicate:

(a) For which routes of administration the containment is guaranteed.

(b) If the device covers all steps in the administration process or if it covers only some of the steps. If the latter applies, then the manufacturer should indicate clearly where the closed properties of the device are NOT retained.

(c) If the device retains its closed characteristics when more than one administration of hazardous drug is to be performed using the same device

(d) If studies have shown the device to fulfil the aim of eliminating or reducing the environmental contamination in daily practice and to what degree.

It is strongly recommended that if a device claims to prevent chemical contamination during drug administration then the term used should be Containment Device (This is a Leakproof, airtight device).

7.4 Techniques to protect the patient

Considerations may be given to the filtering of cytotoxic drug solutions intended for intrathecal administration. Due to the high risk nature of this route of administration, some sources recommend passing the final solution through a 0.22 micron filter during the reconstitution process. However, there are disadvantages to filtering these solutions. Firstly, some drug volume will be lost on the filter, which may be an important issue if very small volumes are involved. Secondly, the use of a 0.22 micron filter will increase the pressure in the system and will pose a risk to the operator performing the manipulation.

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Section 8 – Ventilation tools

Specific equipment is required for the preparation of parenteral cytotoxics. This includes biological safety cabinets and isolators.

Due to the high risk of exposure to workers, horizontal laminar airflow hoods must NEVER be used when preparing cytotoxics.

8.1 Biological safety cabinets

There are several types of biological safety cabinets (BSC). They are classified (EN 12469 2000) into 3 main classes (I, II, III). A Class I BSC is designed to protect only the operator and the environment and must NOT be used for the preparation of sterile products and will not be described here.

8.1.1 Class II Biological safety cabinets

This is a ventilated BSC that protects the operator, the product and the work environment. A Class II BSC has an open front inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection and HEPA-filtered exhausted air for protection of the environment. There are 4 sub classifications of the Class II BSC (A1, A2, B1, B2).

Only Class II cabinets designed and constructed for cytotoxic preparation should be used. Since some cytotoxic drugs vaporize and pass through HEPA-filters (for example, cyclophosphamide), a BSC where air is exhausted into the workroom must be avoided. Class II A cabinets are not recommended as they are not suitable for the manipulation of volatile toxic chemicals (A1) or for only minute quantities of volatile chemicals (A2) unless special containment devices (leakproof, airtight devices) are used during the preparation (see Section 7). In Class II A cabinets, 30–70% of the air is recirculated within the cabinet. A Class II A1 cabinet has a positive plenum, and a Class II A2 cabinet has a positive plenum surrounded by a negative plenum.

Class II B1 (inflow air partially recirculated) or preferably Class II B2 (total exhaust) are suitable for cytotoxic preparation. Class II B2 cabinets maintain a minimum inflow velocity of 0.35 m/s and have HEPA-filtered downflow air drawn from the workroom or the outside. These cabinets exhaust all inflow and downflow air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the workroom. They also have containment ducts and plenums either under negative pressure or are surrounded by directly exhausted negative-pressure ducts and plenums.

Some countries, for example, Australia, require the inclusion of an activated carbon filter fitted downstream of the exhaust HEPA filter to counter the problem of cytotoxic drugs which may vapourise and pass through the HEPA exhaust filter. However, concerns exist over the effectiveness of activated carbon in removal of these volatile substances. These filters absorb vapour in a dynamic equilibrium with the surroundings. Potentially, if the concentration of the drug in the environment drops, the drug may be released from the filter. Australian Standard AS2567–[1] suggests that the minimum mass of activated charcoal must be 28 g/l/s of airflow. The choice and frequency of changing of carbon filters must be validated during the qualification stages.

8.1.2 Class III Biological safety cabinets

A Class III BSC is a totally enclosed vented cabinet of gas tight construction. Operations are conducted through attached gloves and observed through a non opening view window. This BSC is maintained under negative pressure and air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double HEPA filtration. Passage of material in and out the cabinet is generally performed through a double door pass through box. Class III BSCs have the advantage that there is a physical barrier between the products and the handler. Class III BSCs are an intermediate configuration between a Class II BSC and an isolator. See Section 8.2.1 for comparison of definitions of an isolator and a class III BSC.

Definition of compounding aseptic isolator (CAI) (USP <797>)[2]—The CAI is a form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless it has first passed through a microbially retentive filter (HEPA minimum).

There are four transfer systems used in a Class III BSC.

Transfer system A: ("Mouse Hole"): This is a hole in the wall of the BSC III and there is direct contact between the inside air and the surroundings.

Transfer system B: This is a pass-through hatch without any HEPA filtration. Thus, the risk of contamination of the surroundings and/or inside air of the BSC III exists.

Transfer system C: This is a pass-through with one HEPA filter, but there exists a risk of microbiological contamination with the BSC III operating in negative air pressure, and a risk of chemical contamination of surroundings with the BSC III operating in positive air pressure.

Transfer system D: This is a double door pass-through with HEPA filtration. This may be used but note that it is unable to contain the end product and waste.

According to USP <797>[2] Hazardous drugs as CSP's (Compounded Sterile Preparations):

"Hazardous drugs shall be prepared in an ISO Class 5 (see Table 3, Section 6) environment with protective engineering controls in place, and following aseptic practices specified for the appropriate contamination risk levels defined in this chapter. Access shall be limited to areas where drugs are stored and prepared to protect persons not involved in drug preparation. **All hazardous drugs shall be prepared in a Class II or III biological safety cabinet (BSC), or a compounding aseptic isolator (CAI) that meets or exceeds the standards for CAI** in this chapter. When primary engineering controls, e.g., closed-system vial-transfer devices (CSTD) are used, this shall be within the BSC or CAI to provide backup containment and ISO Class 5 (see Table 1 in Section 6) environment."

8.1.3 Airflow

(a) Within the BSC

In a Class II B1 BSC, approximately 60% of descending air is pulled directly through the rear grille of the work area into a dedicated negative pressure plenum. To enhance containment of hazardous materials within the cabinet, all potentially contaminated zones should be under negative pressure relative to their immediate surroundings. All zones under a positive pressure shall be surrounded by zones under a negative pressure relative to the workroom atmosphere. This air passes through an exhaust HEPA filter, then to an appropriate treatment system or outdoors via the facility's exhaust system. Approximately 40% of the descending air is pulled forward where it mixes with room air entering the perforated front grille. This air then passes through a HEPA filter directly below the work surface, and is then circulated under positive pressure through a duct to the top of the cabinet, then through another HEPA supply filter, where the process is repeated.

(b) Recirculation of Air

In a Class II B1 BSC, some of the air produced by the cabinet is recirculated. Approximately 60% of the air is recirculated through a HEPA filter with the remaining 40% of the air exhausted through a HEPA filter and replaced with fresh air. Due to the potential for chemical contamination of the cabinet during the cytotoxic preparation process, it is preferable to choose a BSC that does not use any recirculated air. In Class II B2 and Class III BSCs the air is not re-circulated.

According to USP <797>[2] Hazardous drugs as CSP's (Compounded Sterile Preparations):

The BSC and CAI optimally shall be 100% vented to the outside air through HEPA filtration.

(c) External Exhaust of Air

The external exhaust of air directly to the atmosphere is highly recommended for the protection of both handlers and the environment. A HEPA filter should be employed for the exhaust air and 100% of the filtered air should be exhausted directly to the outside. An extraction system incorporating a booster ventilator at the distal end to ensure a negative pressure in the pipeline is highly recommended to ensure that the air is effectively and permanently exhausted outside the room. The booster ventilator should be coupled to the BSC airflow to prevent the retro-contamination of the air in the event of failure of the laminar airflow. This means that if the BSC airflow fails and the booster ventilator continues to operate, then dirty air would be pulled into the cabinet from the room, resulting in particulate and microbiological contamination of the cabinet. The booster ventilator should also have an alarm that sounds in the event of failure.

(d) HEPA filtration

The Class II BSC specially designed for cytotoxic preparations must have 3 HEPA filters located in accordance with figure 1:

In Australia, the use of an activated carbon filter downstream of the HEPA exhaust filter is compulsory. Figure 2 shows the possible arrangement of the laminar flow cytotoxic drug safety cabinet in accordance with Australian Standard AS2567 – 2002.[1]

Additional non-HEPA filters (pre-filters) are commonly used to increase shelf life of the HEPA filters. When used, these pre-filters are installed on the upstream side of the exhaust HEPA filter.

(e) Alarms

Airflow alarms that detect insufficient internal airflow or insufficient inflow of air must be installed to indicate a disruption in the cabinet's normal airflow pattern. When the airflow alarm sounds, this represents an immediate danger to the operator and the product. Work should cease immediately and the cause of the disruption investigated. Consideration should be given to the installation of visual rather than audible alarms which may startle operators.

8.1.4 Monitoring

Physical monitoring must be performed on a regular basis. The aim is to monitor whether the BSC is performing to specification. A series of physical tests must be carried out upon installation, whenever changes are made to the installation (for example replacement of a HEPA filter), and on a regular basis as a preventative measure. Physical tests include checking the integrity of the HEPA filters (DOP test), checking the airflow velocity, checking the air circulation (smoke test), checking the airflow retention (KI [Potassium Iodide] disk test), checking the pressure, checking particulate contamination, checking temperature and humidity, and also a noise test. The frequency with which these tests should be conducted varies according to the test. The leak test (BSC Class III and Isolators only) and the smoke test should be performed monthly. Air velocity and particulate count tests should be done every three months, and the DOP test every 6–12 months. These tests are discussed more thoroughly below:

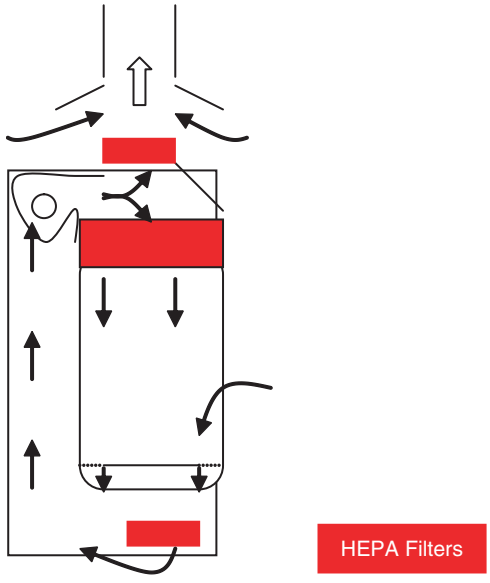

Figure 1. BSC for Cytotoxic Reconstitution The HEPA filter located below the workstation is designed (cassette) to be easily removed during maintenance operations and contributes to operator safety.

(a) HEPA Filter Integrity Test (DOP TEST)[3]

The objective of this test is to check the integrity of all the HEPA filters (inlet, outlet, exhaust, and recirculation if applicable). Each HEPA filter leaves the factory with a manufacturer's certificate. Transport and assembly can affect its performance. It is necessary to test the integrity of the media, lute, seals and assembly of the filter into the BSC. This test may be carried out using the EMERY 3004® aerosol test instead of DOP (Di Octyl Phtalate) which is toxic. The test is usually carried out by applying the aerosol challenge upstream of the filter and measuring the air quality downstream with an aerosol photometer. Acceptance criteria: permeation through the filter must be $<0.01\%$ for HEPA filter type H14 with 99.995% efficiency at MPPS (Most Penetrating Particle Size). In addition there must be no particulate emission detected outside the BSC.

(b) Leak test

The leak test applies only to totally enclosed cabinets (BSC Class III). The objective of the test is to ensure that the enclosure is performing to specification. There are two parameters tested – the presence and position of any leaks and the leakage rate. The leak test is discussed in section 8.2.8 (b).

(c) Smoke test[3]

The objective of this test is to visualize the airflow in order to check the proper circulation of air. The smoke test is a simple test, enabling visualisation of the air circulation. A camera recording makes

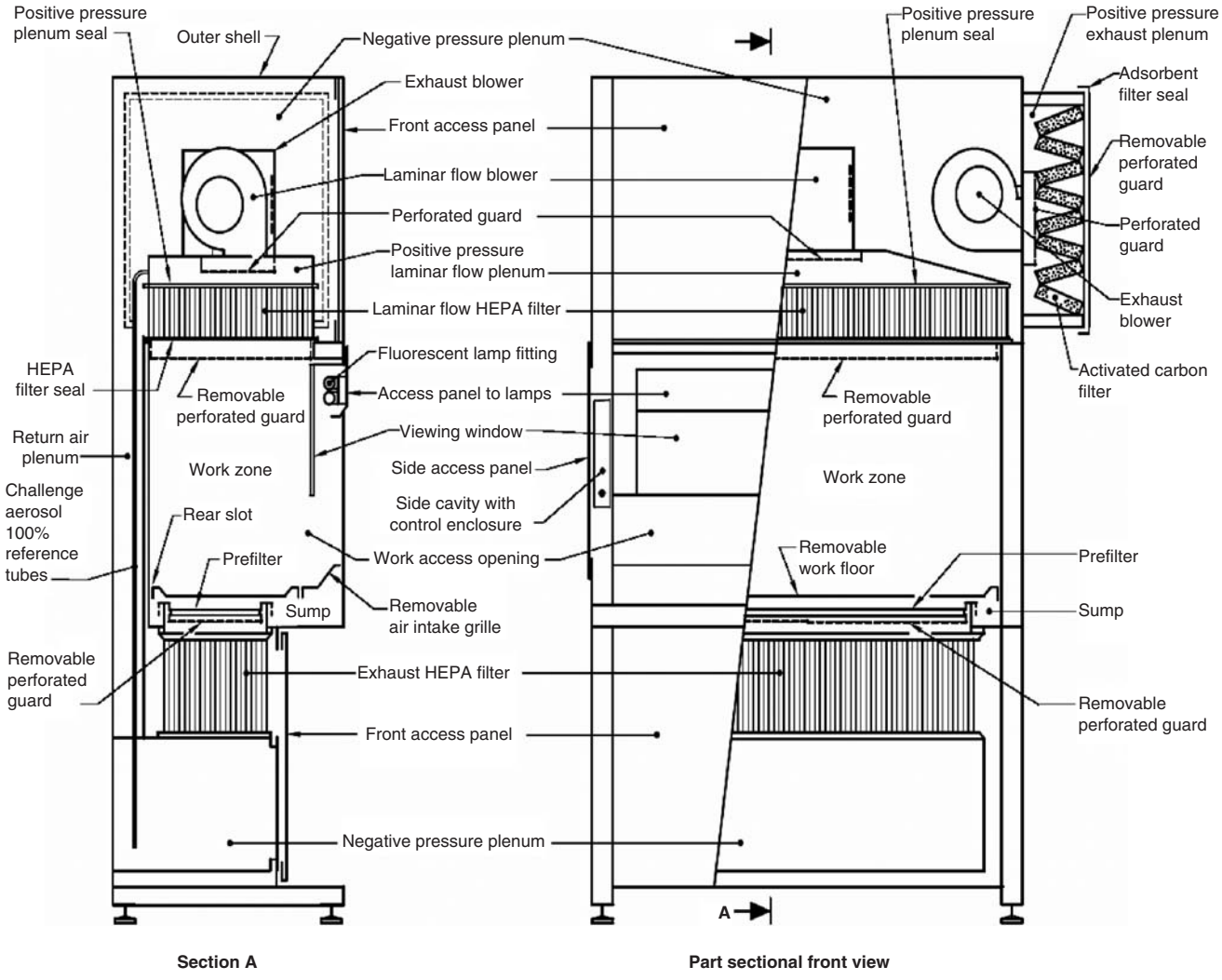

Figure 2. Laminar flow cytotoxic drug safety cabinet.

it possible to obtain an analysis enabling mapping of the air circulation in the cabinet. For unidirectional air flow, the objective is to check its laminarity and the absence of dead zones or turbulence which may result in possible particulate and/or microbiological contamination. For Class III BSCs, where the airflow may be turbulent, this test enables the detection of dead zones. The most common equipment used is a smoke stick (*Dräger*®) of smoking sulphuric acid.

(d) Air velocity test[3]

Airflow velocity is measured using an anemometer. The downflow air speed is measured (between 0.36 and 0.54 m/s) and the mean speed of the incoming air is calculated (minimum 0.4 m/s). At least 8 measurements are done 20 cm from the flow. No value should be different from ±20% of the reference value.

(e) Airflow Retention Test (KI [Potassium Iodide] disk test)

The objective of the KI test is to determine the retention efficacy of a BSC at the front opening. It is measured by creating in the BSC, by means of a rotary disc, an aerosol of a solution of KI and by counting the number of particles detected outside the BSC. The measurement is made by air samplers with a filtration membrane incorporating palladium chloride. The particles of KI show up brown on the filter.

NOTE: A cylinder placed in the front opening makes it possible to simulate the effect of the operator's arm which disturbs the incoming air flow.

