

# ISOPP Standards for the Safe Handling of Cytotoxics

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Since the initial release of the International Society of Oncology Pharmacy Practitioners (ISOPP) Standards for the Safe Handling of Cytotoxic Drugs in 2007, much has evolved in oncology pharmacy. Safe handling practices have been refined and new hazardous agents have been discovered and developed for treatment to pose new challenges for workers caring for their patients.

As ISOPP continues to serve as a global leader to promote safe handling of hazardous agents, the ISOPP Standards task force was appointed by the society to undertake a comprehensive and evidence-based review of 21 old standards and added eight new standards to focus on additional areas of practice.

With the help of many members from across the world, the ISOPP Standards of Practice have been updated for the current state of practice in oncology pharmacy.

The following ISOPP members have contributed to one or more of the new standards:

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As can be clearly seen, the work of updating and releasing these new standards has been contributed to by many of the members of ISOPP, and we must thank them for their willingness to contribute their knowledge.

These Standards of Practice will continue to be used as an advocacy tool for pharmacists around the world

in improving cytotoxic safe handling and care for patients.

Shaun O'Connor (Australia)

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ISOPP Standards Committee Co-Chairs

## Section I – Introduction

Cancer is an uncontrolled growth and spread of cells that may affect almost any tissue of the body. Lung, breast, colorectal, and prostate cancer are the most common cancers worldwide. More than 19.3 million new cases of cancer were diagnosed in 2020. Cancer was responsible for almost 10 million deaths worldwide in 2020.<sup>1</sup>

### 1.1 Hazardous drugs

A hazardous drug is a drug whose inherent toxicity presents a danger to healthcare personnel. These drugs are identified based on one or more of the following characteristics:

- (a) carcinogenicity,
- (b) genotoxicity,
- (c) teratogenicity or other developmental toxicity,
- (d) reproductive toxicity,
- (e) toxicity at low doses in animal models or treated patients,
- (f) new drugs whose structure and/or toxicity profile mimics existing drugs determined hazardous by the five previous criteria.<sup>2-4</sup>

Hazardous drugs include chemotherapy drugs, antiviral drugs, hormones, some bioengineered drugs, and others.<sup>2</sup>

Hazardous drugs require safe handling precautions. The precautions required will depend on potential routes of exposure, anticipated toxicity, and activities involved in handling the drugs.

NIOSH publish the “List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings”<sup>2</sup> and eviQ publish an Australian version which can be accessed online for up-to-date information.<sup>5</sup>

### 1.2 Cytotoxic drugs

Cytotoxic drugs are a subset of hazardous drugs. Cytotoxic drugs (chemotherapy drugs, antineoplastic drugs) have been in clinical use for decades and are of great importance in the treatment of cancer and other diseases.<sup>6</sup> With close to 100 cytotoxic drugs now in use and more under development, cytotoxic drugs have opened new avenues ranging from improving patients’ quality of life to achieving cures.

Cytotoxic drugs are chemicals that affect cell growth and proliferation. Most 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.

Most cytotoxic drugs are myelosuppressive. This puts patients at a high risk of developing severe infections, particularly patients who are immunocompromised prior to treatment. For this reason, when parenteral cytotoxic drugs are prepared enhanced aseptic procedures must be strictly followed to prevent microbial contamination. Because most of these agents have a narrow therapeutic index, the accuracy of the preparation must also be assured. Pharmacy departments must have rigid checking procedures in place (see Section 11).

### 1.3 Occupational exposure

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

Published data related to occupational exposure prompted the US Occupational Safety and Health Administration (OSHA) to issue guidelines in 1986 for handling antineoplastic and other hazardous drugs by healthcare personnel. These guidelines have continued to be updated.<sup>4</sup>

A multitude of national organisations, both governmental and professional, continue to release safe handling guidelines for hazardous drugs, including cytotoxic drugs. Some prominent examples are ASHP,<sup>7</sup> USP,<sup>8</sup> European Commission (Eudralax),<sup>9</sup> and QuapoS.<sup>10</sup>

Some guidelines, including those above, have the status of enforceable national law; others are European directives (to be translated into national laws). Some are pure guidelines (non-enforceable but recommended as “best practice”). Additionally, there may be legislation that governs occupational exposure management.

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

One route of exposure is inhalation via droplets, particulates, and vapours. Many procedures can generate aerosols, including but not limited to the following:

- (a) piercing a vial and adding or removing material from a vial; manipulation of ampoules,
- (b) drug injection into an IV line,
- (c) removal of air from a syringe or infusion line,
- (d) leakage at the tubing, syringe, or stopcock connection,
- (e) clipping used needles,
- (f) drying of contaminated areas resulting in airborne drug particles.

Vapourisation of antineoplastic drugs has been recorded with drugs such as carmustine, ifosfamide, thiotepa, and cyclophosphamide.<sup>11-12</sup> Dermal contamination can arise from cytotoxic drug contamination on the outside of vials.<sup>13-19</sup> Thus, the environment may be contaminated even before cytotoxic reconstitution begins. Researchers have detected 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 the preparation and administration of drugs.<sup>20-23</sup>

Studies have found that most work surfaces in areas where cytotoxic drugs are handled are contaminated with the drugs.<sup>12,13,24-37</sup> In studies from several countries, working surfaces of biological safety cabinets, counter tops, floors, equipment and other surfaces have been shown to be contaminated.

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

Needlestick injuries are another potential route of exposure and sufficient care must be taken with aseptic technique and disposal of contaminated sharps.

The greatest risk is direct skin contact following a spill or leak where contamination of personnel and the environment may occur.

#### 1.4 Impact of hazardous drug exposure

As cytotoxic based cancer treatments have evolved and survivors live longer, secondary malignancies have emerged to be a significant impact of this therapy.<sup>38</sup>

In the 1970s, Falck et al.<sup>39</sup> indicated that unprotected nurses who worked in environments where hazardous drugs were prepared and administered had higher levels of mutagenic substances in their urine than non-exposed workers. This suggested that nursing personnel were being occupationally exposed to cytotoxic drugs, many of which were mutagenic. This was confirmed by numerous studies examining urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and other outcomes in pharmacists and nurses handling cytotoxic drugs.<sup>24,40,41</sup> Research has continued to show evidence of chromosomal abnormalities in workers handling cytotoxic drugs.<sup>42</sup>

Workers experienced other adverse health effects. A review of 14 studies linked exposure to antineoplastic drugs with adverse reproductive effects, and nine studies showed some positive association.<sup>43</sup> The most common reproductive effects found in these studies were increased fetal loss,<sup>44,45</sup> congenital malformations,<sup>46</sup> low birth weight, congenital abnormalities,<sup>47</sup> and infertility.<sup>48</sup>

Because a direct cause-and-effect relationship could not be determined, more direct methods of determining exposure have been developed. Refer to Section 26 for more information on medical surveillance.

#### 1.5 Newer drugs and classes

The introduction of monoclonal antibodies (mABs), conjugated antibodies (both radioactive and cytotoxic), and immunotherapy have posed more questions for pharmacists and staff handling cytotoxic and other hazardous drugs on a regular basis. Conjugated antibodies must be treated as the conjugated moiety. However, mABs and immunotherapy drugs have less clear guidance as these straddle the boundary between cytotoxic drugs and non-hazardous medications. For detailed recommendations on how to assess mABs, consider the advice in Section 22.

#### 1.6 New standards

With the update to these standards, new sections have been developed to improve the safety and quality of oncology pharmacy practice, both for workers and patients. These cover monoclonal antibodies, automation (including robotics), oral chemotherapy, investigational drugs, medical surveillance, electronic prescribing, dispensing and administration systems, dose banding, and safe handling in research facilities.

#### 1.7 Conclusions

Working with 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 leukemia or other cancers. To provide workers with the greatest protection, employers must implement necessary administrative and engineering controls and assure that workers use sound procedures for handling hazardous drugs.

Work practices of employees influence their own occupational exposure and that of those around them. Employees must stay current with the knowledge of the occupational risk posed by these drugs and ensure that their work practices follow the best current recommendations.

These standards provide general guidance to assist with the development of processes and procedures to facilitate safe work systems when dealing with cytotoxic drugs.

The importance of complying with state, national, and international laws and regulations that cover the workplace cannot be overstated. These standards may provide an advocacy tool for changing laws or provide extra safety through increased measures for workers.

While acknowledging the advances made in protecting workers from hazardous and cytotoxic drugs since the first version of these standards, it is still clear there are improvements to be made worldwide in handling hazardous and cytotoxic drugs. These standards represent an international consensus on steps to reduce occupational exposure to cytotoxic drugs in healthcare settings.

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## Section 2 – Transport of cytotoxic drugs

Cytotoxic drugs should be packaged, stored, and transported so as to provide physical and chemical protection for the drugs, personnel handling and transporting them and the environment. Throughout cytotoxic transport, the number of staff potentially exposed to cytotoxic drugs should be minimised. If drugs are spilled or damaged during transport, protection of the handlers is paramount and should be anticipated and planned for.

Transport must be in accordance with all local, state, provincial, and federal legislation concerning the transport of hazardous agents. This includes transport from suppliers and within the institution of commercial products and compounded admixtures.

For transport of cytotoxic waste, see Section 15.

### 2.1 Transport from supplier

#### 2.1.1 Primary containers

Primary containers should be made of materials that resist damage resulting in leakage. These include unbreakable plastic vials and glass vials in unbreakable plastic containers or over-wrapped in unbreakable plastic. Pharmacy departments should preferentially purchase products in unbreakable packs.

#### 2.1.2 Packaging

To prevent damage to primary containers, all products from the manufacturer or wholesaler should be protected with high-impact-resistant molded foam or other protective packaging. The packaging must also ensure containment of cytotoxic material in the event of breakage. The product should be placed in corrugated cardboard or other shippers with strong insulating properties to protect the contents from rough handling during transport.

Use of ice bricks or ice packs for refrigerated products is recommended to maintain temperature within an acceptable range. All refrigerated shipments should have a temperature monitor inside, preferably digital, that constantly monitors internal temperature within the shipper. Packaging should also contain enough foam to ensure the products do not move in transit. The load should be arranged so that movement of cartons is minimised.

#### 2.1.3 Labelling

Cytotoxic drugs must be easily identifiable by all personnel involved in their handling. The outer packaging of containers should display labels stating the goods are cytotoxic. Most countries have a standard symbol for cytotoxic drugs. On most labels, symbols are purple and often include a representation of a cell in telophase. Other labels may be yellow with a crab-like symbol. Labels may say “Danger/Caution Cytotoxic” or include an exclamation mark. Staff at the reception and storage points must be trained to recognise these symbols (see Section 4).

Safe temperature and light storage conditions should be labelled on the outer packaging. The shipper must have full instructions on what to do in case of an emergency, especially a spill or breakage. The label must state that contact with any leaked material should be avoided. Contact details for a source of advice should be included.

#### 2.1.4 Cytotoxic spill management

All personnel involved in the storage and transport of cytotoxic drugs should receive instruction on dealing with breakages and spills, including potential hazards and correct procedures. A cytotoxic spill kit should be available in the delivery vehicle. Delivery personnel should have a mobile phone and a contact number for immediate advice (see Section 14).

#### 2.1.5 Receiving and inventory control

Several studies show that surface contamination can exist on commercially supplied vials and primary packaging of cytotoxic drugs. Receiving and inventory control staff should be informed of this possibility.

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

Packages with signs of damage should be quarantined immediately, and the supplier contacted. Damaged cytotoxic vials should be disposed of as cytotoxic waste rather than returned to the supplier.

Staff should wash their hands after handling cytotoxic drug vials. Gloves are not a substitute for hand washing.

Gloves and other potentially contaminated items should be disposed of as cytotoxic waste.

Employers should make sure the storage area has general exhaust ventilation sufficient to dilute and remove airborne contaminants. Consideration should be given to installing a dedicated emergency exhaust fan large enough to quickly purge airborne contaminants and prevent contamination in adjacent areas (see Sections 1 and 6).

### 2.1.6 Responsibilities of drug manufacturers

Drug manufacturers should supply cytotoxic drugs in containers guaranteed to be free of contamination. Manufacturers should provide written certification by an independent laboratory that vials and primary packaging are not contaminated. Hospitals and buying groups should preferentially purchase products that are verified to be free of contamination.

Manufacturers must provide Safety Data Sheets (SDS) on all cytotoxic products, with explicit details on decontamination and protection measures to be taken for a spill or other accident. SDS should be kept current to accurately reflect the products in use. SDS should be available in all areas where cytotoxic drugs are stored or used (see Section 21). The manufacturer must 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 drugs and the safety measures required depend on the quantity of drugs transported.

### 2.2.1 Packaging

If large quantities of cytotoxic vials need to be transported, wheeled vehicles should be used. The products must be in their original packaging. The outer boxes must be wrapped in protective plastic and fastened to the vehicle using belts.

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 customised molded foam or a sponge-like material to securely position the drugs. The risk of damage can be minimised by vials contained in shock-absorbing unbreakable plastic containers designed to position and protect the vials.

### 2.2.2 Labelling

When transporting large quantities, labelling should indicate that the contents are cytotoxic. Smaller quantities that

need to be transported after unsealing the primary packaging should also have a label attached to the transport box. To avoid cross-contamination, transport boxes should be used solely for cytotoxic drugs.