(f) Noise test[4,5]

The objective of this test is to check that the noise generated by the BSC during normal operation is not too high for the operators. The sound level meter is installed 1 m from the BSC. The noise level must not exceed 85 dB(A), regardless of the room background noise.

(g) Light level[4]

This objective of this test is to ensure optimum lighting conditions for the operator working at the safety cabinet. The lighting of the BSC and the room is turned on and a mapping of luminous intensity is carried out using a light meter on all working surfaces at several points. The luminous intensity measured during normal operations must be at least 400 Luxes.

(h) Temperature and humidity testing

Temperature and humidity are two parameters that must be controlled both for the comfort of the operators and to reduce the risk of microbiological contamination in the BSC. The equipment required consists of a temperature sensor and hygrometer.

(i) Microbiological testing

Microbiological monitoring must be performed routinely as previously described (see Section 6). The maximum level of microbiological contamination must be investigated by air sampling (active and/or passive sampling) and by surface sampling and must correspond to a Grade **A** environment.[6] Surface sampling must be performed upon completion of the manipulation and before the surfaces are cleaned and decontaminated. Immediately after sampling, the zone must be thoroughly cleaned to avoid any culture medium favouring the microbiological contamination of the zone.

The operator's gloves must be checked by dabbing on an agar plate (the five fingers must be simultaneously printed on the growth medium).

Recommended limits for microbiological contamination of glove are:

1 cfu/glove in a Grade **A** environment (BSC)
5 cfu/glove in a Grade **B** environment (immediate surroundings of the Grade **A** environment)

It is recommended that the biological safety cabinet be left running 24 hours a day, 7 days a week in order to prevent microbiological and chemical contamination.

Frequency of monitoring[7]

Table 1. Minimum frequency of physical monitoring

Pressure differential between rooms	Daily
Pressure differential across filters	Daily on BSC's; Every six months on ceiling HEPA filters
Particle counts	Minimum of twice a year at rest and in operational states
Room air changes per hour	Yearly
Air velocities on work stations	Twice a year
HEPA filter integrity check	Yearly

Table 2. Minimum frequency for microbiological monitoring

Settle plates	Every working session in the Grade A (ISO 5) zone. Once a week in clean room
Surface samples	Weekly
Active air samples	Weekly
Glove finger dabs	At the end of each working session

8.2 Pharmaceutical isolators

8.2.1 Definition

A comprehensive definition of an isolator has been published by the Parenteral Drug Association (PDA) and is found in the PDA Technical Report No. 34[8] Design and Validation of Isolator Systems for the Manufacture and Testing of Health Care Products.

> **"An isolator is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed, it uses only decontaminated interfaces or Rapid Transfer Ports (RTPs) for material transfer. Isolators offer significant advantages over barrier systems: isolators can be decontaminated using reproducible and validated methods, do not allow the entry of airborne contamination from the surrounding environment, and prevent the introduction of personnel borne contamination into the isolator. In contrast a barrier system is an open system which can exchange unfiltered air with the surrounding environment, can only be**

manually disinfected, and is directly accessed by gowned personnel." (See Section 8.1.2 above)

Comparison of Definitions for the BSC III and Isolator

The Class III BSC is a unidirectional laminar airflow cabinet where the front is "closed" by a window fitted with sleeves and gloves to allow the manipulation inside the cabinet. Due to the laminar airflow it operates usually in a negative air pressure. Pass through hatches are used for the entry of products and for the exit of the finished preparation. One hatch is used for entry and one for the exit of the finished product and waste. A manual decontamination process (different from sterilisation) is usually performed in the pass through before materials enter the cabinet. The cabinet is NOT sterile and is NOT sterilized. For cleaning and decontamination of the cabinet, the window of the cabinet may be opened periodically.

An isolator, on the other hand, is a totally enclosed system running usually in positive air pressure with turbulent airflow and which is sterilized by gas sterilization. Products and preparation devices are introduced into the isolator using pass-throughs which are always sterilized.

The two definitions may overlap if the Class III BSC is sterilised and provides an uncompromised and continuous isolation by the use of special transfer systems. Examining the ISO 14644–7[9] can lead to further confusion. Here synonyms include isolator = glove boxes = containment enclosures.

In the area of cytotoxic reconstitution, closed isolators intended for asepsis and containment are recommended because they are well suited to the preparation of sterile and toxic materials. The use of supplementary PPE by the workers is highly recommended especially when handling vials or final products outside the isolator.

Isolator specifications for the preparation of parenteral cytotoxics can be summarised as follows:

The air pressure may be positive or negative. Positive air pressure is most commonly used for aseptic preparation. Negative pressure isolators are also used in this application, but in this case additional measures are required to achieve the necessary level of product protection (for example, the location and surroundings of the isolator). Negative pressure isolators are preferable when asepsis is not required, and when the risk for exposure is high; for example, during the handling of powder forms for solid preparations.

Pressure Differential of the Isolator with the Immediate Surroundings

Positive pressure isolators usually run at operating pressures in the range of +35Pa to +60 Pa.

Negative pressure isolators usually run at operating pressures in the range of −50 Pa to −200 Pa.

For the pressure differential between adjacent rooms, that described in Section 6.2.2 is suitable for isolators. Preferably, the positive differential (rooms) [Section 6.2.2 (a)] should be used for negative pressure isolators, and the negative differential (rooms) [Section 6.2.2 (b)] should be used for positive air pressure isolators.

The PDA position[8] of a "closed isolator intended **for asepsis** and **containment**" has been adopted in the writing of this standard.

For asepsis

They must not exchange air with the surrounding environment except when air passes through a microbially retentive filter (HEPA).

They must be decontaminated in a reproducible and quantifiable manner (avoiding the use of manual decontamination). The decontamination to be used is specified precisely which is gas/vapour decontamination (ie. peracetic acid, hydrogen peroxide). (Decontamination is also called surface sterilization or contact sterilization but the term sterilization has been used in this standard to avoid confusion with manual decontamination by spray).

All work or handling of materials within the isolator enclosure must be accomplished remotely; no human operator or part thereof can directly enter the isolator during operation.

All materials that enter the isolator must be decontaminated or sterilized and must enter either directly or through a decontaminating or sterilizing system or via a rapid transfer port.

For containment

They must not exchange air with the surrounding environment and so an external exhaust must be put in place.

All work or handling of materials within the isolator enclosure must be accomplished remotely. No human operator or part thereof can directly enter the isolator during operation.

All material exiting the isolator must be contained in such a way that hazardous materials are not released to the surrounding

environment. This is done by the use of double interlocking doors fitted with closed containers (for example with the E and F transfer systems). They must be cleanable in a reproducible and quantifiable manner.

Since chemical decontamination is not possible with a wide variety of drugs being handled simultaneously and no universal method of decontamination is available, containment using disposable closed transfer systems for the removal of finished products is highly recommended. Products available include Biosafe® containers (IDC), Tubing® and DPTE - BetaBag® (La Calhène). (See Section 8.2.7 Transfer Systems). The use of these devices ensures the containment of any possible contamination up to the point of opening the package. Nursing staff must still wear PPE when opening the sealed bag, and during administration of the drug.

8.2.2 Isolator design

Isolators are either of a rigid walled design, made from polycarbonate, acrylic glass or tempered glass, or of a flexible wall construction and made from polyvinyl chloride (PVC). The flooring material can be stainless steel (316 L) both for the rigid and flexible wall isolator or a one-piece assembly in which the flexible floor (PVC) and flexible wall are of a single unbroken piece.

8.2.3 Airflow

Airflow in the isolator may be either turbulent or unidirectional (formerly called laminar flow). The air change rate should be determined on a case-by-case basis. Normal data used for conventional cleanrooms are often used for isolators, but may not directly apply.

The following values may be useful:

(a) Under turbulent airflow (non-unidirectional) the air change rate should not be less than 20 air changes per hour. The entire volume of the isolator should be purged by the airflow with no stagnant areas or dead zones (poorly ventilated zones).

(b) Under unidirectional airflow, the average airflow velocity is normally within the range of $0.25\,ms^{-1}$ to $0.5\,ms^{-1}$. As a minimum requirement, the isolator air supply system must be equipped with HEPA grade filters.

The air is continuously renewed and removed via an extraction HEPA filter. The air from inside the isolator is vented to the outside of the building via a ducting system, enabling the dilution of eventual contaminants in the atmospheric air. The length of the extraction system must be as short as possible to avoid any Venturi effect. Airflow alarms that detect insufficient internal airflow or insufficient inflow of air must be installed.

8.2.4 Operator interface

The isolator shall be accessed via a glove port and/or a half suit. The system shall be designed to allow operator access to the interior of the isolator whilst maintaining the aseptic environment and containment within the isolator.

(a) Gloves

The Glove/Sleeve assembly is the device used for aseptic manipulations within the isolator. The glove material commonly used is either Neoprene® or Hypalon® and this material should be of a greater thickness than classic surgical gloves, in the order of 0.4 - 0.6mm. Gloves are potentially the weakest link in the isolator system and they must be visually checked before each use and changed regularly. When changing gloves, an aseptic change procedure must be used allowing the old gloves to be replaced by new sterile gloves. This procedure must ensure containment of cytotoxics and maintenance of sterility. Once removed, potentially contaminated gloves must be immediately discarded with cytotoxic waste.

(b) Half-suits

Half-suits offer greater physical flexibility than gloves/sleeves, and are used for large volume isolators (3–5 m^3). For comfort and operator safety, full ventilation should be used and the air supply may be filtered.

8.2.5 Sterilization

Isolators for aseptic preparation must be surface sterilized (or biodecontaminated) by gas or vapour of peracetic acid or hydrogen peroxide. In the hospital pharmacy, the most widely used system is the « on line » evaporation method, without recycling of the agent in the circuit. Sterilizers consist of a tank in which the sterilising agent is heated to approximately 45°C. The vapours produced are then distributed throughout the chamber using a current of compressed air. As the sterilizing agent is a non penetrating component, contact with all the surfaces to be sterilised must be guaranteed in the course of the cycle. Free circulation of the gas must be ensured by

raising components, repositioning them during treatment, and hanging up gloves and sleeves.

Drug vials and preparation devices must also be surface sterilized before being introduced into the sterilised isolator. The principle of surface (contact) sterilization is that the sterilising gas treats only the surface and does not penetrate into the heart of the load. This presupposes that the interior of any element entering the isolator must be sterile.

Containers or transfer devices are used for that operation. The connecting systems between isolator and pass through should use interlocking double doors to ensure the containment and sterility of the enclosure. Sterilization must be confirmed using biological indicators.

The two sterilizing agents that are commonly used are peracetic acid and hydrogen peroxide. Peracetic acid is easy to use and has long proved its efficacy in hospital pharmacies. Peracetic acid is corrosive and irritant, and precautions must be taken when handling this agent. Consideration should be given to collecting it in a closed system. The absence of penetration of plastic materials must be validated.

Hydrogen peroxide is less corrosive than peracetic acid, but requires stringent control of temperature and humidity. The reproducibility of the load is also an important aspect when using hydrogen peroxide, and this may be difficult to achieve in everyday practice in the hospital setting.

8.2.6 Isolator location (immediate surroundings)

There has been much debate about the requirements and classification of the room in which an isolator is located. The PDA Technical Report No. 34[8] states the following:

> **Classification of the isolator room: There need not be a specific particulate clean air classification requirement for the room surrounding isolators. Regardless of their specific usage, properly designed isolators do not allow the exchange of contaminants with the surrounding environment. Therefore, the quality of the surrounding room is a very minor consideration relative to the quality of the internal environment of the isolator. The surrounding room should have a limited access, and should be easily cleanable and well organized. On the other hand, the EC GMP recommends at least a Grade D environment without specifying the pressure differential, and giving no precise details about the isolator pressure.**

Taking into consideration the risk of chemical contamination, the negative pressure differential design (see Section 6.2.2) for the positive air pressure isolator and the positive pressure differential design (see Section 6.2.2) should be implemented. With regards to the risk of microbial contamination, a negative pressure isolator used for aseptic preparation of cytotoxics should preferably be located in a Grade **C** controlled area (see Section 6 – Facilities for Cytotoxic Reconstitution).

8.2.7 Transfer systems

A transfer system should be used which guarantees the sterility of the final product and the containment of cytotoxic drugs. Double interlocking doors and closed transfer systems should be used. For exit of end products, the use of interlocking double doors fitted with a sterile disposable container ensures containment of the toxic product.

The sealed, sterile container associated with a female door is positioned and sealed over the male door. Once in position, communication is possible between the isolator and the sealed sterile container (it is then possible to open the door) enabling the removal of the preparations made in a closed system in the sealed plastic bag. (See Section 8.2.1).

Only the use of transfer systems E and F guarantees permanent enclosure of contents and protection of the operator. All other transfer systems are suitable for aseptic preparation if the isolator is running in positive air pressure, but are not thought to be suitable for chemical containment.

Transfer system A ("Mouse Hole")**:** NOT TO BE USED. This is a hole in the wall of the apparatus and there is direct contact between the inside air and the surroundings.

Transfer system B: NOT TO BE USED. This is a pass through hatch without any HEPA filtration and so there exists the risk of contamination of the surroundings and/or inside air of the apparatus.

Transfer system C: NOT TO BE USED This is a pass through with one HEPA filter, but there exists a risk of microbiological contamination with the apparatus operating in negative air pressure, and a risk of chemical contamination of surroundings with the apparatus operating in positive air pressure.

Transfer system D: NOT TO BE USED. This is a double door pass through with HEPA filtration. This may be used but it is important to note that this system does not to contain the end product and waste.

Transfer system E: This is a pass through with double doors and double HEPA filtration which is always gas sterilised (with or without load) before connection with a previously sterilised isolator. The device is usually dedicated for the entry of products into the sterile area of the isolator

Transfer system F: This system (rapid transfer system) has double interlocking doors, allowing the connection between two separate sterile enclosures (for example, isolators and disposable plastic sterile containers). The F transfer system is usually used for exit end-product in a sealed plastic container without contact with the surrounding environment. It preserves both the sterility of the product and provides containment of any chemical contamination. The double interlocking doors will also allow the connection between two sterile isolators without affecting the integrity (seal) of the enclosure.

There are other sealed removal devices available, including tubing and bin removal. Bin removal enables the removal of waste in a sealed bag without any contact with the outside environment. This is quite distinct from the removal system used for finished preparations

8.2.8 Monitoring

Monitoring must be performed on a regular basis. The goal of monitoring is to determine whether the isolator is performing to specification. Physical tests should have been conducted during the installation of the isolator, and on a routine basis after that as preventive measures. In addition, tests must be repeated whenever changes are made to the installation (i.e. changing of HEPA filters). Physical tests are integrity checks of HEPA filters (DOP testing), airflow velocity for unidirectional airflow isolators, air circulation (smoke test), leak testing, pressure checks, particulate contamination, temperature and humidity, and a noise test.

The leak test should be performed on a monthly basis, the particle count every three months and the DOP test every 6-12 months.

(a) HEPA Filter Integrity Test (DOP TEST)

HEPA-filters must be assessed as previously described in Section 8.1.4 (a).

(b) Leak Test

The sealing of an isolator is an essential and critical factor that must be regularly checked. The objective of the test is to ensure that the enclosure is performing to specification. There are two parameters tested – the presence and position of any leaks and the leakage rate.

Location of any leak

The principle of this test is based upon the evaporation of ammonia inside the chamber and of tracing leaks manually using a developer impregnated with bromophenol. Bromophenol changes colour in the presence of ammonia. To perform the test, a container with a large evaporation surface of ammonia solution is left open inside the chamber that is raised to a maximum overpressure of 100 Pa. After approximately 15 minutes, when the chamber has been saturated with the ammonia, the developer is placed over the entire surface of the envelope and the seals. Any change in colour from yellow to blue indicates the presence of a leak. Other methods may be used but require more complex equipment, for example, the Freon® method, where the ammonia is replaced by Freon®.

As for the isolator gloves, a simple test for their integrity involves filling the gloves with compressed air and then immersing them in water. Any microperforations will produce bubbles. However, this simple and sensitive method for testing the integrity of gloves is not recommended in the case of handling toxic products. The risk of chemical contamination of the environment is too high. In this case it is preferable to systematically change gloves, depending on their thickness and physical strength. It is possible to test the integrity of the gloves using a negative pressure technique. This means that the gloves may be tested in situ without any outside handling. However, this is an expensive procedure and is difficult to perform with gloves that are part of a half suit.

Leak rate[10]

The objective of this test is to determine the leak rate of the isolator (Lr) by pressure drop. The test pressure must be 20 or 50 Pa above the working pressure. For example, 100 Pa for a flexible wall isolator and 150 Pa for a rigid wall isolator. When the test pressure is reached, the pressure drop is recorded with a manometer for one minute. Temperature must be controlled during the test and temperature variation must be no more than $\pm 0.05^{\circ}$C. Common values of Lr are 0.1% for a

flexible wall isolator (test pressure 100 Pa) and 0.5% for rigid wall isolator (test pressure 150 Pa).

(c) Smoke Test

The smoke test must be performed as described in Section 8.1.4 (c).

With an isolator where the airflow may be turbulent, this test enables the detection of dead zones.

(d) Air Velocity Test

For isolators with unidirectional airflow, this test must be preformed as described in Section 8.1.4 (d).

(e) Noise Test

The noise test must be performed as described in Section 8.1.4 (f).

(f) Pressure Differential Test

The pressure of the isolators must be continuously monitored, and alarms must be used to detect pressure failure. The pressure regulation should be checked using a reference manometer. This test allows the evaluation of the reaction time of the isolator when the pressure is altered following operations such as introducing and withdrawing gloves, entering and exiting the half-suit, and connection to an additional volume. The aim of the test is to ensure that the pressure regulation at rest is stable. The test can also be used to determine that the pressure alarm values are compatible with the normal operation of the isolator.

(g) Air Change Rate[3]

The air change rate per hour of the isolator (in V/h) is determined by the ratio of the inlet airflow rate divided by the volume of isolator. Instantaneous speed measurements are recorded by an anemometer. The flow rate is obtained using an average value. The result must be in accordance to the specification of the isolator. For positive air pressure isolators of 1 m^3, a value of 20 Volume/hour is acceptable.

(h) Microbiological Monitoring

Microbiological monitoring must be performed routinely as previously described (see Section 6). The maximum level of microbiological contamination must be investigated by air sampling (active and/or passive sampling) and by surface sampling and must correspond to a Grade **A** environment.[6] Surface sampling must be performed upon completion of the manipulation and before the surfaces are cleaned and decontaminated. After sampling, the zone must be immediately and thoroughly cleaned to avoid leaving behind any culture medium likely to encourage the microbiological contamination of the zone.

The operator's gloves must be checked by dabbing on an agar plate (the five fingers must be simultaneously printed on the growth medium).

Recommended limits for microbiological contamination of glove are:

>1 cfu/glove in a Grade **A** environment (BSC)
5 cfu/glove in a Grade **B** environment (immediate surroundings of the Grade **A** environment)

(i) Particle Counts[11]

The objective of this test is to check that the concentration of particles found within the isolator is in accordance with the specifications of a Grade **A** environment (see Section 6).

The probe of an optical particle counter is the only device which has to be positioned inside the isolator. The locations tested should be those where critical functions are carried out. Examples include work stations, connection and junctions with gloves, sleeves, and doors.

(j) Efficiency of Sterilization

The objective of this test is to check the efficiency of the surface sterilization using Biological Indicators (B.I.). Each B.I. is inoculated with a 6 log of spore of *Bacillus subtilis* or *Bacilus stearothemophilus* and they are distributed at distinct locations within the isolator, with particular emphasis on the critical zones (for example: near doors). After exposure to the sterilizing agent, the BIs are inoculated in culture medium (Tryptocaseine soya) and incubated for 14 days at adequate temperature according to the BI (55–60°C for *Bacillus stearothermophilus* or 30–35°C for *Bacillus subtilis)*. No growth must be found after 14 days and a reduction of 6 log must be achieved on three consecutive tests.

In addition, an aeration test must be performed after a complete sterilization cycle. The aim of this test is to determine the aeration time required to obtain a residual concentration of the sterilizing agent compatible with the safety of operators, the environment and the end product. A reactive *Dräger*® tube (sensitive to hydrogen peroxide or peracetic acid) may be used to perform this test. An aeration delay is defined after the aeration test depending on the cycle of sterilisation, ventilation procedure and the volume of the isolator.

It is recommended that the isolator be left running 24 hours a day, 7 days a week in order to help prevent microbiological and chemical contamination.

Frequency of monitoring[7]

Table 3. Minimum frequency of physical monitoring

Laminar flow cabinets (LFCs)/Biohazard Safety Cabinets (BSCs):	*Frequency*
Pressure differentials between rooms	Before beginning of work, usually daily
Pressure differentials across HEPA filters (workstation)	Before beginning of work, usually daily
Particle counts	Yearly at rest and in the operational state
Room air changes per hour	Yearly
Air velocities on workstations	Yearly
HEPA filter integrity checks	Yearly
Isolators:	
Isolator glove integrity	Visual checks every session
Pressure differentials across HEPA filters	Before beginning of work, usually daily
Isolator pressure hold test (with gloves attached)	Weekly

Table 4. Minimum frequency for microbiological monitoring

Settle plates	Every working session in the Grade A (ISO 5) zone Once a week in clean room
Surface samples	Weekly
Active air samples	Weekly
Glove finger dabs	At the end of each working session

8.3 Validation and certification

All equipment and processes used in the preparation of parenteral cytotoxics which affect product sterility or product attributes should be validated and/or certified. Documentation to this effect should be approved, maintained, reviewed and signed off by a designated pharmacist.

For Certification see Section 6.2.12.

For Process Validation see Section 6.2.13.

Most of the monitoring tests described above may be used for Operational Certification (OC) and/or Performance Certification (PC). Commonly applied tests are listed in Table 5.

Table 5. Common tests performed during operational and performance certification

Test	BSC – Cleanroom	Isolator	OC	PC
HEPA Filter Integrity Test (DOP)	✓	✓	✓	N/A
Airflow: check Unidirectional Flow and Air velocity	✓	✓(1)	✓(2)	✓(3)
Leak Testing of the Enclosure	✓(4)	✓	✓	✓
Air Distribution Studies	✓	✓	✓	✓
Air Change Rate per Hour	✓	✓	✓	✓
Particle Counting	✓	✓	✓	✓
Pressure Regulation and Alarm	✓	✓	✓	✓
Sterilisation	N/A	✓	✓(5)	✓(6)
Aeration/Ventilation after Sterilisation	N/A	✓	✓(5)	✓(6)
Noise Level	✓	✓	✓	N/A
Light Level	✓	✓	✓	N/A
Checking Procedure	✓	✓	N/A	✓

Note: This is not an exhaustive list. (N/A = not applicable)

(1) Applies only to isolator with unidirectional airflow
(2) Without final equipment (for example, shelving, filling pump)
(3) With final equipment
(4) Applies only to Class III biological safety cabinets
(5) Without load
(6) With load.

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Section 9 – Non sterile preparations

Occasionally, oral cytotoxic drugs (tablets, capsules or syrup) or the topical application of a cytotoxic drug may be used by the physician. As more and more agents become available for use by the oral route since this route of administration is becoming more important. This is also an important consideration in paediatric oncology.

The crushing of tablets and the mixing of powders goes hand in hand with the generation of airborne particles of the products used, and is to be avoided wherever possible. The crushing of cytotoxic tablets or the opening of capsules in an open mortar should be avoided. For mixtures, many tablets may be dispersed in pre-calibrated bottles. Single dose mixtures are recommended. Staff are vulnerable to contamination by either direct contact or by the inhalation of these potentially toxic products. The hierarchic order in prevention, as highlighted in Section 5 is also applicable to this kind of activity. As replacement or the use of a contained system is unlikely, reliance is on ventilation and the use of personal protective equipment.

As a general rule, the opening of capsules, crushing tablets, and dissolving powders should not be done outside of the pharmacy.

The extemporaneous preparation of cytotoxic drugs should be performed under the same conditions as for parenteral cytotoxic drugs. This operation should be carried out in a separate room specially dedicated to this purpose

Tablets and capsules must be handled in a manner that avoids skin contact, liberation of drug into the air, and chemical cross contamination with other drugs. All equipment used in the dispensing of cytotoxic solid dosage forms must be dedicated to this purpose and clearly labelled as such. Cytotoxic tablets or capsules should not be counted using a counting machine. Containers with damaged contents should be discarded.

As in the case of preparation of sterile cytotoxic drugs, the preparation of non sterile drugs should be performed **in a separate room**, specially dedicated to this purpose. This room must have a warning sign outside the room and must be restricted in access to trained staff only.

The room should operate at negative pressure, thus minimizing the risk of spreading the "dust" of products throughout the rest of the pharmacy.

All activities likely to result in particle generation, for example, weighing, crushing, mixing or filling capsules, should be performed in a Class I Biological Safety Cabinet (BSC). A Class I cabinet extracts the air from behind the operator, flowing over the arms, hands and the product itself before being exhausted via the top of the cabinet.

A Class II B2 could also be used, but this cabinet should not be used for a mixed activity of sterile and non sterile preparation. This is because of the liberation of powders and other particulate contamination into the clean room. The risk of this type of contamination is high. Possibly some disposable system would be a better option (for example, bag fitted with gloves for containment in laboratory). In addition, a negative air pressure BSC III (MUST be negative) is an alternative to a dedicated BSC Class II B2. Normally a HEPA filter is located within the cabinet exhaust. An additional filter such as an active carbon filter may also be installed.

In order to create a negative pressure in the pipeline of the ducting system, the extracted air should be ventilated to the external environment, supported with booster ventilation on the rooftop.

As for the cabinets used for the sterile preparation, these cabinets should also be validated, preferably every 6 months.

Hygiene conditions similar to those described for the preparation of sterile products also apply to the preparation of non sterile products; no eating, drinking or smoking is permitted.

In addition, personal protective equipment must be used by the personnel. This consists of gowning, the use of non sterile gloves and a mask (P2-3 in Europe/Australasia, N95 in North America) in the case of cleaning activities inside the class 1 cabinet or in the event of spills or other incidents.

All equipment used in the extemporaneous preparation of cytotoxics must be dedicated to this purpose and clearly labelled as such. This equipment should be cleaned immediately after use with a strongly alkaline solution.

Section 10 – Chemical contamination monitoring

10.1 Background

Exposure to cytotoxic drugs in the workplace may result from one or more of the common routes of exposure. While dermal and inhalation routes are likely to be the primary routes of exposure to cytotoxic drugs in health care facilities, hand-to-mouth exposure or accidental needle sticks may also contribute to exposure.

Therefore, surface wipe sampling and sampling for airborne drugs have been the two main procedures for determining work place contamination with cytotoxic drugs. To determine the level and extent of contamination of the workplace and to establish safe working levels for hazardous substances, these methods have been employed routinely in many other occupational settings

10.2 Sampling strategies

The primary method employed for monitoring of chemical (cytotoxic) contamination in the health care facility has been the recovery of a number of marker cytotoxic drugs from wipe samples.[1] Relatively sensitive sampling and analytical procedures have been developed for some of the more commonly used cytotoxic drugs and have been employed as markers of overall surface contamination. The more common drugs sampled include: cyclophosphamide, ifosfamide, 5-fluorouracil, methotrexate, paclitaxel, doxorubicin, and platinum containing drugs (e.g. cisplatin and carboplatin).[1]

10.2.1 Surface contamination sampling

Studies of surface contamination with cytotoxic drugs typically employ a collection matrix (e.g. tissue or filter paper wipes) and a solvent system proven to aid recovery of the drugs being studied.[1] Specific strategies have been developed for collecting wipe samples for other chemicals in various industries and these have been applied to the sampling of cytotoxic drugs.[2,3] Based on published studies, a sampling scheme should be developed for the health care facility to incorporate the areas of interest. Any program designed to examine surface contamination for cytotoxic drugs in the health care facility must have the resources to carry out the appropriate analytical techniques necessary to identify and quantify the drugs that are being measured. Several analytical methods have been employed by researchers and are available in the published literature.[1]

These include high-performance liquid chromatography with ultraviolet detection (HPLC–UV), gas chromatography coupled with mass spectrometry or tandem mass spectrometry (GC–MS or GC–MS–MS) or high-performance liquid chromatography-tandem mass spectroscopy (LC–MS–MS). With the use of CG–MS (or GC–MS–MS) for drugs such as cyclophosphamide and ifosfamide, derivatisation is required prior to analysis.[4] Platinum containing compounds can be analysed using either voltammetry[5,6] or inductively coupled plasma mass spectrometry (ICP–MS).[7,8]

If contract laboratories are used to analyze surface wipe samples, the methods used for collection, storage and shipping must be carefully documented and controlled. Both negative (blanks) and positive (spiked samples) controls should be included for analysis and samples should be coded so that they are analysed blindly.

Since the early 1990s, studies by a number of researchers have examined environmental contamination of areas where cytotoxic drugs are prepared and administered in health care facilities.[4,6,7,9–21] Using wipe samples, all investigators measured detectable concentrations of one or more hazardous drugs in various locations such as surfaces in biological safety cabinets (BSCs), pharmaceutical isolators, floors, counter tops, storage areas, tables and chairs in patient treatment areas, and locations adjacent to drug-handling areas. All of the studies reported some level of contamination with at least one drug, and several reported contamination with all the drugs for which assays were performed.

Several studies have documented that the outer surfaces of cytotoxic drug vials are often contaminated with the drug contained in the vial.[9,22–27] Various methods have been utilized to measure the amount of drug on the outer surface of the vials.

These include wipe sampling, rinsing and total emersion of the vials using a suitable solvent. However, because of the nature of the surfaces being sampled, it is difficult to determine the recovery efficiencies with drug vials. Once the samples are collected, analytical methods similar to those that have been used for surface wipe sampling can be utilized for determination of the external contamination levels.

10.2.2 Air sampling

To a lesser extent, air sampling for cytotoxic drugs has been used to evaluate environmental contamination of workplaces where cytotoxic drugs are handled. The most commonly used drugs in air sampling studies include: cyclophosphamide, ifosfamide, 5-fluorouracil, and methotrexate.[1]

Several studies have measured airborne concentrations of antineoplastic drugs in health care settings.[4,5,10,18,28–33] In most cases, the percentage of air samples containing measurable airborne concentrations of cytotoxic drugs was low, and the actual concentrations of the drugs, when present, were quite low. Most studies have employed glass fiber or paper filters to capture airborne particulates. These low results may be attributed to the inefficiency of sampling and analytical techniques used in the past.[33] A solid sorbant material may be more efficient at collecting particulate forms of cytotoxic drugs. Both particulate and gaseous phases of one antineoplastic drug, cyclophosphamide, have been reported in two studies.[18,33] Many occupational studies have established exposure levels for toxic chemicals. However, no exposure levels have been established for airborne concentrations of cytotoxic drugs. There are, however, some exposure limits set for soluble platinum salts and inorganic arsenic which would include some of the cytotoxic drugs such as cisplatin, carboplatin, and arsenic trioxide.[34,35] Some pharmaceutical manufacturers have developed occupational exposure limits (OELs) that are used in manufacturing facilities.[36] However it should be noted that within the pharmaceutical industry, OELs have been established where a single drug is handled in an almost fully automised production line.

The situation within a hospital pharmacy is completely different and this makes the use of OELs inappropriate. For genotoxic products, there is no such thing as a safe or maximal exposure limit and zero contamination should be the target.

10.2.3 Biological monitoring

A number of methods have been employed to monitor worker exposure to cytotoxic drugs. These include: determining the mutagenicity of urine of workers, or measuring endpoints such as chromosomal aberrations, sister chromatid exchanges and micronuclei induction in white blood cells of the workers. Other studies have measured HPRT mutations and damage to the DNA. However, these endpoints are non-specific and can be affected by smoking and other factors. More recently, the determination of cytotoxic drugs and/or their metabolites in the urine of workers has been employed for monitoring worker exposure to these drugs.[1] This method is very specific for the drugs being analyzed and can be very sensitive, depending on the drug and the analytical procedure that is used. The same drugs that have been assayed for in the environmental sampling studies are typically those used to monitor worker exposure and, to date, have been used primarily in research studies and not for routine monitoring.

The analytical procedures employed in monitoring worker exposure to cytotoxic drugs in the urine are similar to that for the environmental sampling. Urine samples are collected from potentially exposed workers and they may be concentrated or extracted by various procedures.[4,5,7,9,19,37-51]

The analysis of cytotoxic drugs in the urine has been used to determine if workers have been exposed to these drugs. However, because there are no established limits for cytotoxic drugs in the urine, this procedure has only been used on a research basis. Cyclophosphamide, ifosfamide, 5-fluorouracil, methotrexate, and platinum-containing drugs have been the most commonly measured drugs in studies reported in the literature.[1]

10.3 Alternative techniques

The use of fluorescent markers has been employed in some situations to simulate environmental contamination with cytotoxic drugs. Kromhout *et al.*[52] developed a semi-quantitative fluorescent method to evaluate environmental contamination and Spivey and Connor[53] employed a fluorescent marker to demonstrate sources of environmental contamination during simulated drug preparation and administration. Prepared test kits that utilize a fluorescent marker are available to evaluate worker skills and training during drug preparation and administration.[54]

A combined test (visual under ultraviolet light, and a quantitative measurement using a fluorimeter) using quinine hydrochloride as a marker has the advantage that the base is colourless and that the gloves, worksheets etc., can pass a quantitative test indicating the precise amounts of spillage during activities.[55]

Conclusions

Contamination of areas where cytotoxic drugs are prepared or administered has been well documented in a number of studies from countries in many parts of the world. Drug vials themselves are known to be contaminated with the drug that is contained in the vials. Since the majority of worker exposure results from dermal or inhalation routes, surface wipe sampling and air sampling have been employed to estimate the level of environmental contamination in areas where cytotoxic drugs are handled. Sensitive methods have been developed for a number of the more commonly used cytotoxic drugs, but, since there are many cytotoxic and other hazardous drugs in use in the health care setting, studies can only estimate what the actual total exposure might be.