An additional label should state 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

Personnel transporting commercial product within an institution should have a spill kit available. The contents and use of a spill kit are described in detail in Section 14. In the case of an accident, an appropriate staff member should be contacted. Until that staff member arrives, those transporting the drugs should not leave the accident site. They should open the spill kit to don protective clothing and mark the area with a warning sign to deter people from stepping into the contaminated area.

## 2.3 Transport of compounded admixture

### 2.3.1 Packaging

Cytotoxic admixtures should be individually packaged in a labelled, sealed, leak-proof container, with outer bags heat-sealed where possible. The container should offer protection from light and breakage in transit and should contain leakage if breakage occurs. Disposable containers, for example, sealed plastic bags, should be used wherever possible.

### 2.3.2 Drug Transport

Cytotoxic drugs must be delivered directly (without detours) to the wards and day care centers within a hospital. All personnel involved in the transport of cytotoxic drugs should receive instruction concerning potential hazards, correct handling, and procedures for breakages and spills.

Containers used for transporting prepared cytotoxic drugs should be hard-walled and robust. They should be made from molded foam or other material capable of protecting the product from a drop of one meter onto a concrete surface. Containers may be lined with absorbent material. Containers should be dedicated to the transport of cytotoxic drugs only.

The use of pneumatic tubes to transport cytotoxic drugs is not recommended.

### 2.3.3 Labelling

Cytotoxic drugs should be easily identifiable by all personnel involved in their handling. Any opaque outer packaging of containers should display clear warning labels stating the



goods are cytotoxic. Such labels should carry an identifying symbol for cytotoxic drugs. Appropriate temperature and light conditions and expiry dates must be labelled on the outer packaging.

#### **2.3.4 Cytotoxic spill management**

All personnel involved in the storage and transport of cytotoxic drugs must receive instruction on dealing with breakages and spills, including potential hazards and correct procedures. A cytotoxic spill kit should be available.

All training must be documented. Re-training must be carried out yearly and these records kept (see Sections 4 and 21).

#### **2.3.5 Documentation of cytotoxic drugs transport**

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

## Section 3 – Personnel

### 3.1 Responsibility

The preparation of parenteral cytotoxic drugs should be undertaken only by trained and credentialed personnel, ideally from pharmacy. A dedicated person, ideally the pharmacy manager or pharmacy department head, is responsible for developing, organising and supervising all activities related to pharmacy compounding of sterile cytotoxic drug preparations. Appropriate measures must be taken to ensure the safety of personnel during each preparation.

### 3.2 Considerations and exclusions from working in cytotoxic preparation

Personnel must be provided with freedom of choice and have the right not to work with cytotoxic drugs. Skill matched and appropriate duties should be provided to employees who choose not to, or are unable to, work with cytotoxic drugs. Some examples that may require an individual to temporarily not work with cytotoxic drugs are:

**Illness.** Personnel with upper respiratory infections or cutaneous infections should be excluded from preparing cytotoxic drugs. Personnel on immunosuppressive therapy should be risk assessed by an occupational physician.

**Family planning.** Refer to Section 26.

**Abnormal pathology results.** Refer to Section 26.

### 3.3 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 any other jewelry.

### 3.4 Staffing levels

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

#### 3.4.1 Number of staff members

Expected workload must be assessed when determining appropriate levels of staffing. Staffing should allow for the workload during the busiest period and should consider the complexity of products manufactured.

#### 3.4.2 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 biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI – refer to glossary) without a break. Often staff work in isolation, and sufficient breaks must be provided to maintain concentration.

Additionally, different types of gloves are assessed as being impermeable to chemotherapy drugs for a particular amount of time. This must be taken into consideration when determining how long a staff member is allowed to work without changing gloves or having a break.<sup>1,2</sup>

### References

1. ASTM F739, Standard Test Method for Resistance of Protective Clothing Materials by Liquids or Gases under Conditions of Continuous Exposure
2. ASTM D6978, Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs

## Section 4 – Education and training

### 4.1 Education on cytotoxic risks and safe handling

All staff who handle cytotoxic drugs must be provided with sufficient education and training applicable to their role, regarding the risks and safe handling of these drugs. This includes pharmacy, nursing, and medical staff, as well as support staff who transport cytotoxic drugs or clean possibly contaminated areas, where available, specific courses should be attended.

Patients and caregivers involved in the administration of chemotherapy in the home should receive basic education and training on safe handling, dealing with spills, waste disposal, and management of patients' excreta. Written instructions should be provided (see Section 18).

Maintenance staff, especially those external to the organisation (engineers, plumbers, etc.), should be made aware of cytotoxic hazards, and of mandatory safety procedures including appropriate personal protective equipment (PPE) before allowed into the cleanroom (refer to glossary) to operate.

#### 4.1.1 Content of educational courses<sup>1</sup>

An education program covering the risks of exposure to cytotoxic drugs and the measures required for safe handling and preparation should be developed.

This program may be tailored to groups of staff according to their levels of exposure to cytotoxic drugs. The program should contain the following elements for all staff:

- (a) Recognition of drugs that are cytotoxic.
- (b) Risks of handling and exposure to cytotoxic drugs, including institutional work re-assignment policies.
- (c) Location and use of safety stations (e.g. eyewash stations and showers).
- (d) Receipt, unpacking, transport and storage of cytotoxic drugs.
- (e) Handling and disposal of cytotoxic waste.
- (f) Cytotoxic spills and accidental exposure.
- (g) Hospital policies and procedures on cytotoxic management.

The following elements should be added for appropriate staff groups:

- (a) Basic pharmacology of cytotoxic drugs.
- (b) Theory of aseptic technique.
- (c) Operational standards for aseptic cytotoxic drug preparation and cytotoxic drug cleanroom standards.
- (d) PPE (including donning and doffing).
- (e) Safe handling aseptic techniques.
- (f) Safe handling of oral, topical, and pre-packaged hazardous drug dosage forms.
- (g) Theory of containment devices and barriers.
- (h) Theory of hierarchy of protection measures.
- (i) Prescribing cytotoxic drugs.
- (j) Verification of cytotoxic prescriptions and pharmacy medication checks (clinical, computer order entry, and final product release).
- (k) Cytotoxic drug use processes (drug selection, prescription verification, preparation (or purchasing), dispensing, administration, and drug use evaluation).
  - (l) Documentation requirements for pharmacy medication checks and hazardous drug cleanroom standards.
- (m) Specific patient safety and compliance standards, including intrathecal doses, vinca alkaloids, outpatient hazardous drug prescription labelling, and latex allergies.

The education provided should be tailored to the needs of the individual based on job description, level of education, and specific responsibilities. Education should be ongoing, with attendance at in-house or external courses, seminars, and symposia strongly encouraged and documented. Consideration should be given to the re-education of staff members who have had a prolonged break from work.

#### 4.1.2 Education providers

Education should be provided by academic, clinical, or technical specialists, depending on the education required. Staff should attend accredited courses, if available. The course provider or institution should specify the number of hours to be completed.

#### 4.1.3 Documentation

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

#### 4.1.4 Certification

Formal external educational courses offered by professional bodies should preferably have received accreditation from relevant jurisdictional bodies 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 regularly. This may be achieved by a competency test or examination at the end of the program.

#### 4.1.6 Re-education

It is recommended that the education program be repeated every 2 to 3 years to keep pace with the introduction of new drugs and technical innovations. Education should also be repeated whenever any major change in practice occurs. Staff who have been absent from cancer services for 6 months or more should complete the education program before returning to work.

### 4.2 Training in the manipulation and safe handling of cytotoxic drugs

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

Staff responsible for the aseptic preparation of cytotoxic drugs should first be trained and demonstrate competency in the aseptic preparation of non-cytotoxic drugs. Staff working in cytotoxic or non-cytotoxic aseptic preparation must have their competency assessed after the first training session and at least yearly thereafter.

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

This training may be offered in-house or by an external training provider. If internal training is provided, staff with expertise in the area, spill kits, and resources used in the preparation of cytotoxic drugs must be made available.

Staff members handling cytotoxic drugs should be supplied with up-to-date information on all aspects of the safe handling of cytotoxic drugs and the reported hazards of low-level exposure to them.

#### 4.2.1 Content of training courses

A structured training program in parenteral cytotoxic preparation should be developed. Training should be tailored to the needs of the individual based on job description and related risk. This program may contain the following elements:

- (a) Recognition of which agents are cytotoxic.
- (b) Potential risks of exposure to or handling of cytotoxic drugs.
- (c) Operational standards for aseptic cytotoxic drug preparation.
- (d) Operational standards for C-SEC (containment secondary engineering controls) including airflow, pressures and safe operating parameters.
- (e) Use of a relevant C-PEC (containment primary engineering controls: biological safety cabinet (BSC) or Compounding Aseptic Containment Isolator (CACI), including parameters for safe operation
- (f) Safe handling aseptic techniques and protective routines.
- (g) Use of institution-specific specialised equipment, including closed-system transfer devices (CSTDs).
- (h) Safe handling of pre-packaged cytotoxic drug dosage forms.
  - (i) Handling of cytotoxic waste.
  - (j) Dealing with cytotoxic spills and accidental exposure.
- (k) Emergency procedures and location and use of safety stations.
  - (l) Documentation requirements for pharmacy medication checks and hazardous drug cleanroom standards.
- (m) Receipt, unpacking, and storage of cytotoxic drugs.
- (n) Labelling and packaging.
- (o) Transport of cytotoxic drugs.
- (p) Environmental monitoring.
- (q) Cleaning procedures.
- (r) Employee health monitoring.
- (s) Verification of cytotoxic prescriptions and pharmacy medication checks (clinical, computer order entry, and final product).
- (t) Patient safety and compliance standards including intrathecal doses, vinca alkaloids, outpatient hazardous drug prescription labelling, and latex allergies.

Training should be ongoing with regular updates for any new procedures or products and should include periodic tests of competency. Whenever a new hazardous drug is introduced into the workplace, staff should receive information about safe and effective product preparation, documentation requirements, and potential risks of exposure to the drug.

Each institution should develop and maintain a procedure manual which details the policies and procedures for the manufacture and administration of cytotoxic drugs.

This should include a description of aseptic technique, standard operating procedures (SOPs) for cytotoxic preparation and administration, cleaning procedures, dealing with spills, transporting cytotoxic drugs, and health monitoring. It should contain a full description of all personal protective equipment and equipment, robotics, and special containment devices to be used in the preparation of cytotoxic drugs. 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 providing instructional resources and professional publications in the principles and skills of aseptic technique is available, it is recommended that personnel attend. SOPs for training should be developed and maintained. Each type of procedure to be undertaken should have a specific and detailed SOP. Before personnel attempt to prepare or administer a drug for a patient, they must be trained in that particular SOP.

#### 4.2.3 Documentation

The training of staff in parenteral cytotoxic preparation must be structured, and all stages should be documented. Records of training received should be retained indefinitely in the staff member's human resources file.

#### 4.2.4 Validation

*Validation of processes.* The objective of validation is to demonstrate that the staff and processes involved in aseptic preparation are capable of maintaining the sterility of the product. The media fill test (Broth test) is intended to simulate routine aseptic operations using microbiological media to produce units that can be tested for contamination.

The media fill test must use the same devices and transfer methods as the routine procedure to produce an equivalent number of preparations. 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 sterilised CACI are used, the sterilisation method can inhibit the microbiological growth and give false negative results.

The test must be performed at least 3 times and filled units should be incubated at the designated temperature for 14 days. The expected results are that no positive units are found. In the case of a positive result, the cause of the failure must be investigated, focusing on whether the facility, process, or operator is the root cause.

Revalidation of the process should be performed when the root cause is identified. Revalidation should also be performed when any change is made to the process or facilities.

*Validation of the operator.* The first objective is to demonstrate that the aseptic technique of the operator undertaking the aseptic manipulation maintains the sterility of the product. All aseptic manipulation should be broken into a number of key steps, such as withdrawing solution from a vial or addition of a solution to an infusion bag. Each key step may be investigated using a media fill test.

A second objective is to ensure that the operator can carry out these aseptic manipulations without environmental or self-contamination. The operator should also be able to demonstrate an understanding of the safe handling techniques required to prevent exposure of equipment and staff to cytotoxic drugs. The use of a fluorescein dye detected with ultraviolet light is most commonly used.

Revalidation should occur on a regular basis. The frequency will depend on staff turnover, duration of rosters, and other factors. At a minimum, staff who regularly prepare parenteral cytotoxic drugs should undergo a yearly validation test.

*Validation of training.* The objective of validation is to confirm that all staff have a satisfactory level of knowledge and competency for the duties required. The training program should be validated and should include the critical sterile cytotoxic preparation processes, including aseptic process and chemical contamination risks. The impact of training should be validated by competency checks.

#### 4.2.5 Evaluation

Ongoing feedback from both trainees and trainers 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 Retraining

Retraining is required every 2 to 3 years and whenever any major change in practice occurs, such as the introduction of a new cytotoxic agent, process, procedure, or technology.

Retraining of cytotoxic spill clean-up should take place yearly. A record of the retraining should include the date, trainee signature, and trainer signature.