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Section 11 – Checking procedures

Ideally, pharmacists should receive a computerised prescription or at least a printed prescription. The prescription should comply with the following medication safety principles:

All orders written with the full generic name of the drug
No abbreviations should be used (eg. CDDP for Cisplatin is not acceptable)
Spell out the word "units" as this could be mistaken for a zero
A leading zero should always be used (eg. 0.5 mg and not .5 mg)
A trailing zero should never be used (eg. 2mg and not 2.0 mg)

Where possible, the clinical oncology pharmacist who reviews the chemotherapy prescription should not be the same pharmacist involved in the preparation process. There should be as many independent checks as possible built into the checking system. Standard operating procedures should be developed which include signed documentation that all the required checks have been carried out. To allow later analysis and possible future preventative action, any problems detected and rectified should be recorded.

An institution may develop a standardised worksheet for every patient that includes the date, patient demographics, chemotherapy regimen, doses and volumes of each drug, and any other special instructions.

11.1 Clinical checks

It is recommended that before chemotherapy is prepared the prescription is reviewed by a clinical pharmacist. This clinical oncology pharmacist should work with other health professionals in ensuring optimal drug therapy for patients with cancer. Much of this clinical work is beyond the scope of this document, but there are several essential checks that should be completed before preparation work begins.

11.1.1 Chemotherapy regimen

The chemotherapy regimen used must be documented on the patient's profile. A set of standard protocols used by the institution should be developed. The pharmacist should work with other health professionals in the design of both chemotherapy and supportive care pathways aimed at developing optimal drug therapy for patients with cancer. In order to maintain best possible practice, it is important that these treatment protocols are reviewed and updated regularly. A standard procedure must be followed in the case of non-compliance with a standard protocol or the use of a non-standard protocol. It is recommended that deviation from a standard protocol occurs only after consultation with the senior medical officer responsible for the patient. With each treatment, the pharmacist should verify the cycle number, day of cycle and that the appropriate time interval has passed since the previous treatment. The pharmacist should document agreed upon changes including any relevant reference citations.

11.1.2 Patient profile

It is recommended that pharmacy-based profiles be established and maintained for all patients receiving chemotherapy. To do this effectively, pharmacists must have easy and ready access to patient profiles which include, height, weight, calculated body surface area (BSA), treating physician, disease and stage, chemotherapy regimen, aim of therapy, relevant laboratory measurements, allergies and adverse drug reactions, and past and current medications. This information must be current, and referred to prior to each administration of chemotherapy.

11.1.3 Body surface area (BSA)

The pharmacy department must have procedures in place for checking the body surface area calculated by the prescriber. If possible, this should be an automated function of the computer program used in processing cytotoxic prescriptions. A standard operating procedure should be developed which includes signed documentation that this check has been carried out. Any corrective action taken by the pharmacist should also be documented.

11.1.4 Dose calculations

The prescription must be checked against the chemotherapy regimen being used. Doses calculated by the prescriber must be rechecked by the pharmacist using the checked BSA against the appropriate treatment regimen. Consideration must also be given to the patient's renal and hepatic function and any possible drug interactions. When possible,

the calculation function should be automated in an electronic prescription and patient dossier. An institution may also choose to set a maximum daily dose and maximum cumulative dose parameter within the checking system. It must be documented that this check has taken place and any corrective action taken must also be recorded.

11.1.5 Premedications

It must be checked that all appropriate premedications have been included on the chemotherapy order. This may include appropriate anti-emetic therapies, anti-histamines, steroids, fluids, and diuretics.

11.1.6 Laboratory parameters

It is recommended that appropriate laboratory parameters are checked by the pharmacist before cytotoxic preparation commences. This includes full blood examination including differential white cell count, and, where appropriate, serum creatinine, creatinine clearance, liver and lung function tests, and left ventricular ejection fraction. As new agents become available, other tests may be required. If chemotherapy is prepared ahead of time, there must be stringent procedures in place to ensure that chemotherapy is not released from the pharmacy or administered until the appropriate laboratory results have been checked and approved by either the pharmacist or treating physician.

11.2 Preparation checks

There are a number of checks which must be completed at various stages of the preparation process. This will include an assembly check of all raw materials required, a check of dosage and volume calculations and a final check of the finished product including products and volumes used and labelling and packaging. For every preparation, all data should be recorded on a standardised worksheet. Written instructions should be available for the reconstitution, dilution, mixing, labelling, and packaging of all admixtures prepared. There should be a standard procedure in place to retrieve the batch number and expiry of all drugs and diluents used in the preparation of cytotoxic preparations.

11.2.1 Assembly of raw materials

All items required for the preparation of a product should be assembled and then checked by a designated person before entering the safety cabinet or isolator. At this point, the designated person should check that the correct drug and strength has been selected and that the selected reconstitution fluid and infusion bag are appropriate. (This designated person may be a pharmacist or a senior technician given this responsibility). The quantity of full vials and volumes of any partially used vials is checked. The storage conditions and expiry dates of all components should be verified at this time. Labels generated and completed worksheets, if used, should be checked for accuracy. The designated person should sign that this check has been completed.

11.2.2 Preparation

Volumes of drugs should be calculated independently by the operator performing the aseptic manipulation. If this calculation is performed electronically it should be rechecked manually. Preferably, some form of validated computer program should be used if available. If dose-rounding is employed to facilitate easy preparation, this should be documented and standardised. If a volume of drug is added to an infusion fluid, the volume added must be documented by the operator and there must be a system in place to allow checking, particularly if a non-pharmacist performs the manipulation (see Section 11.2.4). The signature of the operator must be recorded against each preparation made.

Only one patient's treatment should be prepared at a time, and only one particular drug should be in the safety cabinet or isolator at any one time.

An institution may choose to select vial sizes closest to the actual dose required. For example, if preparing 70mg doxorubicin, then a 50mg plus a 20mg vial would be used. This approach minimizes the risk of adding too much drug and removes the need to pass cytotoxic solutions back out of the sterile room. This approach also allows the operator to work more independently in the sterile area without multiple volume checks by the pharmacist. Using this method, no unopened or used vials are left in the safety cabinet or isolator for later use. The disadvantage of this approach is that the pharmacy has to stock a range of vial sizes which may potentially lead to selection error.

If multidose vials are used, a procedure must be in place to ensure that the added volume and the selected drug are checked before the preparation is removed from the safety cabinet or isolator. This check must be performed by a pharmacist. Leftover solution should then be kept in a dedicated, visually marked area, for later use. (See also Section 20.5).

The disadvantage of this approach is that volume checking by the pharmacist becomes crucial.

Potentially contaminated vials have to be stored for later use. A validated procedure with regards both chemical and microbiological contamination risk must be in place when keeping partially used vials for later use (See also section 20.5). The advantage of this approach is the reduction in the range of products that have to be stocked by the pharmacy, and will be more economical. In addition, the aseptic manipulation will be simpler, faster, and the whole operation may be safer for the operator.

Procedures must be in place to allow the checking of volumes of drug added to infusion bags. A volume reconciliation method may be used where volumes of drug entering and leaving the safety cabinet or isolator are documented and checked visually by a pharmacist. Some institutions may prefer to check (a) volume marked on syringe before added to infusion bag or (b) used syringes drawn back to the volume of fluid used. Note that (b) may be subject to some recall bias. A product may also be checked by barcode and volume added by weight using integrated balances and software. Whichever method is used, items should be properly sealed before leaving the cleanroom or isolator to prevent contamination.

11.2.3 Finished product

The finished product must be checked by a suitably qualified pharmacist. A volume calculation check should be carried out and the pharmacist must check that all components used are appropriate. A visual inspection of the finished product should be performed by a pharmacist. A system must be in place to allow the checking of volumes used in the preparation process (see Section 11.2.4). Details on the label should be checked including patient name, hospital registration number, drug, dose, fluid, volume, route of administration, duration of infusion, date and time of preparation and expiry, recommended storage conditions and any additional warning or advisory notes. The integrity of the seal of the product should be checked before release. The pharmacist must sign that the final check of the product has been performed.

11.2.4 Non-pharmacist staff

Non-pharmacist staff involved in the preparation of cytotoxics may include qualified pharmacy technicians and pre-registration graduate pharmacists. Different countries will have different requirements for the certification of technicians. They must at least have completed some in-house training to the satisfaction of an experienced pharmacist (See Section 4). Unqualified technicians, unqualified pharmacy assistants and pharmacy undergraduates should not be permitted to prepare these agents.

11.3 Validation

11.3.1 Validation of the product

The objective of validation of the product is to confirm that the processes used will reproducibly result in a product containing the correct constituents at a concentration that is within acceptable limits and that the chemical and microbiological integrity of the product is maintained throughout its designated shelf-life.

Validation of the microbiological quality of the product cannot be performed with conformity to the *European Pharmacopoeia* (sterility test) since preparations are currently adapted for one patient and the final volume of the preparation could be too small to reach the *Pharmacopoeia* requirements. Investigation of the microbiological quality of the final product could be done periodically by a microbiological analysis of extra preparations. The microbiological integrity throughout the product's shelf-life should be tested by the *media fill test*. Alternate methods such as advanced solid phase cytometry can be used as a quantitative and quick test, with results available in less than one hour.

Validation of the concentration of the final product is also difficult to perform. Analytical methods for each cytotoxic drug should be available. The volume of sampling must not affect the final dosage of the preparation to be given to the patient. If an extra volume for sampling is added to the preparation, a risk of error in the final dosage to be given to the patient exists. Methods should be developed during the preparation process to ensure the correct concentration of the final product. Double checking during withdrawing and injection of drug must be implemented. Weighing procedures during the preparation process and on final product check could be a helpful method to guarantee the final concentration. Dosage of extra preparations could also be done periodically.

Chemical integrity throughout shelf-life should be documented using data from international stability studies. Chemical stability is the responsibility of the pharmacist and must take into consideration the following criteria:

(a) Commercial formulation used
(b) Dilution solvent used
(c) Final concentration

(d) Final container used
(e) Storage Temperature
(f) Light protection during storage

11.3.2 Validation of the lack of cross contamination

Cross contamination can be defined as the contamination of one drug with another drug during the preparation process. In the case of cytotoxics prepared in the hospital, many different drugs are simultaneously prepared and the risk of cross contamination cannot be *a priori* dismissed. Nevertheless, the risk is low if the process is performed without opening vials by using containment transfer devices. Taking into account the diversity of analytical methods required, checking of all cytotoxic drugs routinely used is extremely difficult. One method to check cross contamination would be to choose a commonly used cytotoxic drug and to simulate the process with the chosen drug and then search for the drug inside placebo preparations which are simultaneously prepared.

Another method would be to use a tracer instead of the cytotoxic drug and simulate the process in the same way. Special precautions should be taken and special attention paid if the product is of a viable nature, and in the case of gene therapy. Some studies have demonstrated the risk of cross contamination with the use of BCG vaccine and so it is recommended that BCG vaccine is NOT prepared in the same ventilation tool as cytotoxics which will be administered to immuno-compromised patients. The use of one cabinet to prepare both cytotoxics and BCG vaccine is NOT RECOMMENDED.

11.3.3 Validation of computer program

The objective is to confirm that computer hardware and software systems perform to the required standards, delivering an output that is accurate and free of error.

Section 12 – Administration of cytotoxic drugs

Although the administration of cytotoxic drugs is predominantly the responsibility of nursing staff, it is worth highlighting some points of interest.

The safe handling of cytotoxic drugs is a joint responsibility for all departments in the hospital and a multi-disciplinary approach should be taken. The choice of products and devices which are used will have a major impact on daily practice in terms of both cytotoxic reconstitution and administration. For example, the selection of a special containment device for preparation can have implications for the way in which nurses have to administer that drug to the patient. The pharmacy has a very important role to play in the choice of these products and/or devices.

As a general rule, it is clear that safe handling measures do not stop at the door of the pharmacy. Any process undertaken during the preparation of cytotoxic drugs in the pharmacy which may result in contamination outside of the pharmacy must not be permitted.

Nurses may be exposed to the commercial cytotoxic product, or a dilution of this product. If bags or syringes prepared in the pharmacy are contaminated on the outer surfaces, nurses will come into contact with the pure concentrated cytotoxic drug. The same applies when nurses crush tablets or open capsules. During the connection/disconnection of the bag or syringe to the administration device nurses may come into contact with the diluted products, prepared in the pharmacy. The disconnection procedure is a risk for nursing staff and a containment device for administration should preferably be used. Tubing should never be removed from an IV bag containing a cytotoxic drug. Do not disconnect tubing at other points in the system until the tubing has been thoroughly flushed with a non toxic solution. Remove the IV bag and tubing intact whenever possible. Wash hands with soap and water before leaving the drug administration site.

The excreta of the patient can be considered as a second dilution of the drug. (See Section 15).

The same hierarchic order in prevention must be applied for the work of the nurses. If possible, contained systems for parenteral administration should also be used. The use of contained bags with a break-a-way seal, integrated pre-flushed infusion lines, and special devices for bolus injections should be considered.

If contained systems cannot be used, nurses must protect themselves by using personal protective equipment, including gowns of impermeable material, gloves, and in the case of incidents, masks (P2/N95) and goggles.

For capsules and tablets, it is advisable that these oral forms are packed in individual packages (unit-dose) and that where possible patients should self administer. In cases where this is not possible, nursing staff should wear gloves when handling oral cytotoxic preparations.

For patients who are unable to swallow or have a nasogastric or other feeding tube in place, the use of Oral Liquid Dispensing (OLD) syringes is recommended. These syringes have a unique tip size which make it impossible to connect a needle or an IV line or catheter.

An easy way of administering capsules with an OLD is to remove the plunger from the syringe, place the capsule in the syringe, then replace the plunger. Some warm fluid is then drawn into the OLD syringe and after a couple of seconds the capsule is dissolved and the fluid/suspension can be administrated directly into the mouth of the patient or by means of the feeding tube.

Topical applications such as creams or lotions should be covered with bandages if possible in order to protect clothing and linen.

Administration over longer periods using ambulatory pump systems must be managed in such a way that safe filling and administration is assured.

Devices that need to be flushed with cytotoxic drugs instead of a inert solution should not be used.

All methods and strategies employed in the administration of cytotoxic drugs should be documented in written protocols.

If cytotoxics are administered outside the hospital, sufficient information must be made available about the products used and the safe handling required. Consideration should be given to the supply of spill kits and waste containers to ensure compliance with all safe handling recommendations. Additional written protocols about cytotoxic drug administration should be delivered to the health care worker together with instructions for using the pump (electronically or mechanically), what to do in the case of alarms and dealing with incidents or accidents.

Section 13 – Cleaning procedures

13.1 Cleaning the ventilation tool

The cleaning, disinfection, and organizing of the ventilation tool is the responsibility of trained operators (pharmacists and technicians) following written procedures.

13.1.1 Personal protective equipment

Wear personal protective equipment (i.e., goggles or face shield, protective double gloves, fluid resistant closed front gown with long sleeves and tight fitting cuffs, mask – P2/3 in Europe/Australia and N95 in North America, and disposable hair cover) for cleaning and decontaminating work. Make sure the gloves are chemically resistant to the detergent, cleaning, disinfection and deactivation agents used. Wear face shields if splashing is possible. Wash hands thoroughly with soap and water immediately after removing gloves.

13.1.2 Disinfectants and detergents

Disinfectants and detergents should be selected and used to prevent microbial contamination. Careful consideration should be given to compatibilities, effectiveness, and inappropriate or toxic residues. Isopropyl alcohol (IPA) 70% for instance, may harbour resistant microbial spores. Therefore, IPA used in the clean room should either be filtered through a 0.2 um filter to render it sterile or sterile IPA or ethanol 70% may be able to be sourced directly from a supplier. It should be noted that in some isolator applications, IPA 70% may not be used due to an incompatibility with attached neoprene gloves. Here only IPA 50% may be used. Sterile IPA should be checked periodically for microbial contamination.