#### Reference

1. BC Cancer Agency. BCCA Pharmacy Practice Standards for Hazardous Drugs, [http://www.bccancer.bc.ca/pharmacy-site/Documents/Safe%20Handling/8%20Safe%20Handling%20Standards%20Summary\\_September%202016.pdf](http://www.bccancer.bc.ca/pharmacy-site/Documents/Safe%20Handling/8%20Safe%20Handling%20Standards%20Summary_September%202016.pdf) (September 2016, accessed 20 July 2019)



## Section 5 – Hierarchic order in protection measures

Standards for industrial hygiene commonly include an obligation to follow a hierarchic order of level of protection for employees in the 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 risks related to exposure to carcinogens or mutagens at work. Most national regulations and laws on industrial health and safety also include such an obligation.

Taking into account the provisions of relevant laws and regulations, the employer must perform a risk analysis that includes the following steps.

- (a) Definition of the work areas to be evaluated.
- (b) Ascertainment of hazards and burdens (as through classification of substances).
- (c) Evaluation of hazards and burdens.
- (d) Specification of necessary measures to take.
- (e) Testing and evaluation of the effectiveness of the measures and identification of resulting hazards.

The levels of protection measures in descending order of importance (hierarchical order)<sup>1</sup> are discussed below. It is imperative that measures of protection are implemented starting with level 1 and ending with level 5.

### 5.1 + 5.2 Levels 1 and 2: Elimination and substitution

If a less toxic drug has equal or better efficacy with a similar or better side-effect profile, changing drugs may be an option that could be discussed with the treating oncologist. Changing to a less toxic drug is rarely possible in the treatment of cancer patients.

If levels 1 and 2 are impossible, insufficient, or not practical the next level is applied.

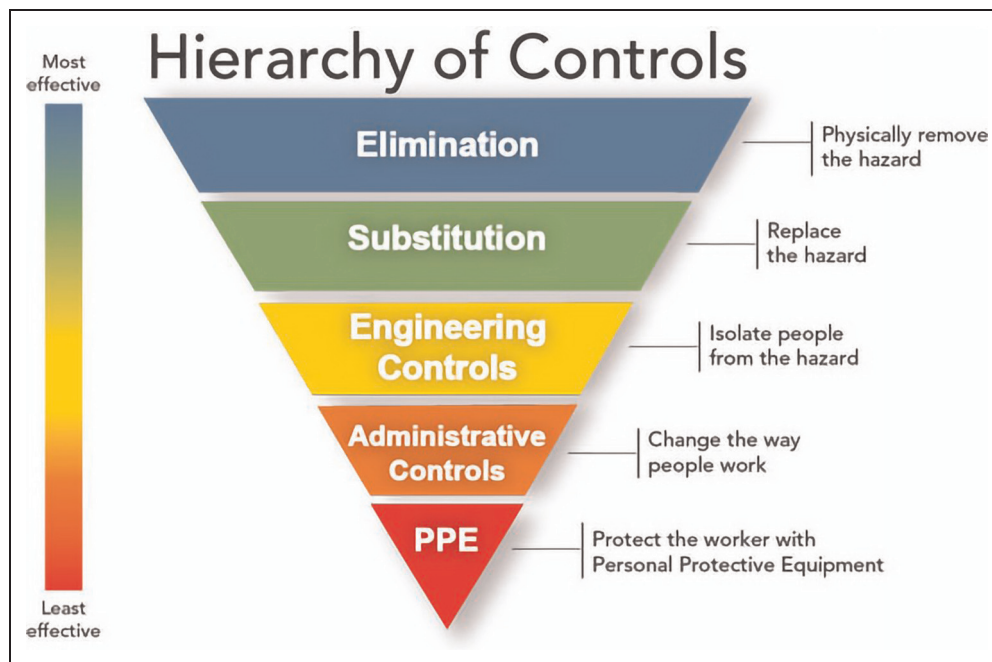


Diagram 1. Hierarchy of controls.<sup>1</sup>

Outsourcing of compounding is a method of elimination, but from a health system wide perspective it still requires appropriate engineering, administrative and PPE controls to fulfil the hierarchy of controls at the external compounding site. The use of licensed Ready-to-Administer products (RTAs) is a new development that can also be considered locally as elimination, as no preparation is needed in the hospital pharmacy. These measures reduce the number of potentially exposed workers in the organisation.

### 5.3 Level 3: Engineering and ventilation controls

Cytotoxic drug safety cabinet (CDSC) and CACIs are level 3 measures. CDSCs provide controlled airflow, protection shields, and HEPA filters. CACI provide hatches, glove ports, HEPA filters, and a physical barrier between the product and operator. CSTDs provide an extra level of protection for employees (see Section 7).

None of these features will completely prevent contamination within the CDSC or CACI. Once contamination has occurred, it will inevitably enter the environment.

Engineering and ventilation controls must be used for cytotoxic compounding, along with levels 4 (administrative controls) and 5 (PPE).

### 5.4 Level 4: Administrative controls, organisation measures

Administrative controls seek to minimise exposure duration, number of workers exposed and maximise effectiveness of engineering controls. Some examples of administrative controls are SOPs, training, and operator validation.

For cytotoxic compounding within CDSC and CACI, training and validation procedures must be in place.

### 5.5 Level 5: PPE (also see Section 6)

The use of PPE is the last line of protection for workers and must be preceded by engineering and administrative controls to minimise toxic products in the environment.

Gloves, masks, gowns, goggles or face shields, and other equipment create a temporary barrier between the contamination and the operator. Training on adequate donning and removal of PPE should be ensured.

Safe work practices should be incorporated into SOPs and 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.

### References

1. NIOSH [2016]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. Connor TH, MacKenzie BA, DeBord DG, Trout DB and O'Callaghan JP. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication Number 2016-161 (Supersedes 2014-138).
2. NIOSH: Hierarchy of controls, <https://www.cdc.gov/niosh/topics/hierarchy/default.html> [Accessed October 2020].
3. Safe Work Australia: Model Code of Practice How to manage work health and safety risks. <https://www.safeworkaustralia.gov.au/resources-and-publications/model-codes-practice/model-code-practice-how-manage-work-health-and-safety-risks> [Accessed October 2020].
4. Diagram source: CDC – NIOSH from <https://www.cdc.gov/niosh/topics/hierarchy/default.html>.

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

Facilities for the sterile reconstitution of cytotoxic agents need to ensure the protection of the product and 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 ensure 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 cytotoxic drugs. Taking into account the pharmaceutical analysis and the quality control implemented, centralised preparation improves the quality of the preparation and the safety of patients. Centralisation of services also provides economic benefits.

Centralisation is commonly located in the pharmacy. Many institutions have a satellite pharmacy with a preparation facility located within an oncology outpatient department or close to the inpatient ward where chemotherapy is most commonly administered. This offers ease of transport of cytotoxic drugs and enhanced communication among pharmacy, medical, and nursing staff.

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

### 6.2 Facilities

Due to the risks of environmental chemical contamination and chemical cross contamination, cytotoxic reconstitution and preparation must be performed in a controlled area room (cleanroom, technically referred to as Containment Secondary Engineering Control (C-SEC)). The cleanroom should be externally vented with autonomous heating, ventilation, and air conditioning systems (HVAC) and dedicated to those tasks with similarly dedicated equipment.

Compounding Aseptic Containment Isolators (CACIs) may not need these requirements.

Access to the cleanroom must be restricted to trained personnel. A warning sign must clearly state this. The use of standard symbols and colours to identify cytotoxic agents is recommended. This sign should use 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. Surfaces should be designed to minimise particle shedding and prevent build-up of particulate matter. The design must facilitate effective cleaning. The cleanroom and anteroom should have fixed walls. Walls must be lined with a smooth, durable surface and lighting recessed into the ceiling. The room should contain as few projecting ledges and shelves as possible. Floors should be poured and seamless if possible. Vinyl tiles have been shown to trap drug particles.

There should be emergency eye wash facilities available. Eyes that become contaminated should undergo sustained irrigation with 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 (“Class”) of cleanrooms is given by the ISO 14644-1 international standard.<sup>1</sup> 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 (GMP) Annex 1, Volume 4, Manufacture of Sterile Medicinal Products,<sup>2</sup> and by the PIC/S Guidelines.<sup>3</sup> EudraLex applies to the pharmaceutical industry while the

PIC/S Guidelines apply to pharmaceutical inspection services controlling hospital pharmacies.

Cleanrooms are technically referred to as Containment Secondary Engineering Controls (C-SEC).

This classification takes into account particulate and microbiological contamination. The room should be designed to facilitate asepsis in the handling and preparation of cytotoxic drugs and provide containment of cytotoxic drugs if there is a failure of the cytotoxic drug safety cabinet (CDSC) or CACI or spillage outside the cabinet or CACI. The requirements for “Class” or “Grade” environments will depend upon the type of preparation and the equipment used.

(a) Type of preparation

Preparation of sterile cytotoxic drugs is 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).

Both unidirectional (formerly called laminar) airflow CDSCs and isolators are able to guarantee a Grade A environment. They differ mainly in the

requirements for the immediate environment of the equipment used. Refer to Section 8 for detailed information on CDSC and CACI.

ISO classes can be found in the ISO 14644 Standards.<sup>1</sup> Grade A/B environments in EudraLex correspond approximately to ISO classification 5, Grade C to ISO 7, and Grade D to ISO 8.

According to the PIC/S Guidelines,<sup>3</sup> when a unidirectional airflow hood (CDSC) is used for aseptic manipulations, the recommended grade of background environment is given in Table 3.

According to USP <800>, when preparing sterile hazardous drugs, the CDSC or CACI (Class 5) must be located in a controlled room, which may either be an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified containment segregated compounding area. If the background environment is not controlled, the beyond-use date (BUD) of all compounded sterile preparations (CSPs) prepared must be limited as described in USP Chapter <797>. According to USP, 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 PIC/S Guidelines,<sup>3</sup> when a unidirectional airflow hood (CDSC) is used for aseptic manipulations, the recommended grade of background environment is as follows:

- (a) Aseptic preparation of products with shelf-life <24 h: at least Grade D.
- (b) Aseptic preparation of products with shelf life >24 h: at least Grade B.\*
  - \* If aseptic procedures are extensively documented, grade C could be accepted for facilities pre-dating the introduction of the PIC/S Guidelines. In that case, grade B clothing should be worn.

If an isolator is used (permanently closed, refer to Section 8), the recommended grade of background environment is as follows:

- (a) Aseptic preparation of products with shelf life < 24 h: at least Grade D.

**Table 1.** Particle classification of controlled atmosphere areas, according to GMP, Annex 1.

Grade	At rest		In activity	
	Maximum number of particles/m <sup>3</sup> ≥			
	0.5 µm	5 µm	0.5 µm	5 µm
A	3520	20	3520	20
B	3520	29	352,000	2900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	Not defined	Not defined

**Table 2.** Microbiological monitoring of controlled areas “in activity,” in accordance with GMP, Annex 1.

Recommended microbiological contamination limits (average values)				
Grade	Air sample CFU/m <sup>3</sup>	Petri dishes (diameter: 90 mm) CFU/4 h <sup>1</sup>	Contact plate (diameter: 55 mm) CFU/plate	Glove print (five fingers) CFU/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

CFU: colony forming unit.

<sup>1</sup>Petri dishes can be exposed for less than 4 h.

**Table 3.** Background environment according to the equipment used to obtain a Grade A environment.

	Working environment	Background environment
CDSC	Grade A	Grade B
CACI	Grade A	Grade D

- (b) Aseptic preparation of products with shelf life > 24 h: at least Grade D.

The background environment for filling terminally sterilised products is at least Grade C.

An anteroom leading to a positive pressure room may be Grade D (ISO Class 8), but an anteroom leading to a negative pressure room must meet at least Grade C (ISO Class 7) criteria so that air drawn into the negative pressure environment is of the same Grade C (ISO Class 7) quality. A pressure indicator should be installed that can be monitored for correct room pressurisation.

The CDSC and isolator should be completely 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 on the pressure type of the isolator, and the type of pass-through hatches. Positive air pressure isolators, which are totally and permanently enclosed, are located in at least a D Grade (ISO 8) environment. Negative air pressure isolators must be located in at least a Grade C (ISO 7) environment (PIC/S Guidelines).

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

For more information regarding types of isolators, see Section 8.

### 6.2.2 Pressure differentials

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. Pressure differentials with the surrounding environment may be positive or negative.

*Positive pressure differential.* Positive pressure differential consists of positive air pressure of the preparation room and negative air pressure of the airlock hatches and the anteroom. The negative air pressure of the hatches and personnel zone acts as a trap to isolate potentially contaminated air.

*Negative pressure differential.* Negative pressure differential consists of negative air pressure of the preparation room and positive air pressure of the airlock hatches and the

anteroom. The positive air pressure of the hatches acts as a barrier.

*Pressure differential between adjacent rooms.* EudraLex<sup>2</sup> recommends a 10–15 Pa pressure difference between adjacent rooms of different grades. This does not apply in the case of a negative pressure room.

A typical graduation configuration for a cleanroom used for aseptic preparation is given below:

- (a) 10–15 Pa between Grades A and B,
- (b) 8–10 Pa between Grades B and C,
- (c) 2–6 Pa between Grades C and D,
- (d) 2 Pa between Grade D and surrounding zone.

This example of graduation has to be adapted to reach the above proposed pressure differential (a) or (b) for aseptic preparation of cytotoxic drugs.