> **The choice of products should be related to the bio-burden, time and application of the product, equipment used, and eventual resistance problems**.

The schedule of use and methods of application should be in accordance with written procedures. Diluted solutions should be kept in previously cleaned containers. They should not be stored for long periods unless sterilized and chemical stability has been established. Partly emptied containers should not be topped up. Apply the cleaning solution to the wiper, in order to avoid soiling the cleaning solution. Cleaning solutions should be applied to the wiper and never sprayed in the BSC to avoid damage to the HEPA filter.

13.1.3 Cleaning materials

Cleaning materials (for example; wipers, mops, and disinfectants) for use in the clean room should be made of materials that generate a low amount of particles. Disposable cleaning materials are recommended and after use these should be disposed of along with other cytotoxic waste.

13.1.4 Timing of cleaning

Beginning of session, after liquids spilled

At the beginning of each compounding activity session, and after liquids are spilled, all items are removed from the ventilation tool. All surfaces are first cleaned with sterile water for irrigation and detergent to remove loose material and water-soluble residues. The same surfaces are then disinfected with sterile 70% IPA, or other effective antimicrobial agent, that is left on for a time sufficient to exert its antimicrobial effect. 70% IPA may damage the clear plastic surface of some ventilation tools.

Class II BSC run continuously

A Class II BSC, which runs continuously, should be cleaned before the day's operations begin and at regular intervals or when the day's work is completed. For a 24-hour service, the BSC should be cleaned 2-3 times daily.

BSC turned off

If the biological safety cabinet is turned off between aseptic processes for routine maintenance or any other reason, it should be operated long enough to allow complete purging of room air from the critical area (for at least 30 minutes), then cleaned and disinfected before use. It should be noted that the actual time required for purging will depend on the design of the ventilation tool and has to be determined during the performance qualification or validation. If the isolator has been turned off for less than 24 hours, a two-minute start-up time is sufficient. For periods greater than 24 hours, the chamber should be disinfected and the isolator should not be used for a period of air purging (at least 10 minutes) after

application of the disinfectant. The actual time required for purging will depend on the design of the ventilation tool and has to be determined during the performance qualification or validation.

13.1.5 Procedure for cleaning BSC

Wipe the surface of the ventilation tool including front, sides, and bottom in the direction of the groove of the surface. Clean from upstream, closest to the HEPA filter, to downstream. Start with the rear wall of the BSC and move down. Wipe in a continuous motion working parallel to the HEPA filter. When a corner is met, 'S' curve and return to the opposite side while overlapping the previous stroke. Continue with fixtures (for example, gas or vacuum valves, bar and hooks, if present), the sides, and then lastly, the work surface. After completing the cleaning, do not use the hood for at least 5 minutes. This allows the alcohol to dry. Do not remove the sharps container until full and ready for disposal.

13.1.6 Procedure for decontamination

Routine decontamination

The ventilation tool should be decontaminated at least weekly, any time a cytotoxic spill occurs, before and after certification, voluntary interruption, or if the ventilation tool is moved. Ideally, the process and the frequency with which it is performed should be validated. Detergent, sterile water for irrigation, and disinfectant bottles will be placed on a plastic backed disposable liner outside of the BSC when not in use. The choice of products should be related to the cytotoxic product, time and application of the decontamination product, equipment used and eventual resistance problems. Wipe from top to bottom, starting with the top grill (controversial – see Section 13.1.10) and following airflow. Repeat using sterile water for irrigation until residue is removed. Finish by disinfecting. An alcohol dampened towel may be used to wipe top (see Section 13.1.9) and front grills. Pull the viewing window down and decontaminate both sides with detergent solution, rinse with sterile water for irrigation then disinfect. Discard outer pair of gloves and used wipers in the sealable bag. Decontaminate the perimeter of the opening into the BSC with detergent solution then rinse with sterile water for irrigation. Thoroughly wash protective eye wear with detergent. The decontamination procedure should be completed at the end of the day whenever possible. If it must be completed during the day, the BSC shall be allowed to run for 30 minutes to purge before using for aseptic preparation.

Decontamination after biological product

If a biological product (e.g., BCG vaccine for bladder instillation) is prepared in the ventilation tool, the tool should be decontaminated following preparation. To prevent iatrogenic transmission of the organism, some centres dedicate one BSC solely to the preparation of BCG and prepare chemotherapeutic agents in a separate pharmacy location.[1] Other centres prepare BCG on the ward using a containment device. The latter two options are preferred and the use of one cabinet to prepare both cytotoxics and BCG vaccine is NOT recommended.

Decontamination before admixing non-cytotoxics

In facilities where the ventilation tool is used for admixing cytotoxics and non-cytotoxics, the ventilation tool should be decontaminated before admixing non-cytotoxics if it has not been decontaminated since it was last used for admixing cytotoxics. The use of one cabinet to prepare both cytotoxics and non-cytotoxics is not recommended.

Decontamination of sump

The lower part of the BSC should be cleaned at least once a week to reduce the contamination level in the BSC. The fan motor (blower) should not be turned off only while cleaning the lower part of the hood (sump), but care must be taken to ensure that nothing will be sucked up into the fan. Some BSCs have a screen on the fan to prevent anything from being sucked up. Raise the work tray and (a) lean on back surface of BSC or (b) use stainless steel wire to suspend or (c) use stainless steel prop to hold up if possible rather than removing from the BSC. To prevent back strain when decontaminating a 1.8 m (6 foot) BSC, two people should lift and replace the work tray. Decontaminate with detergent, rinse with sterile water for irrigation, then disinfect the work tray with alcohol before replacing.

13.1.7 Waste handling

Waste generated throughout the cleaning or decontamination procedures should be collected in suitable plastic bags, sealed and wiped inside the ventilation tool, and removed with minimal agitation.

13.1.8 Documentation

Record on the quality control log when the daily cleaning/disinfection, weekly decontamination and monthly sump cleaning is done.

13.1.9 Gas sterilized isolators

The above procedures for cleaning and disinfecting must be implemented. Compatibility with structural components (for example the plastic wall, isolator gloves, sleeves, half suit) must be checked before use. The cleaning procedure must be implemented with respect to the enclosure taking care never to disrupt the sealed enclosure. For example, the isolator attached gloves are removed following a "safe change" procedure (without breaking the integrity of the system) in accordance with ISO14644-7[2] annexe C. If for maintenance reasons the isolator integrity is disrupted, personal protective equipment (PPE) must be used in conformity with the chemical risk. Cleaning and disinfection of the workstations is performed on a daily basis. The sterilization of the enclosure is implemented periodically and the frequency should be validated.

13.1.10 Controversies

Decontaminating the BSC ceiling grill

There is a lack of consensus regarding decontaminating the ceiling grill in the BSC with detergent. Some references suggest cleaning in place and some say not to wipe the top grill with detergent. The concern is that if the HEPA filter becomes wet, this may affect the integrity of the filter and compromise the function of the filter.

Alternate germicides

The ASHP guidelines on quality assurance for sterile products describe the need to alternate germicides as controversial. According to Akers and Moore,[3] the data do not support alternating germicides. A literature search[4] found little evidence for periodic alternation of disinfectants; the search did find that alternating use of acidic and alkaline phenolic disinfectants reduces resistance arising in pseudomonas adhering to hard surfaces." It has been suggested that reported microbial resistance might be due to situations in which an ineffective disinfectant was used or in which a disinfectant was used at sub-effective dosages or sub-effective contact times.[5]

In general the advice is not to change the disinfectant product unless there is a problem. In this case, the source of the problem has to be identified.

Residues left by disinfectants

There are two prevailing opinions on the issues of residues left by disinfectants. One opinion is that the residues left behind from the use of formulated germicidal detergents may have bacteriostatic properties, in which case the residue would be beneficial. The other opinion is that no residue is acceptable in a clean room, in which case the residue may simply be removed with an alcohol or water for irrigation rinse.[6]

Sporicidal disinfectants

Because routine disinfectants will not be effective against bacterial endospores such as the Bacillus species, a sporicidal agent should also be applied periodically (e.g., weekly or monthly). Since most sporicidal disinfectants are either highly toxic or very corrosive, they should not be considered for daily use.[7]

Deactivation agents

The NIOSH Alert[8] recommends that work surfaces be cleaned with an appropriate deactivation agent (if available) and cleaning agent before and after each activity and at the end of the work shift. Many drug manufacturers recommend the use of a strongly alkaline detergent as an appropriate deactivating agent for some hazardous drugs. Researchers have shown that strong oxidising agents such as sodium hypochlorite (bleach) are effective in deactivating some hazardous drugs where an oxidative action is appropriate. However, bleach may pit the stainless steel surface of the BSC, and may also react with some cytotoxics. For example, the material safety data sheet for mitozantrone notes that chlorine gas may be liberated when the drug is degraded with bleach. Other drugs are deactivated by hydrolysis.

Note that any one product is incapable of decontaminating all hazardous products.

13.2 Cleaning rooms

For the purposes of this standard, the terminology in the USP 797[9] will be used to describe the cleanroom (i.e., the area designated for preparing sterile products). The ventilation tool is located in the buffer zone/room; with the adjacent ante area/room across the buffer zone/room from the ventilation tool.

13.2.1 Buffer zone/room

Personal protective equipment

At a minimum, wear goggles or face shield and protective chemotherapy gloves for cleaning and double gloves for decontaminating work. Wear face shields if splashing is possible. Make sure the gloves are chemically resistant to the decontamination or cleaning agent used. Immediately after removing gloves, wash hands thoroughly with soap and water.

Work surfaces

All work surfaces (e.g., counter tops and supply carts) are cleaned and disinfected daily. The surfaces are first cleaned with water and detergent to remove water- soluble residues. Immediately thereafter, the same surfaces are disinfected with sterile 70% IPA, or other effective antimicrobial agents, and left on for a time sufficient to exert their antimicrobial effects.

Carts and tables

Large pieces of equipment, such as carts and tables, used in the cleanroom should be made of a material that can be easily cleaned and disinfected; stainless steel is recommended. Stools and chairs should be cleanroom quality.

Storage shelving

Storage shelving is emptied of all supplies and then cleaned and disinfected at least weekly, using approved agents. Other hard surfaces, such as carts, tables, and stools should be cleaned and disinfected weekly and after any unanticipated event that could increase the risk of microbial contamination.

Nonporous and washable surfaces

The floors of the cleanroom should be nonporous and washable to enable regular disinfection. Carpet or porous floors, porous walls and porous ceiling tiles are not suitable for cleanroom use because these surfaces cannot be properly cleaned and disinfected.

Floors

Floors in the cleanroom are cleaned by mopping at least once daily when no aseptic operations are in progress. Floor mops may be used in both the buffer zone/room and the ante area/room, but only in that order. Trained and supervised custodial personnel using approved agents described in the written procedures may perform mopping.

Refrigerators, freezers

Refrigerators, freezers, shelves, and other areas where pharmacy-prepared sterile products are stored, should be kept clean.

Other equipment

Equipment that does not come in contact with the finished product should be properly cleaned, rinsed, and disinfected before being placed in the clean room.

Decontamination of exterior of ventilation tool

The exterior surfaces of the ventilation tool should be decontaminated with detergent solution, cleaned with sterile water for irrigation and disinfected weekly. 70% IPA may damage the clear plastic surfaces of some ventilation tools.

Clean from cleanest to dirtiest areas

Cleaning should proceed from the cleanest area to the dirtiest area of the room. This would involve a ceiling to floor cleaning flow, moving outward from the ventilation tool to the exit. The orientation of the HEPA filters (if present) should also be considered when conducting cleaning procedures.

Ceilings and walls

Ceilings and walls should be cleaned at least monthly, or as required to maintain cleanliness.

Disinfectants and detergents

Disinfectants and detergents should be selected and used to prevent microbial contamination. Careful consideration should be given to compatibilities, effectiveness, and inappropriate or toxic residues. The schedule of use and methods of application and products should be in accordance with written procedures. Diluted solutions should be kept in previously cleaned containers. They should not be stored for long periods unless sterilized and chemical stability has been established. Partly emptied containers should not be topped up. In order to avoid contaminating the cleaning solution, it is recommended that the cleaning solution be applied directly to the wiper.

Cleaning materials

Cleaning materials (e.g., wipers, mops, and disinfectants) for use in the cleanroom should be made of materials that generate a low amount of particles. All cleaning tools should be nonshedding and dedicated to use in the clean room. Most wipers are discarded

after one use. (Disposable cleaning materials are recommended and after use these should be disposed of along with other cytotoxic waste.) If cleaning tools are reused, their cleanliness should be maintained by thorough cleaning and disinfection after use and by storing in a clean environment between uses.

Waste handling

An appropriate method of disposing of waste, including needles, should be established which does not allow accumulation in the cleanroom. Trash should be collected in suitable plastic bags and removed with minimal agitation.

13.2.2 Ante area/room

Supplies and equipment

In the ante area/room, supplies and equipment removed from shipping cartons are wiped with a disinfectant. Alternatively, if supplies are received in sealed pouches, the pouches can be removed as the supplies are introduced into the cleanroom without the need to disinfect the individual supply items. No shipping or other external cartons may be taken into the cleanroom.

Custodial personnel

Trained and supervised custodial personnel perform cleaning and disinfection of the ante area/room at least weekly, in accordance with written procedures.

Floors

Floors should be cleaned and disinfected daily, always proceeding from the buffer zone/room to the ante area/room.

Storage shelving

Storage shelving is emptied of all supplies and cleaned and disinfected at least monthly.

13.3 Cleaning material used for oral/external use drugs (non sterile)

Workers may be exposed to cytotoxic drugs when they create aerosols, generate dust, clean up spills or touch contaminated surfaces during the preparation, administration, or disposal of cytotoxic drugs. While commonly associated with cytotoxic drugs given by parenteral routes, exposure can also occur with drugs prepared for administration by the oral or topical routes.

All material used (such as mortar, pestle, glass plate, spatulas, mixing devices, and tube fillers) for the preparation of oral/external use cytotoxic drugs must be identified for that use and reserved soley for these activities. This equipment must not be used for non cytotoxic preparations. This equipment should be cleaned separately from all non cytotoxic equipment.

13.3.1 Preparation in a biological safety cabinet (BSC)

All activities likely to result in particle generation, for example weighing, crushing, mixing, or filling capsules, should be performed in a Class I or II BSC (see Section 9).

Written procedures

Class I BSC should be cleaned and decontaminated following written procedures.

Personal protective equipment

Wear personal protective equipment (i.e., goggles or face shield, protective double gloves, fluid resistant closed front gown with long sleeves and tight fitting cuffs, mask, and disposable hair cover) for cleaning and decontaminating work. Make sure the gloves are chemically resistant to the detergent, cleaning, disinfection and deactivation agents used. Wear face shields if splashing possible. Wash hands thoroughly with soap and water immediately after removing gloves.

Beginning of session, after liquids spilled

At the beginning of each compounding activity session, and after liquids are spilled, all items are removed from the BSC. All surfaces are first cleaned with water for irrigation and detergent to remove loose material and water-soluble residues.

Procedure for cleaning

Wipe the surface of the BSC including front, sides and bottom in the direction of the groove of the surface. Wipe in a continuous motion working. When a corner is met, 'S' curve and return to the opposite side while overlapping the previous stroke. Continue with fixtures (e.g., gas or vacuum valves, bar and hooks, if present), the sides, and then the work surface.

Decontamination

The BSC should be decontaminated at least weekly (ideally, the process and the frequency with which it is performed should be validated.); any time a cytotoxic spill occurs; before and after certification,

voluntary interruption, or if the BSC is moved. Detergent and water for irrigation bottles will be placed on a plastic backed disposable liner outside of the BSC when not in use. Wipe with an aqueous high pH detergent solution (e.g., 5 mL in 235 mL warm tap water), starting with the grill and following airflow. Repeat using water for irrigation until residue is removed. A dampened towel may be used to wipe grill. Discard outer pair of gloves and used wipers in the sealable bag. Decontaminate the perimeter of the opening into the BSC with detergent solution then rinse with water for irrigation. Thoroughly wash protective eye wear with detergent. Discard inner pair of gloves. Wash hands thoroughly immediately after removing gloves.

Waste handling

Waste generated throughout the cleaning or decontamination procedures should be collected in suitable plastic bags, sealed inside the ventilation tool, and removed with minimal agitation.

Documentation

Record on the quality control log when the cleaning/disinfection and weekly decontamination is done.

Class II BSC also used for sterile compounding

A Class II BSC, which is also used for sterile compounding, should be cleaned, decontaminated and disinfected as described in Section 13.1. Compounding non-sterile forms of hazardous drugs in equipment designated for sterile products is not recommended and must be undertaken with care.

13.3.2 Preparation outside a BSC

Personal protective equipment

Wear personal protective equipment (i.e., goggles or face shields, protective double gloves, fluid resistant closed front gown with long sleeves and tight fitting cuffs) for cleaning and decontaminating work. Make sure the gloves are chemically resistant to the decontamination or cleaning agent used. Wash hands thoroughly with soap and water immediately after removing gloves.

Work surfaces

Clean work surfaces with an aqueous high pH detergent solution (e.g., 5 mL in 235 mL warm tap water), then rinse with water before and after each activity.

Equipment

Contaminated equipment should be cleaned initially with gauze saturated with water; decontaminated with detergent and then rinsed. The gauze should be contained and disposed of as cytotoxic drug contaminated waste.

Waste handling

Disposal of unused or unusable non-injectable dosage forms of cytotoxic drugs should be performed in the same manner as for hazardous injectable dosage forms and waste.

13.4 Validation of cleaning processes

The objective is to confirm that microbiological, chemical, and other contaminants are removed or inactivated during the cleaning process.

13.4.1 Microbiological validation

Microbiological validation of the cleaning process uses contact plates and/or swabs before and after the cleaning operation. In the case of a sterile isolator, a specific investigation must validate the efficiency of the sterilisation process using biological indicators (B.I.).

13.4.2 Chemical validation

Due to the large diversity of drugs used simultaneously in the same controlled area, chemical validation of the cleaning process is more complex when handling cytotoxic drugs. One approach would be to investigate the most commonly used cytotoxic drugs (eg. 5-fluorouracil, methotrexate, ifosfamide, cyclophosphamide) by wipe sampling of the surfaces before and after cleaning. If an analytical procedure is available, investigation of lipophilic drugs (eg. carmustine, paclitaxel) would also be done to ensure that the cleaning procedure is efficient for both for lipophilic and hydrophilic drugs. In addition, the cleaning carried out should not degrade the cytotoxic drug into more toxic components.

Definitions

ante area/room = clean area that precedes the buffer zone/room, for donning of personal protective equipment

buffer zone/room = area in which the cleanest work surface (i.e., ventilation tool) is located.

clean room = the area designated for preparing sterile products (i.e., a room in which the concentration of airborne particles is controlled, that is constructed and used in a manner to minimize the

introduction, generation, and retention of particles inside the room.
deactivate = treat a chemical agent (such as a hazardous drug) with another chemical, heat, ultraviolet light, or other agent to create a less hazardous agent.
decontamination = inactivation, neutralization, or removal of toxic agents, usually by chemical means.
detergent = cleaning agent with wetting-agent and emulsifying-agent (tensio active) properties.
disinfect = destroy pathogenic microorganisms or inhibit their grown and vital activity.
HEPA = high efficiency particulate air filter
IPA = isopropyl alcohol
non-shedding, non-linting, low-lint or **lint-free** = materials that generate a low amount of particles
sanitize = to free from dirt, germs, by cleaning
sump = a chamber at the bottom of a machine into which wastes gather before disposal.
wiper = that which wipes (eg, towel, sponge, gauze, cloth, etc)

Note: for the purposes of this Standard, the term **disinfectant** is used and includes antimicrobial agent and sanitizing agent

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Section 14 – Cytotoxic spills, extravasation and other incidents

14.1 Cytotoxic spills

A standard operating procedure must be developed and maintained for the handling of cytotoxic spills within the institution. **When a cytotoxic spill is cleaned, all cleaning should begin from the outside of the spill area and gradually work towards the centre.** All personnel who may be involved in handling cytotoxic drugs must be given appropriate training in the procedures to be followed in the event of a spill. Records of staff undergoing this training should be maintained.

14.1.1 Spills within safety cabinet or isolator

When a cytotoxic spill occurs within the safety cabinet or isolator, work should stop and the spill should be cleaned up immediately. Small spills may be easily cleaned using absorbent gauze. Large spills may require a spill pillow to absorb a larger volume of fluid. The area should then be washed with an appropriately diluted strongly alkaline detergent, rinsed thoroughly with sterile water, and then wiped with sterile isopropyl alcohol (70%) or other suitable agent.

14.1.2 Spills within cleanroom and anteroom

Cytotoxic cleanrooms which have a positive pressure in relation to the external environment should be fitted with a spill switch. When activated, this switch will alter the pressure differentials within the cytotoxic suite to minimise any contamination of the external environment. The switch should also be fitted with an audible alarm to alert other staff working in the immediate vicinity. The spill should then be cleaned following the procedures outlined in Section 14.1.6.

14.1.3 Spills within storeroom

All staff working in the pharmacy store must be trained in the procedure to be followed in the event of both a liquid and powder cytotoxic drug spill. Wherever cytotoxic drugs are stored, spill kits with written procedures for use must be readily available.

14.1.4 Spills during transport

Personnel transporting cytotoxic drugs must be familiar with the procedure to be followed in the event of a spill.

14.1.5 Contents of spill kit

A spill kit should contain:

(a) Written instructions for use of the spill kit.
(b) Warning signs to alert other staff to the hazard and isolate the area of the spill.
(c) Impermeable protective gown, boots/overshoes, headcover, goggles or face shields and suitable respirator mask.
(d) Pair of large size gloves. May be either gloves manufactured specifically for handling cytotoxics (with proven resistance), or if not, two pairs of gloves.
(e) Plastic broom and dustpan to clean up any broken glass.
(f) Spill mat (alginate impregnated) to absorb small volumes of spilled liquid.
(g) Large quantities of swabs for absorbing and cleaning liquid spills.
(h) Concentrated alkaline detergent solution.
(i) Bottled water (correct quantity for dilution of detergent).
(j) Clearly labelled cytotoxic waste container.
(k) Spill report/incident form.
(l) Spill pillow capable of absorbing large volumes of liquid. This may an integral part of the spill kit or may be supplied separately when required.

An institution may choose to supply all of these items within the final cytotoxic waste container.

14.1.6 Spill clean up procedure

In the event of a cytotoxic spill in any area other than the safety cabinet or isolator, the following clean up procedure should be followed:

(a) Alert other staff in the area to the potential hazard and limit access by placing the warning sign in a prominent position.

(b) Remove the contents of the spill kit and put on in this order: the mask, the head cover, the goggles or face shield and the gloves.
(c) For a liquid spill, carefully place a sufficient quantity of swabs or the alginate impregnated mat (or the spill pillow if a large volume of liquid is involved) over the spilled liquid. If the spill involves a powder, carefully place sufficient swabs over the powder and then carefully wet the mat with water so that the powder dissolves and is absorbed by the swab.
(d) Gather up the contaminated swabs/mat/pillow and carefully clean up any broken glass with the broom and pan. Discard all of this waste into the cytotoxic waste container.
(e) Repeat steps (c) and (d) until all the spill has been cleared. **When a cytotoxic spill is cleaned, all cleaning should begin from the outside of the spill area and gradually work towards the centre**.
(f) Add the detergent concentrate to the bottled water.
(g) Wash the area of the spill thoroughly, discarding all waste generated into the waste container.
(h) Rinse the area well with clean water.
(i) Dry the area completely to prevent accidental slippage on wet floor.
(j) Discard all used items into the cytotoxic waste container. Do not compact waste.
(k) Arrange for collection of waste according to institution policy.
(l) Wash hands thoroughly with soap and water.
(m) Arrange for hospital cleaning staff to re-clean the area.
(n) Complete the spill report card and forward to pharmacy department. Arrange for a replacement spill kit to be obtained.

14.2 Contamination of staff and/or patient

In the event that staff become contaminated with a cytotoxic agent, the following procedure should be followed:

(a) All overtly contaminated protective clothing should be removed and placed in the cytotoxic waste container.
(b) All contaminated clothing should be removed and if heavily contaminated should be discarded into the cytotoxic waste container. Clothing with minimal amount of contamination should be laundered separately and rinsed well.
(c) An emergency shower should be used if appropriate. If this is not available, then the contaminated area of skin should be washed with soap and rinsed with large amounts of water.
(d) Eyes that have become contaminated should be thoroughly irrigated with 0.9% sodium chloride or other suitable ophthalmic irrigation solutions. It is not recommended to irrigate the eye directly with running water from a tap (faucet) because of the potential for water pressure damage to the eye. In all cases where the eye is thought to be contaminated, ophthalmological advice should be sought.
(e) If the skin is broken, the affected area should be irrigated with water and bleeding controlled.
(f) Medical attention should be sought as soon as practical.
(g) An incident report should be completed if this is institution policy.

14.3 Extravasation

Each institution should develop a policy on dealing with the extravasation of vesicant cytotoxic drugs. This policy will require input from pharmacy, medical, and nursing personnel. The medical and pharmaceutical literature should be consulted and a consensus decision made about which agents to use to treat each extravasation. An institution may or may choose not to use a specific antidote for the drug which has extravasated.

Recently, a formulation of dexrazoxane (Savene®) has become available in some countries for the management of extravasation following anthracycline administration. To fully protect against the tissue damage caused by extravasation, the drug should be given as soon as possible and within 6 hours of the extravasation accident. Dexrazoxane is administered as a 1–2 hour infusion on three consecutive days. Cooling and Dimethyl Sulphoxide should not be used during treatment with dexrazoxane.

A policy on warming or cooling the area should be developed for specific drugs.

A list of vesicant cytotoxics should be maintained by the pharmacy and this information should be on the label of any admixtures prepared by the pharmacy.

General recommendations for handling extravasation include:

(a) Stop injection/infusion immediately
(b) Leave needle in place
(c) Replace infusion lead with 5 ml disposable syringe and aspirate slowly as much as possible; **Caution!** Do not exert pressure
(d) If blisters occur: aspirate with 1 ml syringe and subcutaneous cannula
(e) Elevate limb and immobilise
(f) Always consult a plastic surgeon and/or physician immediately
(g) Start substance specific measures on advice of plastic surgeon.
(h) Remote IV access while aspirating after approval of plastic surgeon.
(i) Complete extravasations documentation sheet
(j) Inform and instruct the patient and relatives
(k) Regular control (aftercare)

Some protocols include a drastic approach, particularly with products known for tissue damage.

An example of such a protocol is (personal communication, Johan Vandenbroucke, 2007):

> The (Plastic) Surgeon in that case will within the 24 hours after the extravasation infiltrate the extravasation zone with normal saline followed by a liposuction.
> In case of extravasation with products having an effect on the alpha-receptors, the infiltration is done with 10 to 15 mg phentolamine in 10 to 15 ml normal saline, followed with an extra infiltration of normal saline and liposuction.

An extravasation kit may be prepared by the pharmacy to make treatment readily available to commence as soon as possible. Any such kit must contain written instructions for treatment of the affected area and the use of any specific antidotes contained in the kit.

An incident report which reflects the institution's policies should be completed whenever a case on extravasation occurs. This will most likely be the responsibility of nursing staff. An institution may choose to include an extravasation report within the extravasation kit in a similar way to that described for cytotoxic spills – see previous and following sections.

Consideration should be given to having both an extravasation kit and an anaphylaxis kit available in areas where chemotherapy is administered. In this way, these items are immediately available when required.

14.4 Inadvertent intrathecal administration of vincristine

Vincristine, and the other vinca alkaloids, are all neurotoxic and must only be administered by the IV route. If given intrathecally, this error in route of administration results in a fatal outcome in 85% of cases with devastating neurological effects in the few survivors. Each institution must develop policies and procedures to ensure that the risk of accidental intrathecal administration of these agents is minimised. The following are some suggestions:

> Vinca alkaloids should NEVER be supplied in a syringe. As intrathecal administration has been reported despite dilution to 10 and 20 ml, it is recommended that vincristine and other vinca alkaloids be supplied in a minibag of at least 50 ml.
> All vinca alkaloids products should be labelled clearly with the intended route of administration. For example **"FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES."** The use of negative labels such as "Not for Intrathecal Injection" should be avoided as the inclusion of the word "intrathecal" may actually promote administration by this route.

If a patient is scheduled to receive an IV vinca alkaloid plus an intrathecal dose of a drug, these should be administered on different days or at least at different times. The timing of IV vincristine and any intrathecal injections occurring in the same location should be separated.

All medications INTENDED for intrathecal administration should be packaged separately from other types of medications, and should be supplied by the pharmacy in a distinctive container to prevent confusion with IV drugs. They should display a prominent warning stating "FOR INTRATHECAL INJECTION ONLY."

Health professionals who prescribe, prepare or administer chemotherapy should be educated about the published case reports or fatal intrathecal administration of vincristine.

14.5 Documentation of incidents

Each institution should develop procedures for documenting spills and other incidents that occur with cytotoxic drugs. It is recommended that such records be maintained indefinitely and that a regular review takes place to ensure any procedural changes may be implemented as required. In the case of

cytotoxic spills, a pharmacist must be involved in any changes to procedures.

14.5.1 Cytotoxic spills

In the case of cytotoxic spills the institution may choose to include a spill report card or incident form within the spill kit to ensure these are readily available when required. These should be returned to the pharmacy department when completed for review and filing. The following information may be included on such a spill report from:

(a) Date and time of spill
(b) Location of spill
(c) Persons involved and titles (eg. nurse, pharmacist)
(d) Drugs involved
(e) Brief description of incident
(f) Was medical attendance sought
(g) Details of doctor if consult occurred
(h) Suggestions to avoid future spills

14.5.2 Chemotherapy extravasation

In the case of extravasation, the institution may choose to include a report card or incident form within the extravasation kit to ensure proper documentation of the incident. Details of the incident should be filed in the patient's medical history and also forwarded, if required by hospital procedures, to the hospital administration for insurance reasons. These reports should be returned to a designated person within the institution; possibly a member of the nursing or pharmacy staff. The information from the report should be retained indefinitely. The following information may be included on such an extravasation report form:

(a) Date and time of extravasation
(b) Location of incident within the institution
(c) Persons involved
(d) Drugs involved
(e) Brief description of how extravasation occurred
(f) Action taken
(g) Details of follow up

In addition, the inclusion of a photograph of the affected area can be very useful when following up an extravasation event. Some institutions may want to use a diagram for marking the extent of extravasation.

Section 15 – Waste handling and patient excreta

15.1 Handling of cytotoxic waste

The institution shall have written policies describing requirements for the segregation, packaging, collection, transport, storage, and on site treatment of cytotoxic waste within the institution.

The institution shall dispose of all cytotoxic waste in accordance with all relevant federal, regional and municipal regulations and legislation.

15.1.1 Cytotoxic waste

Cytotoxic waste is considered to be all those materials which have come into contact with cytotoxic drugs during the process of reconstitution and administration. This will include syringes, needles, empty or partially used vials, gloves, single use personal protective equipment, respirator masks, and materials from the clean-up of cytotoxic spills. Air filters from ventilation tools are also included. In addition, hazardous drugs which have expired, or for any other reason must be destroyed, are also treated as cytotoxic waste. This waste must be collected in clearly marked dedicated containers made from hard, robust material, which is shock-resistant and can withstand external pressure during transportation. These containers should be of a dedicated colour and display a recognizable symbol for cytotoxics.

All cytotoxic waste must be placed in a closed system before removal from the ventilation tool. All sharps waste must be placed in puncture resistant containers. All cytotoxic waste must be placed in secondary packaging and sealed to ensure that leakage cannot occur, and must be clearly labelled to indicate the presence of cytotoxic waste.

This waste must be segregated, packaged, and disposed of in a way that personnel and the environment are not contaminated. All relevant regulations concerning the disposal of cytotoxic waste must be followed. Personnel involved in transporting cytotoxic waste must receive instruction on procedures for safe transport and for dealing with spills.

15.1.2 Contaminated waste

Some countries may differentiate between cytotoxic waste and contaminated waste. Contaminated waste may be considered to consist of any device used from patients who have undergone chemotherapy. This will include syringes, needles, catheters, and used serum bags. These so-called soft trace contaminated items should be placed in separate chemotherapy waste containers (traditionally yellow chemotherapy waste containers) to protect workers from injury.

Containers are collected by the cleaning personnel, are sealed so that they are airtight and are transported on wheel-driven carts. These carts can be cleaned and disinfected easily and at the same time offer protection for the handling personnel. These carts must not be used for any other kind of waste.

Some countries may not differentiate between wastes based on any concentration of contamination. Here all cytotoxic waste is disposed of in the same cytotoxic waste container.

15.1.3 Labelling

All cytotoxic contaminated waste must be clearly marked as cytotoxic and clearly identifiable to all staff who will be involved in handling this waste. All containers and wheel-driven vehicles must be marked with the same label. A second label on the containers may be used with the date of waste production.