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

According to USP 800,<sup>5</sup> there is no option for the pressure of the preparation room which should be negative (between 0.01 and 0.03 inches of water column (between ~ 2.5 and 7.5 Pa) relative to all adjacent areas).

According to the PIC/S Guidelines,<sup>3</sup> aseptic preparations, either open or closed procedures, are to be prepared in Grade A environment with surrounding environment placed in positive pressure. Preparation of hazardous pharmaceuticals, such as cytotoxic drugs, radiopharmaceuticals, and radio-labeled blood products, can be prepared under negative pressure to protect the operator and environment from contamination, but only with appropriate precautions (appropriate background room air quality, positive pressure airlock systems) against microbial contamination of the product.

Both PIC/S and USP 800 state that laminar airflow workbenches (LAFWs) are not suitable for compounding sterile hazardous products and recommend the use of CDSCs with a vertical downflow exhausting vertically from the cabinet, not towards the operator.

Combining both recommendations, CDSCs 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).

Anterooms must be ISO Class 7 or better and maintain a minimum of 30 air changes per hour of HEPA-filtered supply air and a positive pressure of at least 0.2 inches of water column relative to all adjacent unclassified areas.



### 6.2.3 Air changes

A minimum air change per hour (ACPH) of 20 room volumes is required. Areas known to generate large number of particles, such as changing rooms, may have up to 60 ACPH. According to USP <800>, if the room is Grade C (ISO 7), the minimum should be 30 ACPH. If the room is not controlled, the minimum should be 12 ACPH.

### 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. According to USP 800, all engineering controls for sterile hazardous drug compounding must be externally vented (preparation room, buffer room, anteroom) even for unclassified areas.

A HEPA exhaust filter should be used to decrease contamination of the air exhausted. However, some anticancer drugs are vapourised and pass through HEPA filters. Some countries, for example Australia, mandate the use of activated carbon filters to trap vapourised cytotoxics. However, these filters may not guarantee complete retention (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

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

The humidity must be controlled to prevent corrosion and condensation on work surfaces and provide operator comfort. In addition, for CACIs which are sterilised by hydrogen peroxide vapour, the humidity of the surrounding environment must be strictly controlled. The human comfort zone is generally in the range of 30–70% relative humidity. For CACIs sterilised 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. 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.

The anteroom must be the only access to the cytotoxic cleanroom. If possible, this anteroom should not share access to other non-cytotoxic cleanrooms to prevent cross contamination. 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 staff can check that they are appropriately gowned before 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. Separate circulation zones should be identified to allow discarding of 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. These hatches may be between the cleanroom and the anteroom or between the cleanroom and the external environment. If the latter option is selected, interlocking doors must be used and the unit must be HEPA filtered. Hatch doors should be fitted with an audible or visual alarm to prevent doors being opened simultaneously. For specific hatches used for entry to a pharmaceutical CACI, see Section 8.

Separate hatches for entry and exit of products are preferable to minimise cross-contamination.

### 6.2.8 Storage room

According to USP 800, hazardous drugs should be stored separately from other stock to prevent contamination and personnel exposure.<sup>5</sup> These drugs must be stored in an externally ventilated, negative-pressure room with at least 12 ACPH. Refrigerated antineoplastic hazardous drugs must be stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH (e.g. storage room, buffer room, or containment segregated compounding area). If a refrigerator is placed in a negative pressure buffer room, an exhaust located adjacent to the refrigerator's compressor and behind the refrigerator should be considered. Hazardous drugs should be handled with caution using appropriate chemotherapy gloves during distribution, receiving, storage, preparing for administration, and disposal.

### 6.2.9 Monitoring of facilities

A monitoring program should be established. In controlled workplaces, parameters to be monitored include 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 checklist should be used to record 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 use of manometer alarms, preferably visual, that 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). Active air sampling should be done regularly. Testing must be carried out more frequently if any abnormality is detected or if any maintenance or repair work is carried out.

The frequency of monitoring required is listed in Tables 4 and 5.<sup>3</sup>

### 6.2.10 Microbiological monitoring

Passive air sampling should be performed using settle plates placed according to a sampling plan. 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 h. Maximum acceptable levels of microbiological contamination depend on the environment grade<sup>2</sup> and are given in Table 2.

Active air sampling is performed using biocollectors. 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<sup>2</sup> and are given in Table 2.

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 s is likely to be satisfactory. Maximum acceptable levels of microbiological contamination for contact plates depend on the environment grade<sup>2</sup> and are given in Table 2.

### 6.2.11 Air particle sampling

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

Maximum acceptable levels of particulate contamination depend on the environment grade (see Table 1).<sup>2</sup> Maximum permitted levels should be given at rest and under normal operating conditions. The particulate conditions at rest should be achieved after a clean-up period of 15–20 min (guidance value) after completion of operations. For a 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 (e.g. over-wrapping of sterile medical devices). In this case, particle counts above the specifications can be generated without compromising the quality of the preparation.

**Table 4.** Minimum frequency of physical monitoring.

Cytotoxic drug safety cabinets (CDSCs)	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
CACI glove integrity	Visual checks every session
Pressure differentials across HEPA filters	Before beginning of work, usually daily
CACI pressure hold test (with gloves attached)	Weekly
Pressure differentials between rooms	Before beginning of work, usually daily

**Table 5.** Minimum frequency for microbiological monitoring.

Method	Frequency
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

Consequently, particle control should be focused on at-rest conditions.

### 6.2.12 Certification and quality assurance

Whenever possible, all equipment and processes used for cytotoxic preparation that affect product sterility or attributes should be qualified or validated. Certificates issued should 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 equipment used. This includes the CDSC, CACI, and automated filling pump. This qualification process consists of four steps.

1. *Design qualification (DQ)*. Documented verification that the proposed design of facilities, systems, and equipment is suitable for the intended purpose. Approval of the design and drawing must be obtained in accordance with local regulations by the body responsible for pharmacy practice (state board of pharmacy, pharmaceutical society, licence inspector), and by the pharmacist responsible for the unit.
2. *Installation qualification (IQ)*. 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. *Operational qualification (OQ)*. 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:
  - (a) HEPA filter integrity test,
  - (b) functional check of pressure regulation and alarms,
  - (c) air change rate per hour (ACPH),
  - (d) particle count,
  - (e) pressure differential,
  - (f) noise level,
  - (g) light level.
4. *Performance qualification (PQ)*. 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:
  - (a) checking procedures of use and monitoring of the installation,
  - (b) air distribution studies.

### 6.2.13 Validation

Validation is the documented evidence that a process operating within established parameters can effectively and consistently produce cytotoxic drugs meeting all specifications and quality attributes. In sterile facilities, validation is required that the processes used during aseptic preparation maintain the sterility of the end product (see Section 4.10).

## 6.3 Clothing and PPE

The selection and use of PPE should ensure the sterility of the end product and protect the operator.

PPE must be worn to protect personnel during cytotoxic reconstitution and other activities where they may come into contact with cytotoxic drugs. Activities 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 on the grade of room in which the operator is working. The highest level of protection is for zones A/B where aseptic manipulations are performed (CDSC in a Grade B room). The examples of PPE required by grade are shown in Table 6.

### 6.3.1 Gowns

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

- (a) long and closed at the neck,
- (b) long sleeves with cuffs gripped at the wrist,

**Table 6.** Clothing required for differing grades of environment.

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 that does not shed fibres or particles Sterile clothing capable of retaining particles shed by operator

- (c) disposable sleeve covers to protect the wrist and lower arm,
- (d) waterproof material for the front and sleeves,
- (e) sterile,
- (f) non-linting.

Additionally, USP 800 recommends the following characteristics:

- (a) shown to resist permeability by hazardous drugs,
- (b) made of polyethylene-coated polypropylene or other laminate materials as these offer better protection from hazardous drugs,
- (c) closure in the back (no open front),
- (d) closed cuffs that are elastic or knit,
- (e) no seams or closures that could allow hazardous drug to pass through.

Integrated coveralls that include head and foot coverings are suitable for protecting against microbiological and chemical contamination.

According to USP 800, gowns must be changed according to manufacturer's data on permeation. If no permeation information is available for the gowns used, gowns must be changed every 2 to 3 h or immediately after a spill or splash. To prevent cross contamination and exposure, gowns worn in hazardous drug handling areas must not be worn to other areas.

Head and hair covers (including beard and moustache), shoe covers, and sleeve covers provide protection from contact with hazardous drug residue according to USP 800.

Disposable sleeve covers may be used to protect areas of the arm that may come in contact with hazardous drugs. Disposable sleeve covers made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials.

Overshoes should be worn. Dedicated shoes should be used for this purpose. According to USP 800, a second shoe cover is recommended in the hazardous drug compounding area. It should be donned before entering and doffed when exiting to limit contamination of other areas.

### 6.3.2 Masks

When compounding hazardous drugs, surgical masks must not be used as they do not provide respiratory protection. A type P2 or P3 mask for solids or liquids should be used when changing a pre-filter, in the event of any accidental contamination, and for oral preparations.

USP 800 specifies that an appropriate full-face piece, chemical cartridge-type respirator, or powered air-purifying respirator (PAPR) should be worn when there is a risk of respiratory exposure to hazardous drugs, including the following:

- (a) attending to hazardous drug spills larger than what can be contained with a spill kit,
- (b) deactivating, decontaminating, and cleaning underneath the work surface of a CDSC,
- (c) when there is a known or suspected airborne exposure to powders or vapours.

### 6.3.3 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). USP 800 states that eyeglasses alone or safety glasses with side shields do not protect the eyes adequately from splashes. Face shields in combination with goggles provide a full range of protection against splashes to the face and eyes. Face shields alone do not provide full eye and face protection.

### 6.3.4 Gloves

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

- (a) sterile, non-powdered,
- (b) latex (consider latex-sensitive workers), nitrile, or neoprene gloves may be used if they have been validated for cytotoxic reconstitution.

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

It is important to use resistant materials that have been tested for the specific environmental conditions and cytotoxic products used. Products identified by general nomenclature, such as "cytotoxic glove," may not ensure adequate protection in certain situations. Some examples of conditions which require consideration of resistance via further testing are:

- (a) HIPEC procedure (direct contact with cytotoxic drug for 30 min at 42.8 °C),
- (b) temperature of glove after 3 min on the hand reaches 34.8 °C,
- (c) continuous stretching of the glove during preparatory or administration activities versus static test conditions,
- (d) contact with diluents other than saline that could damage the integrity of the glove material.

### 6.3.5 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 beard cover.

### 6.3.6 Personal protective equipment for CACI and CDSC users

The gowning procedure will depend on the grade of the room where the CACI or CDSC is located (see Table 2). Personal protective equipment should be considered for tasks such as handling vials outside the barrier enclosure where the risk of chemical contamination is present.

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## Section 7 – Containment systems (including closed-system transfer devices (CSTDs))

### 7.1 Primary packaging based containment systems

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 30–50% of the vials examined. This was the result of contamination during the manufacturing process (e.g. foam forming or dust from powder form of drug) and/or inadequate washing of the vials before packaging. Many companies have now focused 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 cytotoxic drugs in plastic shrink wrap for this purpose. Some manufacturers supply their cytotoxic drugs encased in specially designed molded 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 Closed-system transfer devices (CSTDs)

CSTDs have been developed for use in the preparation and administration of cytotoxic drugs.<sup>1</sup> The most comprehensive definition of a CSTD is presented by NIOSH.

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

Studies have shown substantially less environmental contamination and occupational exposure to cytotoxic drugs with CSTDs compared to traditional techniques.<sup>2–10</sup> Exposure may have occurred during routine handling of drug vials and ampoules, aseptic preparation, drug administration, and cytotoxic waste disposal. The observations have been confirmed mainly in surface wipe sampling studies.<sup>11–24</sup>

In most countries, the use of CSTDs is recommended but not mandatory.<sup>25</sup> An exception is the US, where USP General Chapter <800> requires the use of CSTDs for administration.<sup>26</sup>

CSTDs can be used in addition to collective and individual protections. Contamination of external surfaces of vials and packaging is still an issue, and contributes to spread of contamination on surfaces and working areas during the process.<sup>14,27,28</sup>

In 2012, the US Food and Drug Administration (FDA) issued the ONB product code for CSTDs, but performance standards were not set to obtain 510(k) clearances.<sup>29</sup> So there remains concern whether approved CSTDs are truly closed systems. In 2015, NIOSH released a test protocol to evaluate CSTDs for drug containment by simulating preparation and administration tasks using a surrogate.<sup>30</sup> The test protocol was updated in 2016 and has been used for the validation of several CSTDs.<sup>31</sup> The final protocol has not been set. The test is not required to file for the ONB code, but it is recommended.

Current FDA approvals can be found at DevicesFDA and searching for “onb.”<sup>32</sup>

Consideration should be given to identifying compatibility of the CSTD with agents used in compounding, as incompatibility may affect total dose in the compounded product.