15.1.4 Transport and storage

Cytotoxic waste would normally be collected by hospital auxiliary personnel. This waste is most likely taken to some temporary storage areas within the hospital. Cytotoxic waste should be stored in a dedicated, easily identifiable secure storage area with adequate lighting and ventilation. It should be located away from drains and other sensitive areas. Waste bins should be sealed prior to collection and should not be reopened or reprocessed on site. If it is essential that waste be stored for more than 72 hours prior to disposal, consideration should be given to refrigerating the waste, particularly where waste is mostly organic and can decompose. A specialized company makes the transportation of waste from the temporary storage areas, to the areas of destruction. These operators should be familiar with the emergency procedures to be followed in the event of a spill.

15.1.5 Disposal

Cytotoxic waste must be incinerated in a facility approved by an environmental protection authority for the destruction of cytotoxic waste.

It should be noted that many countries have their own guidelines and regulations concerning the disposal of cytotoxic waste. As described in the introduction to the Standard, these guidelines and regulations should be followed in addition to this Standard.

15.2 Handling patient excreta

Body fluids from patients receiving chemotherapy may contain traces of cytotoxic drugs and their active metabolites.

Precautions should be taken for up to 7 days after treatment, as it is known that the majority of cytotoxic drugs will be excreted within this time. Further information is provided in Table 1 below.

15.2.1 Contamination period

All excreta, from patients who have received chemotherapy, should be considered contaminated for up to 7 days.

15.2.2 Risk to care-givers

All care-givers, including relatives, should be informed about the risk of handling contaminated excreta.

15.2.3 Precautions during contamination period

For up to 7 days following treatment, gloves, mask and a non–permeable gown (Personal Protective Equipment) should be worn when handling excreta from patients who have received chemotherapy.

Personal Protective Equipment (PPE) should be worn when cleaning bathrooms and toilet facilities.

Table 1. Excretion rates for selected cytotoxic agents

Cytotoxic agent	Excretion rate	Duration after therapy for which PPE is recommended when handling excreta*	
5-Fluorouracil	Urine: unchanged up to 15% over 24 Hours	Urine: 2 Days	Faeces: 5 Days
Bleomycin	Urine: unchanged up to 68% over 24 Hours	Urine: 3 Days	
Carboplatin	Urine: 60% over 24 Hours	Urine: 1-2 Days	
Carmustine	Urine: 55-65% over 24 Hours	Urine: 4 Days	
Chlorambucil		Urine: 1-2 Days	
Cisplatin	Urine: unchanged plus metabolites up to 75% over 5 Days	Urine: 7 Days	
Cyclophosphamide	Urine: unchanged up to 25% over 48 Hours; unchanged plus metabolites up to 62% over 48 Hours	Urine: 3 Days	Faeces: 5 Days
Faeces: up to 4% after IV dose Traces in sweat and saliva (in saliva up to 77% of plasma concentration)			
Cytarabine	Urine: 90% within 24 Hours	Urine: 1 Day	
Dacarbazine		Urine: 1 Day	
Daunorubicin		Urine: 7 Days	Faeces: 7 Days
Docetaxel	Urine: 60% within 24 Hours	Urine: 1 Day	Faeces: 2 Days
Doxorubicin	Urine: unchanged and metabolites up to15% over 5 Days Faeces: unchanged and metabolites up to 85%	Urine: 6 Days	Faeces: 7 Days
Epirubicin	Urine: unchanged up to 11% over 24 Hours	Urine: 3 Days	
Etoposide	Urine: unchanged 40-50% over 24 Hours Faeces: unchanged 2-15% over 24 Hours	Urine: 3 Days	Faeces: 5 Days
Fludarabine	Urine: 40-60% over 24 Hours	Urine: 3 Days	
Gemcitabine		Urine: 1 Day	
Ifosfamide		Urine: 2 Days	
Idarubicin		Urine: 3 Days	Faeces: 2 Days
Melphalan	30-60% over 24 Hours	Urine: 2 Days	Faeces: 7 Days
Mercaptopurine	Urine: unchanged 10-20% over 24 Hours; metabolites 10-40% over 24 Hours	Urine: 2 Days	Faeces: 5 Days

Table 1. Continued

Cytotoxic agent	Excretion rate	Duration after therapy for which PPE is recommended when handling excreta*	
Methotrexate	Urine: unchanged and metabolites 40-50% (low doses) and up to 90% (high doses) over 48 Hours Faeces: up to 9%	Urine: 3 Days	Faeces: 7 Days
Mitomycin C		Urine: 1 Day	
Mitozantrone (=Mitoxantrone)	Urine: unchanged up to 6.5% over 5 Days; metabolites up to 3.6% over 5 Days Faeces: up to 18% over 5 Days	Urine: 6 Days	Faeces: 7 Days
Oxaliplatin	Urine: 40-50% over 24 Hours	Urine: 3 Days	
Paclitaxel	Urine: unchanged up to 13% over 24 Hours Faeces: more than 13% over 24 Hours		
Procarbazine	Urine: unchanged 5% over 3 Days; metabolites 25-70% over 3 Days	Urine: 3 Days	
Teniposide		Urine: 3 Days	
Thioguanine		Urine: 1 Day	
Thiotepa		Urine: 3 Days	
Topotecan		Urine: 2 Days	
Vinblastine	Urine: unchanged and metabolites 13-33% over 3 Days Faeces: unchanged and metabolites 10-41% over 3 Days	Urine: 4 Days	Faeces: 7 Days
Vindesine			
Vincristine	Urine: unchanged 8% over 3 Days; metabolites 4% over 3 Days	Urine: 4 Days	Faeces: 4 Days
	Faeces: unchanged 30% over 3 Days; metabolites 40% over 3 Days	Urine: 4 Days	Faeces: 7 Days
Vinorelbine		Urine: 4 Days	Faeces: 7 Days

**If not specified, at least 48 hours.*
Table 1 reproduced with kind permission from Cass and Musgrave.[1]

A face shield should be worn if splashing is likely. PPE should be treated and disposed of as contaminated.

15.2.4 Disposable items

Disposable items, such as bedpans and urinals, should be used in preference to re-usable products. When re-usable items are used, they should be rinsed twice following use.

15.2.5 Dedicated toilets

If possible, there should be toilets dedicated for the use of patients receiving chemotherapy. In order to reduce or eliminate the risk of splashing and aerosolisation, men should be instructed to be seated when urinating.

15.2.6 Collection of body fluids

Closed systems of collecting body fluids are preferred. Drainage systems for body fluids should be disposed as intact.

15.2.7 Contaminated linens

Contaminated linen should be placed in a bag labelled "Hazardous Contamination" and forwarded to the laundry (See Section 16). Contaminated linen and clothing should be pre-laundered before washing with other linen.

15.2.8 Patient protection

Patients suffering from incontinence should have their skin protected from their excreta by cleaning with soap and water and applying a barrier cream to

the perineal area. Disposable incontinence pads should be used.

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Section 16 – Laundry

The risk of contamination exists when people come into contact with patient excreta either directly or indirectly.

One example of indirect contact is with clothing and linen which has come into contact with urine, faeces, vomit, sweat, saliva, or blood from a patient treated with cytotoxic drugs.

In order to minimize the exposure (the ALARA principle = As Low As Reasonably Achievable) the following measures are recommended:

(1) Gloves should be worn when handling the linen and clothing of a patient receiving cytotoxic chemotherapy. This should continue for several days after a patient has completed treatment with the cytotoxic agent. In the absence of any specific detailed information, general recommendations should be followed for up to 7 days. (See Section 15).
(2) Consider that the middle of the linen and especially the pillow-case the feet and pelvic area could be highly contaminated.
(3) Contaminated linen should be labeled as Hazardous Contamination.
(4) To avoid the generation of dust, do not stir up the linen.
(5) If possible, use disposable linen.
(6) In order to reduce or contain contamination, patients who need to be washed in bed should be washed with disposable moist tissues. When using this technique, no water will be spilled.
(7) Linen and clothing should be considered as potentially contaminated materials, and should be gathered in labeled containers.
(8) Keep the contaminated laundry separate from other laundry.
(9) Wash the contaminated laundry separately from other laundry.
(10) Start the washing process with a cold water cycle.
(11) Restart the washing process with the normal washing process.

These recommendations are valid for both the hospital and the home situation.

Section 17 – Warning staff of presence of cytotoxic agents

It is imperative that all staff are aware of the presence of cytotoxic agents and the potential, in any situation, for contamination. This applies when cytotoxic drugs are being stored, reconstituted, transported, administered, and when cytotoxic waste is being handled. In addition staff must be warned to avoid an area where a cytotoxic spill has taken place.

17.1 Storage

Dedicated storage areas are required for cytotoxic drugs. These areas must be clearly defined and labelled as containing cytotoxic agents exclusively (See Section 2). Easily recognisable warning labels should be attached to shelving to alert staff to the fact that the contents are cytotoxic. Cytotoxic spill kits should be available near the storage area.

17.2 Reconstitution

The area where cytotoxic drugs are reconstituted should be restricted to authorised personnel only and should be clearly labelled to alert staff to the presence of cytotoxic agents. (See Section 6). This warning must be clear to all cleaning staff entering the area.

17.3 Transport

Clear and easily recognisable warning signs must be displayed whenever cytotoxic agents are transported both within the institution and externally (See Section 2). Staff must also be notified of who to contact in case of emergency.

17.4 Administration

It is very important that staff members are aware that a particular patient is receiving cytotoxic chemotherapy. The drug itself will be clearly labelled with a prominent warning, but an additional recommendation is that nursing staff attach stickers to the IV line indicating that the infusion running is cytotoxic in nature. This is particularly important if the cytotoxic agent must be protected from light and any labels attached by the pharmacy may be hidden. Whenever patients are transported around the hospital, (for example; to radiology or to another ward), it is important that all staff are aware that a cytotoxic infusion is running.

Patients who have received cytotoxic chemotherapy in the previous 7 days must also be identifiable to hospital staff. This may be achieved by attaching a warning sign or sticker to the patient's bed. In this way, staff will be aware that the patient's excreta may have to be handled as potentially contaminated (See Section 15).

17.5 Cytotoxic waste

During collection, transport and storage, cytotoxic waste must be clearly identifiable (See Section 15). This includes any trolleys dedicated to this purpose and also dedicated temporary storage areas within the institution.

17.6 Spills

Staff must be warned whenever a cytotoxic spill occurs in an area. This will usually be achieved by the use of a specific warning sign contained within the spill kit (See Section 14).

17.7 Home care

Patients receiving chemotherapy at home, either by a home care nursing service or by self/relative administration must be made aware of the importance of warning other people in the household and visitors about the use of cytotoxic agents in the home. In particular, special care should be taken with the use of toilets (See Section 15).

17.8 Pathology and other laboratories

If it is not routine practice for an institution's laboratory to handle all samples/specimens as potentially dangerous, then, in order to alert laboratory personnel, blood samples/specimens taken from a patient having received chemotherapy in the preceding 7 days should be labelled as cytotoxic.

Section 18 – Home care

Patients may receive cytotoxic drug therapy at home or in a residential care facility for the elderly. Nursing,medical staff, and others often care for patients in these situations.

Households that are unable to provide the appropriate facilities and level of care as described in this Section should not attempt to provide home care to patients receiving cytotoxic drug therapy. Instead, these patients should receive treatment in a hospital or other healthcare centre.

Any unused medications in the patient's home should be returned to the pharmacy for appropriate disposal.

18.1 Home care by nursing staff

Cytotoxic drugs should be administered only by licensed nurses with documented knowledge and experience with cytotoxic agents.

It is the responsibility of the institution providing the home care service to ensure that all cytotoxic drugs taken into the patient's home are appropriately packaged and labelled, and that the facilities and equipment meet recommended standards. All chemotherapy used in the home care situation must be prepared under the same conditions as all other chemotherapy; specifically in the hospital pharmacy department or in a community pharmacy complying with the same requirements.

Nursing staff must not reconstitute cytotoxic drugs in the patient's home.

All nurses administering chemotherapy in the patient's home must be adequately trained and have significant experience in the administration of cytotoxic agents.

Before proceeding with chemotherapy in the home, the nurse must verify that the following facilities are available:

(a) Hand washing facilities
(b) Laundry facilities
(c) Access to sewered toilet
(d) Secured waste storage

The nursing staff must also verify that the following equipment is available:

(a) Spill kit (as described in Section 14)
(b) Strong alkaline detergent with a pH $>$ 10
(c) Approved container for sharps
(d) Cytotoxic waste container
(e) Personal protective equipment

The transport of cytotoxic drugs from the pharmacy to the patient's home must be in accordance with procedures described in Section 2. Nursing staff should have a spill kit available and details of whom to contact in case of emergency.

18.2 Home care by relatives and/or patient

If the home care is to be provided by either relatives or by the patient, it is very important that this care is organized and coordinated in advance. In this way, with close cooperation between hospital staff, all aspects of the treatment may be explained and full education and training provided. Carers of patients receiving cytotoxic drug therapy should be provided with written information about cytotoxic drugs and the precautions to be taken while caring for patients during the time the drug may be excreted. Carers should be advised about special requirements of the particular drug used.

Written instructions should address:

(a) General information about the treatment the patient is to receive.
(b) Detailed information about the drugs which will be administered. For patients receiving oral chemotherapy, this should include information about potential interactions with over-the-counter medications.
(c) Detailed information on the storage and stability of the prepared drugs.
(d) Information and training on the routes of administration which will be utilised.
(e) If applicable, training on the care of infusion lines, catheters care, port systems and any other venous access devices likely to be used.

(f) Instructions and training on the use of various types of apparatus which may be used; for example, contained transfer devices, elastomeric infusion devices or ambulatory electronic pumps.
(g) Instructions and training in the use of any personal protective equipment (PPE)
(h) Details of safety precautions required in the handling of cytotoxic drugs, waste handling, excreta, and laundry.
(i) Strict instructions on how to proceed in the event of an emergency or other incident. For example, extravasation of any vesicant, any hypersensitivity reaction of the patient to the drug being administered, alarm of any electronic device being used, or the spill of a cytotoxic drug.
(j) Disposal of drugs that are no longer required.
(k) Provision of contact details for all staff likely to be of assistance. This will include home care nurses and hospital staff including medical and pharmacy personnel.
(l) Precautions to be taken where a care giver is pregnant or breast feeding.

In some countries there may be legal implications of having home care provided by a relative or by the patients. It may be that the administration of parenteral drugs is restricted to physicians and nurses. In the event of any accident or other incident it may be that the person administering the drug could be prosecuted for the illegal exercise of a medical act. This area may be quite controversial in the paediatric setting.

Section 19 – Risk management

19.1 Introduction

19.1.1 Hazard identification

In the past, safe handling guidelines have only dealt with cytotoxic or antineoplastic drugs with respect to health care worker exposure issues.[1,2] More recently, organizations and agencies have expanded the concept to include all hazardous drugs.[3–5] The National Institute for Occupational Safety and Health (NIOSH) in the United States identifies approximately 140 agents that fit its definition of hazardous drugs. The classification was based on a six-point definition modified from the ASHP definition of what constitutes a hazardous drug.[2] Two-thirds or approximately 90 of the hazardous drugs identified are classified as antineoplastic drugs.

Therefore, the first step in hazard identification for a health care institution would be to compile a list of all drugs used in the facility and to identify those drugs that are listed as hazardous drugs. A list of hazardous drugs should be made available to anyone who has the potential to come in contact with these drugs, including pharmacists and pharmacy technicians, nursing personnel, physicians, operating room personnel, shipping and receiving personnel, waste handlers, maintenance workers, workers in veterinary practices, and health and safety personnel.

19.1.2 Exposure assessment

Once the hazardous drugs for a facility have been identified, an exposure assessment should be completed by identifying the path that the hazardous drugs follow from when they enter the facility to when they leave as patient waste, contaminated laundry, IV bags, contaminated medical equipment etc. This includes materials receiving, transportation within the facility, storage (including refrigerators and freezers), drug preparation and administration, operating rooms, and laundry and waste handling. All potential sources of exposure should be identified. It is also important to identify all individuals who have the potential to come into contact with the hazardous drugs.

Environmental contamination within these areas can be determined by surface wipe samples or air sampling (see Section 10). Based on published reports, any area where hazardous drugs are used will most likely be contaminated with those drugs. Because only 6-8 drugs are commonly used as "markers" of exposure, this approach can only estimate the overall exposure from the dozens of drugs that may be in use.[6]

19.1.3 Exposure control (see also Section 5)

The basic components in a hierarchy of industrial hygiene controls have been identified and applied to many industrial settings. These include:

(a) Elimination of the hazard or substitution with a less hazardous chemical (this is not feasible in health care) or substitution of a work practice with a less hazardous one (the use of needle-less systems)
(b) Isolation of the hazard (storage of hazardous drugs separate from other drugs, limiting preparation of hazardous drugs to dedicated areas)
(c) Engineering controls (the use of biological safety cabinets, isolators or closed systems)
(d) Administrative Controls (training and education programs, availability of Material Safety Data Sheets)
(e) Personal Protective Equipment (the use of protective gloves, gowns, respiratory protection and eye protection)

19.1.4 Work organization

Personnel schedules and duties and work processes can be modified to help reduce the potential for exposure to hazardous drugs. These include:

(a) Rotation of staff to reduce fatigue
(b) Alternative duty for pregnant or nursing women
(c) Proper identification of hazardous drugs
(d) Safe and orderly flow of hazardous drugs through the facility

19.1.5 Medical surveillance

Medical surveillance involves collecting and interpreting data to detect changes in the health status of working populations potentially exposed to hazardous substances.