A distinction must be made between a CSTD in the context of microbiological contamination versus chemical contamination and occupational exposure. The NIOSH containment test verifies that the CSTD prohibits the

escape of particles and vapours from the system. It does not validate the role of CSTDs in maintaining the microbial integrity of solutions within. Separate microbial ingress studies are required to verify that the CSTD prohibits the transfer of environmental contaminants into the system.<sup>33</sup>

Some studies have examined extension of single vial expiry dates and vial sharing with the use of particular CSTDs. These may offer additional economic benefit and offset the cost of CSTD usage.<sup>34–38</sup>

A Cochrane review on CSTD with safe handling vs safe handling was released in 2018.<sup>39</sup> The review makes reference to a number of studies that examined the effects on workplace contamination with the introduction of a CSTD, whilst a limited number attempted to address operator exposure by measuring urine levels of cytotoxic drugs. As discussed in Section 10 and 26 and common Occupational Health and Safety practice, current evidence does not suggest there is a safe level of cytotoxic exposure, and therefore exposure must be limited using CSTD until there is sufficient evidence to prove that practice without CSTD is safe for operators.

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## Section 8 – Containment primary engineering controls (C-PECs)

Specific equipment is required for the preparation and manipulation of cytotoxic drugs to promote patient and worker safety and protect the environment. This equipment includes the following:

- (a) Containment primary engineering controls (C-PECs), such as biological safety cabinets (BSCs), restricted access barrier systems (RABSs), and isolators.
- (b) Containment secondary engineering controls (C-SECs), such as clean rooms (refer to Section 6).
- (c) Supplemental engineering controls, such as closed-system drug transfer devices.

Horizontal airflow hoods and positive pressure RABS/isolators must NEVER be used for preparing cytotoxic drugs due to the high risk of exposure to workers.

Sterile and non-sterile cytotoxic drugs must be compounded or manipulated inside a C-PEC within a C-SEC. If a C-PEC aids in maintenance of the negative pressurisation of the C-SEC or is used for the preparation of sterile products, it must not be turned off.

Handling of final dosage forms such as counting or repackaging of tablets and capsules is not manipulation of cytotoxic drugs as particles, aerosols, or gasses are not produced. However, this handling does have a lower risk of exposure to the cytotoxic drug and procedures should be followed to protect the handler. Refer to Section 9.

C-PECs used for non-sterile compounding must be externally vented (preferred) or have redundant high efficiency particulate air (HEPA) filters in series. C-PECs used for sterile compounding must be externally vented.

Sterile cytotoxic drugs must be compounded inside a C-PEC that does the following:

- (a) Maintains an ISO Class 5 or better environment during dynamic operating conditions.
- (b) Provides unidirectional HEPA-filtered air moving from the top of the cabinet towards the work surface at a velocity sufficient to sweep particles away from the critical area.

- (c) Exhausts air to the atmosphere after filtration through at least one HEPA filter.
- (d) Is externally vented to the outside atmosphere through a dedicated duct away from any air intake vents.
- (e) Does not recirculate air back into the workroom.

The C-PEC should be attached to an uninterruptible power supply (UPS) and attached to a surge protector. If the C-PEC turns off for any reason, such as a power loss, activities within the C-PEC must immediately stop. Once the C-PEC can be powered back on, all surfaces inside must be decontaminated, cleaned, and disinfected. The C-PEC must purge for the amount of time specified by the manufacturer to re-establish airflow.

It is imperative that operators are told and understand that the C-PEC does not prevent the generation of cytotoxic drug contamination within the cabinet and that the effectiveness of containing contamination depends on the operator's proper use and technique.

If supplemental engineering controls are used, they must be used within a C-PEC.

### 8.1 Location of C-PECs

It is recommended that a C-PEC be placed in a C-SEC characterised by the following<sup>2</sup>:

- (a) Has fixed walls
- (b) Is externally vented
- (c) Meets or exceeds ISO Class 7 air quality
- (d) Maintains negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas
- (e) Provides a minimum of 30 air changes per hour of HEPA-filtered supply air
- (f) Is adjacent to an ISO Class 7 or better anteroom that maintains a minimum of 30 air changes per hour of HEPA-filtered supply air and a positive pressure of at least 0.2 inches of water column relative to all adjacent unclassified areas



### 8.1.1 C-PECs not located in C-SECs

Cytotoxic compounding in a C-PEC that is not placed in a C-SEC is not recommended.

A C-PEC may be located in a Containment Segregated Compounding Area (C-SCA) that has fixed walls, maintains a negative pressure between 0.01 and 0.03 in water column relative to all adjacent areas, and provides a minimum of 12 air changes per hour. The C-SCA must be externally vented. A hand hygiene sink must be located at least 1 m away from the C-PEC.

Non-cytotoxic compounding in a C-PEC that is not placed in a C-SEC as described above affects the beyond-use date (BUD) that can be assigned to a final preparation.

A reduced BUD must be applied to a final preparation that is compounded in a C-PEC located in a C-SCA.<sup>2</sup>

## 8.2 Biological safety cabinets (BSCs)

There are several types of BSCs. They are classified (EN 12469 2000) into three main classes (I, II, and III).

### 8.2.1 Class I BSCs

A Class I BSC is designed to protect only the operator and the environment. Room air constantly enters the cabinet front to flow across the work surface. All exhaust air is removed directly from the work zone to a dedicated exhaust duct. These cabinets must NOT be used for the preparation of sterile products. A Class I BSC may be used for the preparation of non-sterile cytotoxic drugs to protect the operator and the environment.

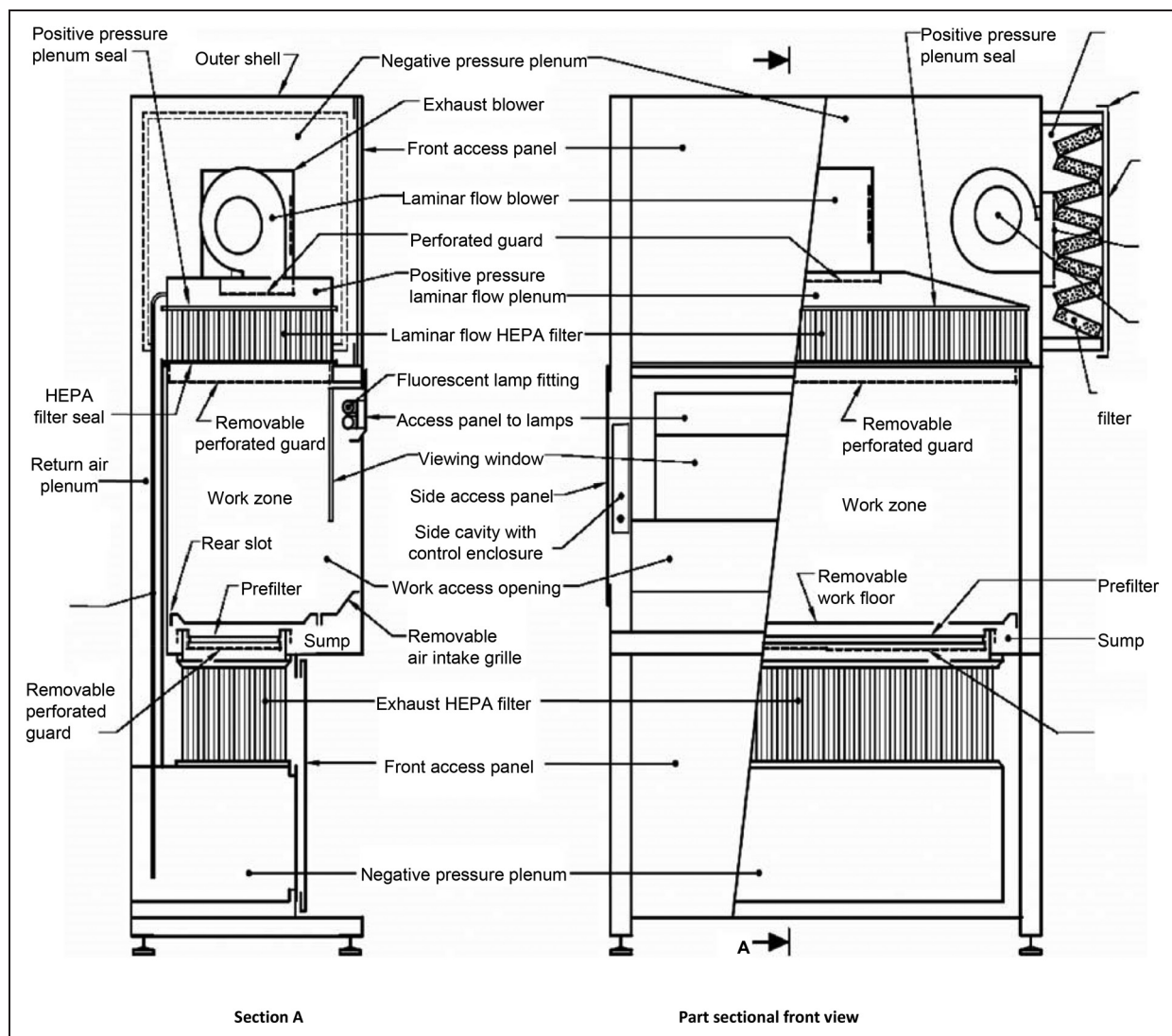


Figure 1. Example of Class II Type B1 laminar flow cytotoxic drug safety cabinet.<sup>3</sup>



### 8.2.2 Class II BSCs

A Class II BSC protects the operator and the product. A Class II BSC has an open front with inward airflow for personnel protection, HEPA-filtered downward, unidirectional airflow for product protection, and HEPA-filtered exhaust air to the room or to a facility's exhaust system. When the exhaust air exits through the facility's exhaust system, Class II BSCs also protect the environment. Because Class II cabinet designs permit different airflow patterns, velocities, HEPA filter position, ventilation rates, and exhaust methods, there are subclassifications of the Class II BSC (A1, A2, B1, and B2).

When selecting a Class II BSC for the preparation of cytotoxic drugs, only Class II cabinets designed and constructed for use with cytotoxic drugs must be used. Because some cytotoxic drugs vapourise and pass-through HEPA filters (e.g. cyclophosphamide), a BSC that exhausts air into the workroom must be avoided.

Class II Type A cabinets are not recommended. Type A1 cabinets are not suitable for the manipulation of volatile cytotoxic drugs. Type A2 cabinets are suitable only for minute quantities of volatile cytotoxic drugs.

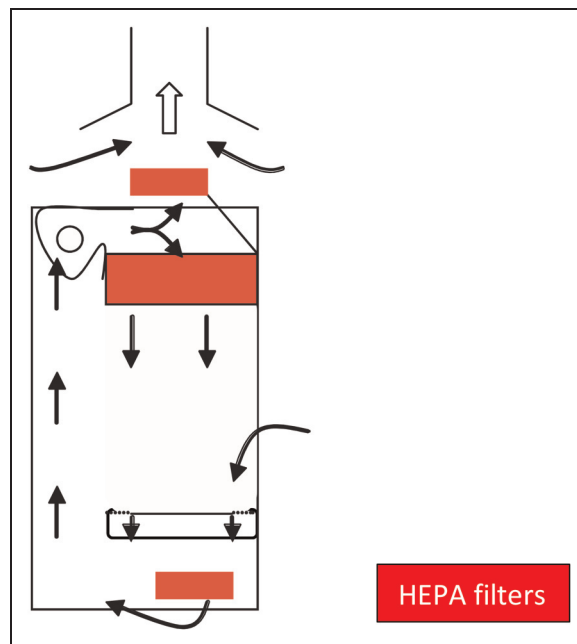
Class II Type B1 (inflow air partially recirculated) must only be used for minute quantities of volatile cytotoxic drugs. Class II Type B2 (total exhaust) are suitable for use during preparation of cytotoxic drugs.

### 8.2.3 Class III BSCs

A Class III BSC is a fully enclosed vented cabinet of gas-tight construction. Operations are conducted through attached gloves and observed through a non-opening, completely sealed view window. This BSC is maintained under negative pressure. Air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double HEPA filtration or by HEPA filtration and incineration. Passage of material in and out the cabinet is generally performed through a dunk tank or double-door pass-through box. Class III BSCs are designed for use with highly infectious microbiological and other agents. Class III BSCs are not generally used by the pharmacy for cytotoxic drug compounding.

### 8.2.4 Airflow

**Plenums.** A plenum is the space between the C-PEC and the building's heating, ventilation, and air-conditioning (HVAC) system. It is usually located between the structural ceiling and a drop-down ceiling. The plenum can be the interface into a common space where both ducts meet or it can be hard ducting between the C-PEC and the building's exhaust system. When compounding cytotoxic drugs, the ductwork and plenum must be considered contaminated with cytotoxic drug residue.



**Figure 2.** BSC for cytotoxic drug preparation. The HEPA filter located below the workstation is designed to be easily removed during maintenance operations and contributes to operator safety.<sup>3</sup>

**Within the BSC.** In all Class II BSCs, an inflow of air is drawn through the front opening into the front grill, aiding in personnel protection. The top-to-bottom unidirectional downflow of HEPA-filtered air inside the cabinet splits, with half the air drawn through the rear grill and half drawn through the front grill, combining with the air drawn from the clean room. The air drawn through the front grill creates a protective air curtain that minimises the chance of air from the BSC leaving the front opening and the chance of room air entering the work zone of the BSC.

In Class II Type A cabinets, 70% of the air is recirculated through a HEPA filter back into the cabinet's work zone and 30% is HEPA-filtered and then exhausted from a common plenum to the room or to a facility exhaust system through an exhaust canopy.

A Class II Type A1 cabinet maintains a minimum inflow velocity of 75 feet per minute (0.38 m/s). The HEPA-filtered downflow air is a combination of downflow and inflow air from a common plenum. Type A1 cabinets may have positive pressure contaminated ducts and plenums that are not surrounded by negative pressure plenums. Class II Type A1 cabinets are not appropriate for use during preparation of cytotoxic drugs.

A Class II Type A2 cabinet maintains a minimum inflow velocity of 100 feet per minute (0.51 m/s). The HEPA-filtered downflow air is a combination of mixed downflow and inflow air from a common exhaust plenum.

All contaminated ducts and plenums are under negative pressure or surrounded ducts and plenums that are under negative pressure relative to the workroom atmosphere. Class II Type A2 cabinets cannot be hard-ducted to the building's exhaust system and should interface via an open canopy. Type A2 cabinets that exhaust HEPA-filtered air outside (not back into the work room) are not recommended but may be used when working with minute quantities of volatile cytotoxic drugs.

A Class II Type B1 cabinet maintains a minimum inflow velocity of 100 feet per minute (0.51 m/s). The total of 30–40% of the air is recirculated within the cabinet through a HEPA filter and 60–70% of air is HEPA-filtered and exhausted through an exhaust canopy. The contaminated ducts and plenums are under negative pressure or surrounded by ducts and plenums that are under negative pressure relative to the workroom atmosphere. Because the HEPA-filtered down-flow air is composed of largely uncontaminated recirculated inflow air, Type B1 cabinets may be used for work involving non-volatile cytotoxic drugs or minute quantities of volatile cytotoxic drugs.

A Class II Type B2 cabinet maintains a minimum inflow velocity of 100 feet per minute (0.51 m/s). HEPA-filtered downflow air is drawn from the room or environment in which it is located. These cabinets exhaust 100% of the inflow and downflow air to the outside through a HEPA filter without recirculation inside the cabinet or return to the workroom. The contaminated ducts and plenums are under negative pressure or are surrounded by directly exhausted negative-pressure ducts and plenums. Class II Type B2 cabinets must be hard-ducted to the building's exhaust system. These cabinets are appropriate for use with all cytotoxic drugs.

**External exhaust of air.** Hard-ducted C-PECs must incorporate a blower located at the terminal end of the exhaust ductwork that operates continuously to provide adequate ventilation and to prevent backflow of contaminated air into the BSC or workroom. A HEPA filter must be employed for the exhaust air. 100% of the filtered air should be exhausted directly to the outside through a stack that extends straight upwards at least 10 feet (3 m) above the roof away from any air intake vents.

An extraction system incorporating an in-line duct fan or booster fan 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 in-line duct or booster fan 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 would occur if the BSC airflow fails and the booster fan continues to operate, pulling dirty air into the cabinet from the room, resulting in particulate and microbiological contamination

of the cabinet. The booster fan should also have an alarm that sounds in the event of failure.

Procedures must allow for exhaust fans to be shut down for inspection and maintenance.

**HEPA filtration.** HEPA filters trap 99.97% of particulate matter and aerosols 0.3  $\mu\text{m}$  and larger to provide ultra-clean air. HEPA-filtered air is not sterile. However, the presence of microorganisms in the air stream is very unlikely. HEPA filters do not capture cytotoxic drug vapours.

Air entering the work zone of a C-PEC must pass through at least one HEPA filter. Air exiting the work zone of the C-PEC must also pass through at least one additional HEPA filter. Consideration should be given to the use of bag in/bag out HEPA filters where effective in situ decontamination is not feasible.

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. In Australia, the use of an activated carbon filter downstream of the HEPA exhaust filter is compulsory.

**Alarms.** The front viewing window in a BSC must be equipped with an alarm that indicates when the window is not in the correct position during compounding.

Airflow alarms that detect insufficient internal airflow or insufficient inflow or exhaust of air must be installed to signal a disruption in the cabinet's normal airflow pattern. When the airflow alarm sounds, there is 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 both visual and audible alarms.

### 8.2.5 Monitoring

Lights and gauges on the front control panel of the C-PEC should be monitored to ensure the cabinet is performing to specification. Operators should be informed of what the gauges should read during proper functioning of the cabinet.

A series of physical tests must be carried out upon installation, whenever changes are made to the installation (e.g. replacement of a HEPA filter), and on a regular basis as a preventative measure. Physical tests check the following:

- (a) integrity of the HEPA filters (DOP test),
- (b) airflow velocity,
- (c) air circulation (smoke test),
- (d) airflow retention (KI disk test),
- (e) pressure,
- (f) particulate contamination,
- (g) temperature and humidity,

(h) noise test.

**HEPA filter integrity test (DOP test)<sup>3</sup>.** This test checks the integrity of all HEPA filters (inlet, outlet, exhaust, and recirculation). 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 (DiOctyl Phtalate), which is toxic. The test consists of applying an aerosol challenge upstream of the filter and measuring the air quality downstream with an aerosol photometer. Permeation through the filter must be 50.01% 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. In most circumstances, these tests are performed by registered contractors.

**Total particle count test.** The total particle count test verifies ISO Class 5 air cleanliness of the work zone under dynamic operating conditions. The particle counter detects particles 0.5 microns and larger. A minimum volume of air must be sampled over a specific amount of time to determine the cleanliness of the air.

**Leak Test.** The leak test applies only to fully enclosed cabinets (BSC Class III). This test determines if 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 8.3.7.

**Smoke test<sup>4</sup>.** The smoke test checks for proper circulation of air during dynamic operating conditions. The smoke test is a simple test enabling visualisation of the air circulation. A camera recording enables mapping of the air circulation in the cabinet. For unidirectional airflow, the objective is to check laminarity and the absence of dead zones or turbulence, which can result in particulate or microbiological contamination. For Class III BSCs, where the airflow may be turbulent, this test enables the detection of dead zones. Note that C-PECs used for preparation of sterile products must provide unidirectional, not turbulent, airflow. The most common equipment used is a smoke stick of smoking sulfuric acid.

**Air velocity test<sup>4</sup>.** Airflow velocity is measured using an anemometer to determine if air from the supply HEPA filter is operating within the manufacturer’s specifications and moving at the appropriate speed to sweep away particles. 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 eight measurements are done 20 cm from the flow. No value should differ from the reference value by more than 20%.

**Intake velocity and inflow volume.** This test assesses containment and operator protection by calculating supply airflow and exhaust inflow at the front opening. Readings are collected using a direct inflow method. Intake velocity is calculated using the volume and the work opening area.

**Airflow retention test (KI disk test).** The KI (potassium iodide) test determines the retention efficacy of a BSC at the front opening. It is measured by creating an aerosol of a solution of KI in the using a rotary disc. The number of particles detected outside the BSC is then counted. Air samplers make the measurement with a filtration membrane incorporating palladium chloride. The particles of KI show up brown on the filter.

A cylinder placed in the front opening makes it possible to simulate the effect of the operator’s arm, which disturbs the incoming airflow.

**Noise test<sup>5,6</sup>.** The noise test determines if the noise generated by the BSC during normal operation is not too loud for the operators. The sound level meter is installed 1 m from the BSC. The noise level must not exceed 85 dB, regardless of the room background noise.

**Light level<sup>5</sup>.** The light level test determines if lighting conditions for the operator working at the safety cabinet are optimal. The lighting of the BSC and room is turned on and a mapping of luminous intensity is carried out using a light meter at several points on each working surface. The luminous intensity measured during normal operations must be at least 400 lux.

**Table 1.** Minimum frequency of physical monitoring.

Pressure differential between rooms	Daily
Pressure differential across filters	Daily on BSC’s; every 6 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

**Temperature and humidity testing.** Temperature and humidity must be controlled for the comfort of the operators and to reduce the risk of microbiological contamination in the BSC. A temperature sensor and hygrometer are used.

**Microbiological testing.** Microbiological testing must be performed routinely (see Section 6). The maximum level of microbiological contamination must be determined by air sampling (active or passive) and surface sampling and must correspond to an ISO Class 5 environment.<sup>6</sup> Surface sampling must be performed on completion of the manipulation 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.

*It is recommended that the BSC be left running 24 h a day 7 days a week to prevent microbiological and chemical contamination.*

**Frequency of monitoring<sup>8</sup>.** Tables one and two specify the minimum frequency of physical and microbiological monitoring. Local guidelines and legislation must also be considered.

### 8.3 RABSs and pharmaceutical isolators

RABS is a relatively new term used to describe a containment system that provides a physical separation between the interior work area and the operator or workroom. A RABS supplies HEPA-filtered ISO Class 5 air enclosed in a rigid-wall enclosure with glove access ports. The viewing window can be opened for manual cleaning and disinfecting. Supplies are introduced using aseptic procedures, which may include a transfer system.

Types of RABS include compounding aseptic isolators (CAIs) and CACIs. A CAI is a positive pressure RABS and as such must not be used to prepare cytotoxic drugs. A CACI is a negative pressure RABS and may be used to prepare cytotoxic drugs.

An isolator is a fully enclosed and sealed containment unit that provides physical isolation of the interior work area. It supplies HEPA-filtered ISO Class 5 air enclosed in a rigid wall enclosure. Isolators may be supplied with turbulent or unidirectional air. Supplies are introduced through sterile transfer systems. Some isolators can bio-decontaminate via an automated cycle using hydrogen peroxide gases. All access is through glove ports and sterile transfer systems.

Compared to isolators, RABS offer faster start-up time, ease of changeover, and reduced capital costs, particularly with retrofits and renovations.

CAIs and CACIs are RABS despite the term isolator being in their name.

**Comparison of definitions for the RABS and isolator.** The RABS is a unidirectional laminar airflow cabinet where the front is closed by a window fitted with sleeves and gloves to allow manipulation inside the cabinet. A CACI operates at negative air pressure in a negative pressure room. 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 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 sterilised. 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 unidirectional or turbulent airflow and sterilised by gas sterilisation. Products and preparation devices are introduced into the isolator using pass-throughs, which are always sterilised.

When compounding cytotoxic drugs, RABS and isolators intended for asepsis and containment are recommended: they are well suited to the preparation of sterile and toxic materials. The use of appropriate personal protective equipment (PPE) by workers is required, especially when handling vials or final products outside the RABS and isolator (see Section 6).

#### 8.3.1 RABS and isolator design

RABSs are rigid-walled, made from polycarbonate, acrylic glass, or tempered glass. The flooring in the pass-through and main chamber is stainless steel.

Isolators are either rigid-walled, made from polycarbonate, acrylic glass, or tempered glass, or flexible-walled, made from polyvinyl chloride (PVC). The flooring can be stainless steel 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.

#### 8.3.2 Airflow

A RABS interior is supplied with unidirectional HEPA-filtered air that is returned through sealed ductwork.

An isolator's interior is supplied with turbulent or unidirectional HEPA-filtered ISO Class 5 air that is returned through sealed ductwork.

Airflow alarms that detect insufficient internal airflow or insufficient inflow of air must be installed in both RABS and isolators.

When compounding parenteral cytotoxic drugs, RABS and isolators that provide unidirectional airflow must be used.



### 8.3.3 Operator interface

The RABS and isolator must be accessed via a glove port or a half-suit. The system must be designed to allow operator access to the interior of the isolator while maintaining the aseptic environment and containment within the cabinet.

**Gloves.** The glove/sleeve assembly is used for aseptic manipulations within the RABS or isolator. The glove material commonly used is Neoprene or Hypalon. Gloves should be thicker than standard surgical gloves: about 0.4–0.6 mm. Gloves are potentially the weakest link in the system and therefore 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 cytotoxic drugs and maintenance of sterility. Once removed, potentially contaminated gloves must be immediately discarded with cytotoxic waste.

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

### 8.3.4 Sterilisation

Isolators for aseptic preparation must be surface-sterilised (or bio-decontaminated). This may be accomplished through 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.

A steriliser consists of a tank in which a sterilising agent is heated to approximately 45 °C. The vapours produced are then distributed throughout the chamber using a current of compressed air. Because the sterilising agent is a non-penetrating component, contact with all 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.

The connecting systems between the RABS or isolator and pass-through should use interlocking double doors to ensure containment of the enclosure and sterility in the isolator. Sterilisation in the isolator must be confirmed using biological indicators.

The two sterilising agents that are commonly used in isolators 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; 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 important when using hydrogen peroxide. This may be difficult to achieve in everyday practice in the hospital setting.

When an isolator is used for multiple days between decontamination cycles, the frequency adopted should be justified. This frequency, established during validation studies, should be re-evaluated and increased if production data indicate deterioration of the microbiological quality of the isolator environment.

A breach of isolator integrity should lead to a decontamination cycle. Integrity can be affected by power failures, valve failure, inadequate overpressure, holes in gloves and seams, or other leaks. Breaches of integrity should be investigated. If it is determined that the environment may have been compromised, any product potentially impacted by the breach should be rejected.

### 8.3.5 RABS and isolator location

There has been much debate about the requirements and classification of the room in which a RABS or isolator is located.

The location of the RABS or isolator and its ability to maintain an ISO Class 5 workspace affect the BUD that can be applied to the sterile cytotoxic drug preparation. See Section 8.1 for specifications of the clean room that houses a C-PEC for cytotoxic drug compounding.

The BUD applied to preparations that are compounded in a C-PEC located in a clean room as described in Section 8.1 may be applied to preparations that are compounded in an isolator placed in a clean room that meets ISO Class 8 air quality if the following criteria are met.