The elements of a medical surveillance program are used to establish a baseline of workers' health and then monitor their future health as it relates to their potential exposure to hazardous drugs. The elements of a medical surveillance program for hazardous drugs should include (at a minimum):

(a) Reproductive and general health questionnaires completed at the time of hire and annually thereafter.
(b) Blood work, including complete blood count, liver function tests, and urinalysis completed at the time of hire and annually thereafter
(c) Physical examination completed at the time of hire and then annually for any worker whose health questionnaire or blood work indicates an abnormal finding.
(d) Follow up for those workers who have shown health changes and/or have been exposed to hazardous drugs (e.g., through spills or during routine handling).

19.1.6 Early therapeutic intervention

This can involve medical treatment or intervention following:

(a) Contact of a drug with skin or eyes
(b) Development of a rash from exposure to a drug
(c) Abnormal laboratory findings

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Section 20 – Medicines management

20.1 Procedures for drug selection

20.1.1 Medication selection
Medication selection should be a multidisciplinary process, overseen by the respective institution's Pharmacy and Therapeutics Committee (P&T Committee) or other appropriate group. The process should involve medical staff (oncologist/haematologist), pharmacists, nursing and administrative staff.

20.1.2 Documentation – P&T committee
Written policies and procedures should be developed and implemented to define the functioning of the P&T committee or other appropriate group.

20.1.3 Documentation – medication selection
Written policies and procedures about the process of medication selection in an institution should be developed, approved and implemented, that include:

(a) How to request additions, changes or deletions to/from the formulary
(b) Evaluation process
(c) Dissemination of information about P&T Committee decisions
(d) Mechanism for updating the formulary or list (at least annually based on emerging information).

20.1.4 Criteria for medication selection
Medication selection should be based on safety, cost-effectiveness, and/or any pharmacotherapy innovation (for example, easier route of administration, reduced dosing frequency). Comparison should be made with alternatives already available at the institution.

20.1.5 Criteria for request(s)
Qualitative and/or quantitative criteria should be developed and implemented to evaluate the request, including:

(a) Clinical aspects (efficacy, safety)
(b) Availability of scientific evidence/documentation
(c) Pharmacotherapeutic criteria (dosages, administration route, premedication regimens, interactions)
(d) Pharmaceutical criteria (drug strength, stability and compatibility, convenience of drug presentation to usual doses, ease of manipulation, risk of breaking, potential for medication errors (sound alike, look-alike, labelling, packaging, etc.).
(e) Cost
(f) Specific criteria

20.1.6 Procuring non-formulary medication
A procedure for procuring non-formulary medication should be established.

20.1.7 Medication selection decisions
Medication selection decisions (additions/deletions/changes) and recommendations must be disseminated to health care professionals involved in patient care.

20.1.8 Updates
An updated hospital formulary or pharmacotherapeutic guide (printed or online) should be distributed to all the health-care staff (physicians, pharmacists and nurses). These documents summarise drugs available from the multidisciplinary process of medication selection, policies and guidelines of drug use at the institution and the minimum information needed to enhance drug rational use.

20.2 Procedures for drug purchasing

All drugs should enter the hospital through the hospital pharmacy, even those intended for clinical trial or compassionate use program and samples.

20.2.1 Purchasing decisions
Purchasing decisions are based on the medication selection process.

20.2.2 Criteria to evaluate purchasing process
Criteria are developed and implemented to evaluate the purchasing process, including: usage, generic policies, economic offers (industry promotions, flexible pricing and public tenders), pharmaceutical criteria (unit-dose packaging, strength of doses available, bar-coding), laboratory facilities (logistics, laboratory information), and labelling and patient safety considerations.

20.2.3 High cost/use medications review
High cost or/and high use medications should be reviewed regularly to ensure appropriate use of resources and compliance with formulary guidelines. Contracts for drug purchase, if entered into by the institution or group purchasing organisation of which the institution is a member, must be honoured.

20.2.4 Purchase approvals
Purchase of medication from wholesalers or manufacturers should be approved by a pharmacist or designate (such as a pharmacy technician) and must follow all applicable local regulatory laws and regulations. Products with very similar packaging should be avoided wherever possible

20.2.5 Purchase history
There should be a computerised system that provides information on purchase history and use for all medications managed by the pharmacy department.

20.2.6 Purchasing updates
Periodic updates on purchasing and use of medication should be made available to the hospital administration, directors of clinical units and the P&T Committee (to be used in their review process).

20.3 Procedures for stock control

20.3.1 Medication security
Medication must be secured in all storage areas in accordance with all local laws, regulations, and organisational policies.

20.3.2 Discrepancies
Drugs received are checked against the manufacturer's/wholesaler's delivery note/invoice and the pharmacy order form. Discrepancies should be reconciled by the responsible pharmacist or designate.

20.3.3 Update drug inventory
An updated (computerised or manual) drug inventory should be available that includes information about drug batch and expiry dates.

20.3.4 Drug inventory documentation
Written policies and procedures should be developed and implemented to regularly review drug inventory information with actual drug stock. Discrepancies should be analysed and corrective action(s) taken.

20.3.5 Discrepancies documentation
Written policies and procedures should be developed and implemented for handling drug shortages, outages and recalls including proper processes for communicating this information with other health care professionals.

20.3.6 Expiry dates
There should be a strict procedure for the checking of expiry dates (manual/automated) throughout the institution and for the removal of expired stock.

20.3.7 Disposal
Policies and procedures should be established for the disposal of expired or damaged stock and must comply with all applicable local regulatory laws and regulations.

20.3.8 Documentation – medication storage
Written policies and procedures about medication storage system/organisation (alphabetical order, pharmaceutical forms) and labelling (generic, brand names, expiry, appropriate warnings) should be developed and maintained.

20.3.9 Error prevention
To prevent errors from occurring, medication that can be easily mistaken for another (sounds alike, looks alike, similar labelling) must be separated in all areas of the health care organisation. This must include the modification of the medication storage system/organisation.

20.3.10 Storage guidelines
Drugs are stored in accordance with the manufacturer's recommendations and storage conditions are monitored periodically following organisational policy to ensure their effectiveness and safety (temperature, moisture, light protection).

20.3.11 Documentation – high manipulation risk drugs
Policies and procedures about drugs with high manipulation risk (cytotoxic or hazardous drugs) are developed and implemented that include: identification of special handling requirements, separate storage areas with measures to prevent/minimise breakage and personnel protection equipment should be available. Ideally this storage area should have an extraction fan which can be activated in an emergency. Cytotoxic spill kits should be available where appropriate

20.4 Procedure for re-use of drugs

20.4.1 Responsible parties
The pharmacy department is responsible for the management of all unused medications returned that were compounded and/or dispensed for oncology patients.

20.4.2 Documentation – medication return(s)
Written policies and procedures about the process/method of medication return to the pharmacy should be developed and implemented.

20.4.3 Quality control
A quality control policy on returned medications should be developed and implemented to address patient safety, including technical (integrity/packaging, labelling, defective devices, expiry dates) and physicochemical aspects (colour/precipitation).

20.4.4 Documentation – disposal
Written policies and procedures for the safe reuse or disposal of returned medication based on efficacy and safety criteria should be developed and implemented. This is mandatory for pharmacy-prepared sterile products. These criteria should consider stability and compatibility under actual handling conditions including storage or transportation when outside the pharmacy (temperature, humidity and light exposure) and microbial risk level according to potential for microbial growth. Only drugs which have remained within formal system controls may be reused. Drugs that have released to a patient, or into the community, should not be reused for other patients.

20.4.5 Causes for medication return
Causes/reasons of medication return are documented and recorded (manual/computerised) and the pharmacotherapy history is updated if needed.

20.4.6 References for accepted expiration dates
There is an updated table or chart of accepted expiration dates for commonly pharmacy-prepared sterile products according to stability and compatibility at the usual/standardised concentration range, vehicle and environmental conditions.

20.4.7 Documentation – medication re-use
Written policies and procedures for safely re-dispensing or recycling returned medication should be developed and implemented that include but are not limited to: process of new expiry date assignment, identification and labelling as recycled, re-dispensing process, dose banding, and optimum storage conditions to its immediate re-use. Health-care professionals involved in all these medication re-use processes are recorded.

20.4.8 Disposal
Policies and procedures for the disposal of expired or other unusable returned medication must follow all applicable local regulatory laws and regulations.

20.4.9 Bibliographies
Bibliographic sources (product approved labelling and reliable published stability data) used to establish criteria are referenced and available and basic information (tables/charts) is periodically updated.

20.5 Procedure for partial vials

20.5.1 Final concentrations
Irrespective of different dosage strengths of a drug which may be available, the final concentration should be the same to avoid medication preparation errors and facilitate stability concentration limits.

20.5.2 Maximal accepted expiration dates
There should be a table or chart available within the preparation area listing the maximal accepted expiration dates for drugs reconstituted in the sterile area using validated aseptic technique. This data should be based on the stability and compatibility at the final concentration, type and volume of reconstituent, microbial risk level, and optimal storage conditions (light protected, refrigerated).

20.5.3 Drugs in solution
Drugs provided in solution (not requiring reconstitution) which are manipulated using validated aseptic technique, should have a maximal expiry based on when they are first used. The institution should base this expiry on the microbial risk level and optimal storage conditions.

20.5.4 Labelling
Residual volume in multidose vials generated during antineoplastic compounding should be labelled with the reconstitution/first used date and time and the expiry according to recommended storage conditions.

20.5.5 Storage
Residual volumes in vials should be stored appropriately (strictly adhering to temperature, light, etc. criteria) and should be used before a new vial is opened.

20.5.6 Disposal
Policies and procedures for the disposal of expired or other unusable vials must follow all local applicable regulatory laws and regulations.

20.5.7 Bibliographies
Bibliographic sources (product approved labelling and reliable published stability data) used to establish criteria are referenced and available and basic information (tables/charts) should be regularly updated.

20.6 Procedures for use of unlicensed drugs

20.6.1 Documentation – unlicensed drugs
There should be written policies and procedures in place regarding the rational and safe use of unlicensed drugs in accordance with regulatory laws, patients' rights and ethics. Unlicensed drugs include: drugs not approved or licensed in a country but available in a foreign country used for a labelled indication (foreign drugs), off-label use of licensed drugs, and investigational drugs in the setting of clinical trials.

20.6.2 Foreign drug procedures
A procedure for purchasing, storage and stock control of foreign and compassionate use drugs should be developed and implemented.

20.6.3 Documentation – off label use drugs
Written policies and procedures should be developed and implemented for the effective and safe use of approved drugs for off-label use. This should include selection, prescription, preparation, dispensing, administration, and monitoring.

20.6.4 Documentation – foreign drugs
Written policies and procedures for the effective and safe use of foreign drugs should include selection, prescription, preparation, dispensing, administration, and monitoring.

20.6.5 Procedures – investigational drugs
A procedure for approving, receiving, storage and stock control of investigational drugs is developed and implemented.

20.6.6 Documentation – investigational drugs
Written policies and procedures for the effective and safe use of investigational drugs should be developed and implemented including prescription, preparation, dispensing, administration and monitoring according to local regulatory laws and institutional policies.

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Section 21 – Documentation

21.1 Staff

21.1.1 Health monitoring
If an institution offers employees routine blood testing, or any other test relating to the exposure to cytotoxic drugs, then this should be documented. If such routine health monitoring occurs it is recommended that a baseline measurement be taken prior to work in the area begins. Any abnormal test result and the resulting action taken should also be documented.

21.1.2 Exposure to cytotoxics
A log for all operators preparing cytotoxic drugs should be maintained indefinitely. At a minimum, this log should reflect the daily reconstituting activities of all operators. If more than one cabinet/isolator is available, the actual cabinet/isolator used should be noted. In the event of any incident or accident, additional details should be recorded including the name of the operator, the name of each drug involved, the number of products of each drug involved, the estimated drug exposure (for example, mg) the duration of exposure, and the location. This information should be available for both past and present employees.

21.1.3 Education and training
A record of all staff undergoing training in cytotoxic reconstitution should be maintained indefinitely. Similarly, a log should be kept of staff trained in the clean up of a cytotoxic spill. This will include any staff working in a pharmacy store where cytotoxics are kept, and any individual involved in the transport of cytotoxics around the hospital or outside the institution. A signature of the staff involved and the date that the training was completed should be recorded.

21.1.4 Validation
Details of validation of operators permitted to reconstitute cytotoxic drugs should be maintained on an ongoing basis.

21.2 Facilities

21.2.1 Microbiological monitoring
The results of any microbiological testing performed in the cytotoxic suite should be maintained for a period of 3 years or other specified time dictated by local or institutional requirements. This may include settle plates, finger dabs, broth inoculations, and any end product testing that is performed.

21.2.2 Contamination monitoring
The results of any monitoring for chemical contamination that is performed should be maintained for a period of 10 years or other specified time dictated by local or institutional requirements.

21.2.3 Maintenance log
An equipment maintenance log should be maintained. This will include the dates and results of all routine maintenance and certification relating to the cytotoxic facilities and isolators/cabinets. If equipment fails any test, the follow-up action taken should be detailed in this log. Details of any repairs, filter replacements, and any technical problems with equipment should be recorded on an ongoing basis.

21.2.4 Pressure differentials
On a daily basis, the pressure differentials within the cytotoxic suite should be checked and recorded in a log. This will include pressure differentials between any cleanrooms, airlock, and the external environment. Any pressure readings on an isolator cabinet should be checked daily and documented.

21.2.5 Temperature logs
Both a refrigeration temperature and a room temperature log should be maintained on a daily basis and kept for at least 3 years. Follow-up action taken as a result of temperature excursion should be documented.

21.2.6 Particle counts
The results of any particle counts performed should be documented.

21.2.7 Qualification and re-qualification
The results of qualification and re-qualification should be maintained indefinitely.

21.3 Transport

21.3.1 Outside the institution

A record should be kept of any cytotoxic preparations being transported out of the institution by courier to either a second institution or to a patient's home. The details should include the destination, contact details at destination, identity of person collecting the item, contents of package, storage conditions for package, date and time of collection, and identity of person packing the items.

21.3.2 Within the institution

A record may be kept of any cytotoxic preparations being transported. The details could include the destination, contents of package, date and time of delivery, and identity of person transporting the items.

21.4 Cytotoxic spills

A log of all cytotoxic spills occurring within the institution should be maintained for a period of 10 years or other specified time dictated by local or institutional requirements. The information collection should be that recorded on the spill report card or incident form detailed in Section 20.4.1. Details should also be recorded in the personal exposure record of employees involved in the spill and/or clean up.

21.5 Extravasation

A log of episodes of extravasation occurring within the institution should be maintained for a period of 10 years or other specified time dictated by local or institutional requirements (see Section 20.3). Details of follow up action taken should be recorded. This may be either a pharmacy or nursing responsibility.

21.6 Cleaning

21.6.1 Cabinet/isolator

A written procedure must be maintained for the cleaning of the biohazard cabinet or isolator. An institution may wish to have this routine cleaning documented on a daily basis. If any unusual event occurs requiring the shut down of the appliance or if a major spill occurs, this cleaning should be documented.

21.6.2 Sterile room

If sterile areas are cleaned by a member of the institution's cleaning staff, the date of the cleaning and the initials/signature of the cleaner should be recorded.

21.7 Workload statistics

Each institution should keep statistics which outline the workload of the cytotoxic preparation suite. These statistics should reflect not only the quantity of items prepared but include some measure of the complexity of the various items prepared. These figures should be reviewed on a regular basis in relation to the staffing level and mix of staff working in the area.

21.8 Procedure manual

Each institution should develop and maintain a procedure manual which details the policies and procedures for the appropriate manufacture of cytotoxic agents. This should include a description of aseptic technique, standard operating procedures for cytotoxic reconstitution, cleaning procedures, information on dealing with spills, transporting cytotoxics, and information on health monitoring. It should contain a full description of all personal protective equipment and special containment devices to be used in the preparation of cytotoxics. This manual should be regularly updated and should be available to staff at all times.

21.9 Material safety data sheets (MSDS)

Each institution should retain a compilation of these Material Safety Data Sheets, should ensure that they are current and reflect the actual products used within the institution, and should update the list whenever purchased products change. These MSDS should be readily available in all areas where hazardous drugs are stored or used.