- (a) High-integrity transfer ports are used to move supplies, ingredients, components, and devices into and out of the isolator.
- (b) The isolator is decontaminated using a generator that distributes a sporicidal chemical agent throughout the isolator chamber.
- (c) The isolator maintains constant overpressure of at least 0.05-inch water column.
- (d) The manufacturer has provided documentation that the isolator will continuously meet ISO Class 5 conditions, including during material transfer.

### 8.3.6 Transfer systems

A transfer system is used to transfer drugs and supplies into and final preparations out of the main chamber of the RABS or isolator. The transfer system aids in maintaining the



sterility of the final product and containment of cytotoxic drugs. Double interlocking doors must be used so that the door between the cabinet and the room and the door between the transfer chamber and the main chamber cannot be opened at the same time.

**Isolator transfer systems.** Only transfer systems E and F guarantee 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. There is a risk of contamination of the surroundings 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 system does not contain the end product and waste.

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

**Transfer system F:** This rapid transfer system has double interlocking doors allowing a connection between two separate sterile enclosures (e.g. 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 the sterility of the product and provides containment of any chemical contamination. The double interlocking doors 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 distinct from the removal system used for finished preparations.

### 8.3.7 Monitoring

Monitoring must be performed on a regular basis. Monitoring determines whether the RABS or isolator is

performing to specification. Physical tests are conducted during the installation of the cabinet and periodically afterwards. Tests must be repeated whenever changes are made to the installation, such as changing HEPA filters. Physical tests include the following:

- (a) integrity checks of HEPA filters (DOP testing),
- (b) airflow velocity for unidirectional airflow cabinets,
- (c) air circulation (smoke test),
- (d) leak testing,
- (e) pressure checks,
- (f) particulate contamination,
- (g) temperature and humidity,
- (h) noise test.

**HEPA filter integrity test (DOP test).** HEPA-filters must be assessed as previously described in Section 8.1.5. The DOP test should be performed every 6–12 months.

**Leak test.** The sealing of a RABS or isolator is an essential and critical factor that must be regularly checked. There are two parameters tested: the presence and position of any leaks and the leakage rate.

The leak test determines if there are unsealed construction joints, seams, gaskets, glove ports, or entry/exit points to the main chamber.

The leak test should be performed monthly.

**Smoke test.** The smoke test must be performed as described in Section 8.2.5.

**Air velocity test.** For isolators with unidirectional airflow, this test must be performed as described in Section 8.2.5.

**Noise test.** The noise test must be performed as described in Section 8.2.5.

**Pressure differential test.** The pressure of the RABS and isolators must be continuously monitored. 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 RABS or isolator when the pressure is altered following operations such as introducing and withdrawing gloves, entering and exiting the main chamber, and connection to an additional volume. The test determines if the pressure regulation at rest is stable. The test can also determine if the pressure alarm values are compatible with the normal operation of the cabinet.

**Air change rate<sup>4</sup>.** The air change rate per hour (in V/h) is determined by the ratio of the inlet airflow rate divided by the volume of RABS or isolator.

An anemometer records instantaneous speed measurements. The flow rate is obtained using an average value. The result must be in accordance to the specification of the RABS or isolator.

**Microbiological monitoring.** Microbiological monitoring must be performed routinely as described in Section 6. The maximum level of microbiological contamination must be investigated by active or passive air sampling and surface sampling and must correspond to an ISO Class 5 environment.<sup>7</sup> Surface sampling must be performed upon completion of the manipulation before 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.

**Particle counts<sup>12</sup>.** Particle counts determine whether the concentration of particles found within the isolator is in accordance with the specifications of an ISO Class 5 environment (see Section 6).

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

Particle counts should be performed every 3 months.

**Efficiency of sterilisation of an isolator.** This test determines the efficiency of surface sterilisation using biological indicators (BIs). Each BI is inoculated with a 6 log of spore of *Bacillus subtilis* or *Bacillus stearothermophilus*. BIs are then distributed at distinct locations within the isolator, with particular emphasis on critical zones, such as near doors. After exposure to the sterilising agent, the BIs are inoculated in culture medium (tryptocaseine soya) and incubated for 14 days at adequate temperature according to the BI (55 °C–60 °C for *Bacillus stearothermophilus* or 30 °C–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.

**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	Every 6 months at rest and in the operational state
Room air changes per hour	Every 6 months
Air velocities on workstations	Every 6 months
HEPA filter integrity checks	Every 6 months
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

In addition, an aeration test must be performed after a complete sterilisation cycle. This test determines the aeration time required to obtain a residual concentration of the sterilising 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 volume of the isolator.

*It is recommended that the RABS or isolator be left running 24 h a day, 7 days a week to help prevent microbiological and chemical contamination.*

**Frequency of monitoring<sup>8</sup>.**

### 8.4 Validation and certification

All equipment and processes used in the preparation of parenteral cytotoxic drugs that affect product sterility or attributes should be validated or certified. Documentation to this effect should be approved, maintained, reviewed, and signed off.

For certification see Section 6.2.12. For process validation see Section 6.2.13.

**Table 5.** Common tests performed during operational and performance certification.

Test	BSC – cleanroom	Isolator	OC	PC
HEPA filter integrity test (DOP)	X	X	X	N/A
Airflow: check unidirectional flow and air velocity	X	X(1)	X(2)	X(3)
Leak testing of the enclosure	X(4)	X	X	X
Air distribution studies	X	X	X	X
Air change rate per hour	X	X	X	X
Particle counting	X	X	X	X
Pressure regulation and alarm	X	X	X	X
Sterilisation	N/A	X	X(5)	X(6)
Aeration/ventilation after sterilisation	N/A	X	X(5)	X(6)
Noise level	X	X	X	N/A
Light level	X	X	X	N/A
Checking procedure	X	X	N/A	X

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

1. Applies only to isolator with unidirectional airflow.
2. Without final equipment (e.g. shelving, filling pump).
3. With final equipment.
4. Applies only to Class III BSCs.
5. Without load.
6. With load.

Most of the monitoring tests described above may be used for operational certification (OC) or performance certification (PC). Commonly applied tests are listed in Table 5.

## References

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## Section 9 – Nonsterile preparations

Many cytotoxic drugs are administered via non-parenteral routes such as oral and topical. The oral route is being used increasingly more as new drugs become available.

Personnel are vulnerable to exposure to cytotoxic drugs by direct contact and inhalation. As with sterile cytotoxic drug preparations, the hierarchic order in protection measures must be implemented when making nonsterile cytotoxic preparations (see Section 5).

### 9.1 Handling of tablets, capsules, and other solid dosage forms

Tablets and capsules must be handled in a manner that avoids skin contact, release of drug particles into the air, and chemical cross-contamination with other drugs. Safe work procedures should be documented and should include the following:

- (a) Use gloves when handling tablets or capsules.
- (b) All equipment used in the dispensing of cytotoxic tablets and capsules must be dedicated to this purpose and clearly labeled as such.
- (c) Cytotoxic tablets and capsules should not be counted using a counting machine.
- (d) They should not be stored in automated dispensing cabinets (ADCs) without blisters or original packaging as they can generate particles and contaminate the device.
- (e) Tablets and capsules should not be crushed or broken.
- (f) Containers with damaged contents should be discarded.
- (g) Equipment should be cleaned immediately after use.

### 9.2 Extemporaneous compounding

Crushing tablets, opening capsules, and mixing powders generate airborne particles and should be avoided whenever possible. If unavoidable, these actions should be performed in a cytotoxic drug safety cabinet (CDSC) or compounding aseptic containment isolator (CACI – refer to glossary).

Some tablets may be dispersed in pre-calibrated bottles or syringes to form mixtures. Single-dose mixtures are recommended. Any instructions provided by the

manufacturer should be followed. Published formulae may be available for some drugs.

Some extemporaneous solutions can be compounded using ampoules or vials by following referenced procedures.

Final products of nonsterile preparations should be labelled as cytotoxic to warn all personnel associated with further steps in the workflow.

All equipment used in extemporaneous compounding of cytotoxic drugs must be dedicated to this purpose and clearly labeled as such. Equipment should be cleaned immediately after use with a strongly alkaline solution followed by a neutraliser, then rinsed with water or wiped with water-absorbent pads to avoid residue (see Section 13).

For batch documentation requirements, see Section 11.

### 9.3 Facilities, biological safety cabinets (BSCs), and personal protective equipment (PPE)

The extemporaneous preparation of cytotoxic drugs should be performed under the same conditions as for parenteral cytotoxic drugs. Preparation should be carried out in a separate room dedicated to this purpose. This room must have a warning sign outside and be restricted to trained staff only. A spill kit should be readily available.

The room should operate at negative pressure to minimise the risk of spreading particulate contamination throughout the rest of the pharmacy.

All activities likely to result in particle generation, such as weighing, crushing, mixing, or filling capsules, should be performed in a Class I BSC. A Class I BSC extracts the air from behind the operator, flowing over the arms, hands, and product, before being exhausted at the top of the cabinet. See Section 8 for more information.

A Class II B2 BSC could also be used, but should not be used for a mixed activity of sterile and non-sterile preparation due to the high risk of release of powders and particulate contamination into the clean room. In this case, a disposable system, such as a bag fitted with gloves for containment in the laboratory, is preferred.

A negative air pressure BSC III is an alternative to a dedicated BSC Class II B2. A HEPA filter located within the cabinet exhaust and an additional filter such

as an active carbon filter may be installed. 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.

Cytotoxic drug safety cabinets should be validated every 6 months.

Hygiene conditions similar to those described for the preparation of cytotoxic sterile products also apply to the

preparation of nonsterile products. Hands should be washed before donning and after doffing gloves. Eating, drinking, and smoking must not be permitted.

PPE must be used by personnel when preparing extemporaneous nonsterile cytotoxic preparations. PPE consists of gowning (see Section 6), nonsterile gloves (resistant to chemotherapy and labelled as chemotherapy gloves), and a mask (P2-3 in Europe/Australasia, N95 in North America).



## Section 10 – Cytotoxic drug contamination monitoring

### 10.1 Background

The risk to healthcare personnel from handling cytotoxic drugs depends on the inherent toxicity of the drugs and the extent of exposure that can reach the professional during daily activities. There are various routes of exposure to cytotoxic drugs in healthcare facilities. While dermal and inhalation routes are likely to be the most common, hand-to-mouth exposure and accidental needle sticks may also contribute.

Many occupational settings have established exposure limits for toxic chemicals. No exposure limits have been established for airborne concentrations of cytotoxic drugs. However, some exposure limits have been set for soluble platinum salts and inorganic arsenic, which would include the cytotoxic drugs cisplatin, carboplatin, and arsenic trioxide.<sup>1,2</sup>

Surface wipe sampling and sampling for airborne drugs have been the two main procedures for determining workplace contamination with cytotoxic drugs. These procedures have been employed in many other occupational settings to determine the level and extent of contamination of the workplace and to establish safe working levels for hazardous substances.

Attempts to measure environmental (e.g. wipe sampling) and health worker (e.g. urine sampling) contamination have not been correlated to health outcomes for workers.

Some pharmaceutical manufacturers have developed occupational exposure limits (OELs) for use in manufacturing facilities.<sup>3</sup> However, these OELs are used where a single drug is handled in a nearly fully automated production line. For hospital pharmacies, OELs are not appropriate. For genotoxic products, including many antineoplastic drugs, there is no safe level: zero contamination should be the target.

### 10.2 Conditions for exposure

Workers may be exposed to a drug during manufacture, transport, preparation, distribution, administration in healthcare or home care settings, or waste disposal. Exposed workers may include physicians, nurses, and personnel in shipping and receiving, pharmacies, operating

rooms, and environmental services. Workers in veterinary practices where cytotoxic drugs are used are also at risk. Workers may be exposed when they create aerosols, generate dust, clean up spills, or touch contaminated surfaces.

### 10.3 Environmental contamination

Since the early 1990s, studies have examined environmental contamination of areas where cytotoxic drugs are prepared and administered in healthcare facilities.<sup>4–18</sup>

Using wipe samples, investigators measured detectable concentrations of one or more hazardous drugs in various locations. These included BSCs, CACI – refer to glossary, floors, counter tops, storage areas, tables and chairs in patient treatment areas, and locations adjacent to drug-handling areas. All 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 found that outer surfaces of cytotoxic drug vials were often contaminated with the drug contained in the vial.<sup>14,19–24</sup> Sampling methods included wipe sampling, rinsing, and total emersion of the vials using a suitable solvent. Because of the nature of the surfaces being sampled, it is difficult to determine the recovery efficiencies with drug vials. Once samples are collected, analytical methods similar to those used for surface wipe sampling can be applied.

In addition to the cytotoxic agents currently used to treat cancer, there are many other drugs that are considered hazardous.<sup>2,25,26</sup> Therefore, sampling for a small fraction of the drugs that may be present only gives an estimate of overall workplace contamination.<sup>27</sup>

For genotoxic products, including many antineoplastic drugs, there is no safe level: zero contamination should be the target.

### 10.4 Sampling strategies

Before measuring cytotoxic contamination, current work practices, equipment, and work area layout should be analysed to identify appropriate sampling locations. The primary method for monitoring cytotoxic contamination

in the healthcare facility has been the recovery of marker cytotoxic drugs from wipe samples.<sup>27,28</sup>

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. Drugs commonly sampled include cyclophosphamide, ifosfamide, fluorouracil, methotrexate, paclitaxel, doxorubicin, and platinum-containing drugs such as cisplatin and carboplatin.<sup>27,28</sup>

A sampling strategy should be developed by the healthcare facility, taking into account the following:

- (a) Identification of possible contaminated sites. The ISOPP Audit Tool can help characterise the pharmacy and identify weaknesses in the circuit of cytotoxic drugs.
- (b) Identification of the drugs most often prepared. These drugs should be used for wipe sampling as indicators for occupational exposure to antineoplastic drugs.
- (c) Identification of the day of the week with the highest volume of preparations. The sampling should be done on that day.

There is no evidence regarding how frequently routine sampling should occur. At least yearly is recommended, however it is important to refer to institutional procedures. Monitoring of environmental contamination is also recommended a month after, there are any major changes in the area where cytotoxic drugs are prepared or administered such as moving furniture.

In the presence of a positive result for contamination, consideration must be given to decontamination of the work environment, review of SOPs for cytotoxic handling and compounding, safety of consumables used for compounding (including CSTDs). After an initial decontamination, manufacturing can continue with regular environmental sampling. Changes to equipment and processes to support reductions in contamination should be completed in 1 month.

## 10.5 Surface sampling and analysis

Studies of surface contamination with cytotoxic drugs typically employ a collection matrix such as tissue or filter paper wipes and a solvent system proven to aid recovery of the drugs being studied.<sup>27,28</sup>

Strategies have been developed for collecting wipe samples for other chemicals in various industries that have been applied to the sampling of cytotoxic drugs.<sup>26,29</sup> A sampling scheme should be developed for each healthcare facility based on published studies and on the initial characterisation of its pharmacy.

Any program designed to examine surface contamination must have the means to carry out the analytical techniques necessary to identify and quantify the drugs being

measured. Several analytical methods have been employed by researchers and are available in the published literature.<sup>27,28</sup> 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), and high-performance liquid chromatography-tandem mass spectroscopy (LC-MS-MS). With the use of GC-MS or GC-MS-MS for drugs such as cyclophosphamide and ifosfamide, derivatisation is required before analysis.<sup>13</sup> Platinum-containing compounds can be analysed using voltammetry<sup>12,30</sup> or inductively coupled plasma mass spectrometry (ICP-MS).<sup>9,31</sup>

Analytical methods have not been based on adverse health effects in healthcare workers because of the difficulty in matching sampling values to health outcomes.

Sessink<sup>32</sup> developed a “traffic-light” model with reference values correlating environmental contamination with cancer risk for healthcare professionals. Risk level reference values are 0.1 ng/cm<sup>2</sup> for “green” (acceptable) and 10 ng/cm<sup>2</sup> for “red” (not acceptable). Alert and action levels for wipe test results were set in the Netherlands corresponding to these values. The aim is to have contamination levels below 0.1 ng/cm<sup>2</sup> after cleaning.<sup>33</sup>

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

Newer technologies are being developed which can give results shortly after testing in the workplace. These technologies give positive readings for a threshold level of certain marker compounds detected by the device. These techniques do not rely on sending samples for analysis and can be used as part of a sampling strategy. The threshold levels do not indicate safe operating conditions however, given the target of zero contamination.

## 10.6 Air sampling

A number of studies have measured airborne concentrations of antineoplastic drugs in healthcare settings.<sup>6,7,13,30,34-41</sup>

In most cases, the percentage of air samples containing measurable airborne concentrations of cytotoxic drugs was low, as were the concentrations of the drugs found. These results may reflect the inefficiency of sampling and analytical techniques used, including the use of glass fiber or paper filters to capture airborne particulates.<sup>36</sup> A solid sorbent material may be more efficient. Both particulate and gaseous phases of the antineoplastic cyclophosphamide have been reported in two studies.<sup>6,36</sup>

## 10.7 Alternative techniques

Fluorescent markers have been used to simulate environmental contamination with cytotoxic drugs. Kromhout et al.<sup>42</sup> developed a semi-quantitative fluorescent method to evaluate environmental contamination. Spivey and Connor<sup>43</sup> employed a fluorescent marker to demonstrate sources of environmental contamination during simulated drug preparation and administration. Prepared test kits that use fluorescent markers are available to evaluate worker skills and training during drug preparation and administration.<sup>44</sup>

## 10.8 Conclusion

Contamination of areas where cytotoxic drugs are prepared or administered has been documented in studies from countries in many parts of the world. Drug vials themselves are known to be contaminated with the drug contained in the vials. Because most exposures are via dermal or inhalation routes, surface wipe sampling and air sampling are most often used to estimate the level of environmental contamination in areas where cytotoxic drugs are handled.

Sensitive methods have been developed for the more commonly used cytotoxic drugs. But because many cytotoxic and other hazardous drugs are used in the healthcare setting, studies can only estimate total exposure.

To reduce chemical contamination, it is necessary to assess the hazards in the workplace, handle drugs safely, and use and maintain equipment properly.

Monitoring of environmental contamination by surface wipe sampling is recommended at least yearly to check cleaning procedures and potential exposure of healthcare workers to cytotoxic drugs, however it is important to refer to institutional procedures. Monitoring of environmental contamination is also recommended a month after there are any major changes in the area where cytotoxic drugs are prepared or administered such as moving furniture.

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## Section II – Checking procedures

Pharmacists play an integral role in ensuring that the treatment a cancer patient receives is accurate and appropriate for them and their diagnosis. Pharmacists or technicians completing these roles must be authorised and credentialled according to local policies and comply with jurisdictional regulations. The key steps a pharmacist must take when checking prescriptions for cancer therapy follow.

The pharmacist should receive an electronic prescription or, in the absence of an electronic prescribing system, a printed prescription using a standardised template. The prescription should comply with the following medication safety principles.<sup>1</sup>

- (a) All prescription should include the full generic name of the drug.
- (b) No abbreviations should be used (e.g. 5-FU for fluorouracil).
- (c) “Units” should be spelled out: “U” could be mistaken for a zero.
- (d) A leading zero should always be used (0.5 mg, not .5 mg).
- (e) A trailing zero should never be used (2 mg, not 2.0 mg).

The pharmacist should check the prescriber’s details and signature and confirm the prescriber is authorised to prescribe the protocols. Where possible, the clinical oncology pharmacist who reviews the chemotherapy prescription should not be the pharmacist involved in the preparation process. There should be as many independent checks as possible built into the checking system. SOPs should be developed that include signed documentation that all required checks have been carried out. Any problems detected and rectified should be recorded to facilitate analysis and future preventive action.

A standardised manufacturing worksheet may be developed specifying the date, patient demographics, chemotherapy protocol, doses, and volumes of each drug, and other special instructions for the care of the patient.

### II.1 Clinical verification

Before chemotherapy is prepared, the prescription should be verified by an authorised clinical oncology pharmacist.

Verification should be performed at a minimum before each treatment cycle. The clinical oncology pharmacist should work with other health professionals in pursuing optimal chemotherapy. This section outlines a number of essential checks that should be completed before preparation work begins. Pharmacists should also refer to national and international guidelines regarding clinical verification of chemotherapy.<sup>2,3</sup>

#### II.1.1 Chemotherapy protocol

The chemotherapy protocol used must be documented in the patient case notes. A list of standard protocols used by the institution should be developed. The pharmacist should work with other healthcare professionals in the design of optimal chemotherapy and supportive care pathways. These treatment protocols should be reviewed and updated regularly to maintain best practice. There must be a standard procedure to be followed for non-compliance with a standard protocol or the use of a non-standard protocol.

It is recommended that deviation from a standard protocol and use of a protocol not on the list of approved protocols conform to the locally approved governance procedure. This may include consultation with the senior medical officer responsible for the patient and with a consultant having expertise in the tumour stream being treated.

For each verification, the pharmacist should verify the cycle number, day of cycle, and time interval since the previous treatment. The pharmacist should document any agreed changes including reference citations.

#### II.1.2 Patient profile

Pharmacy-based profiles should be established and maintained for all chemotherapy patients. To do this effectively, pharmacists must have ready access to the following:

- (a) patient demographics, including dosing variables (age, height, weight, calculated BSA, amputation);
- (b) treating physician;
- (c) current treatment plan, including disease and stage, chemotherapy protocol, and aim of therapy;
- (d) laboratory measurements;



- (e) allergies and adverse drug reactions;
- (f) past medical history;
- (g) past and current medications.

This information must be kept current and referred to before each dispensing of chemotherapy.

### **11.1.3 Body surface area**

The pharmacy department must have procedures in place for checking the body surface area calculated by the prescriber. The method of calculation and the type of BSA used should be consistent throughout the institution and agreed upon by all oncologists and hematologists who treat chemotherapy patients. If possible, this should be an automated function of the computer program used in prescribing. A standard operating procedure (SOP) should be developed that includes signed documentation that this check has been carried out. Any corrective action taken by the pharmacy should also be documented.

### **11.1.4 Dose calculations**

The prescription must be checked against the chemotherapy protocol being used. The interval since last treatment should be appropriate. All doses must be checked against the protocol. Any deviations should be verified and documented. Any doses based on patient parameters such as BSA, weight, or creatinine clearance must be re-calculated using up-to-date values.

Consideration should be given to dose rounding or dose banding, according to local guidelines, to facilitate preparation and supply of chemotherapy. Consideration must also be given to the patient's renal and hepatic function and any possible drug interactions. If possible, the calculation function should be automated in an electronic system 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 along with any corrective action taken.

### **11.1.5 Supportive medications**

All supportive medications must be included on the chemotherapy prescription. These may include anti-emetic therapies, antihistamines, steroids, fluids, and diuretics.

### **11.1.6 Laboratory parameters and patient organ function**

Laboratory parameters should be checked by the pharmacist before treatment preparation begins. This check should include full blood values including differential white cell count, serum creatinine, creatinine clearance, LFTs, and

electrolytes as indicated in the chemotherapy protocol. Specific organ functions, such as lung function and left ventricular ejection fraction, should also be checked where indicated by the protocol or toxicity profile of the agent. Other tests may be required as new agents become available. If chemotherapy is prepared in advance, there must be stringent procedures in place to ensure that the chemotherapy is not released from the pharmacy or administered until appropriate laboratory results have been checked and approved by the pharmacist or treating physician.

## **11.2 Preparation checks**

Checks must be completed at various stages of the preparation process. These 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, labelling, and packaging. The required container and diluent must be checked to ensure the therapy is stable and shelf life is optimised. All data should be recorded on a standardised worksheet or electronically for every preparation. Written instructions should be available for the reconstitution, dilution, mixing, labeling, and packaging of all admixtures. There should be a standard procedure in place to retrieve the batch number and expiration date 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 checked by a designated pharmacist or senior technician before entering a safety cabinet or compounding aseptic containment isolator (CACI - refer to glossary). This check must comply with regulations covering compounding in the relevant jurisdiction. This check should ensure that the drug and strength are correct and the reconstitution fluid and infusion bag (volume, fluid, and container) are appropriate. The quantity of full vials and volumes of any partially used vials should be checked. The storage conditions and expiration dates of all components should be verified. Labels generated and completed worksheets should be checked for accuracy. The designated person should sign that these checks have been completed.

### **11.2.2 Preparation**

Volumes of drugs to be used should be recalculated independently by the operator performing the aseptic manipulation. A 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 should be a system in place to allow checking. The signature of the operator must be recorded for each preparation made.

Only one patient's treatment should be prepared at a time. Only one drug should be in the safety cabinet or CACI at any time.

An institution may choose to select vial sizes that can be combined to dispense actual doses required. For example, if preparing doxorubicin 70 mg, then a 50 mg plus a 20 mg vial would be used. This approach minimises 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 should be left in the safety cabinet or CACI for later use. The disadvantage of this approach is that the pharmacy must stock a range of vial sizes that may potentially lead to selection error.

If multi-dose 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 CACI. This check must be performed by a pharmacist. Any leftover solution should then be kept in a dedicated marked area for later use. This approach will reduce the range of products that have to be stocked by the pharmacy, and most likely will be more economical. In addition, the aseptic manipulation will be simpler, faster, and safer for the operator. The disadvantage of this approach is that volume checking by the pharmacist becomes crucial.

Procedures must be in place to allow checking of drug volumes added to infusion bags. A volume reconciliation method may be used where volumes of drug entering and leaving the safety cabinet or CACI are documented and checked visually by a pharmacist. An institution may prefer to check the volume marked on a syringe before being added to an infusion bag or the remainder volume in a syringe for subtractive measurement of what was added.

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 CACI to prevent contamination.

Verification may also be conducted by a safety cabinet or CACI camera and monitor. Monitoring must be performed before the compounded cytotoxic is delivered to the patient. If the verifying pharmacist or pharmacy technician notices that one or more procedures have not been followed correctly, all cytotoxic drugs compounded during this period must be discarded, and the discarding of preparations must be entered in the preparations log.

Additional quality control measures can be implemented using high-performance liquid chromatography (HPLC), however the high cost of this is often prohibitive.

### 11.2.3 Finished product

The finished product must be checked before release by a pharmacist or experienced certified technician (the checker) following strict SOPs as allowed by regulations in the jurisdiction. A volume calculation check should be done. All components used should be verified as appropriate. A visual inspection of the finished product should be performed by the checker for particulates, clarity, and colour and to check the container for possible leaks. A system must be in place to allow the checking of volumes used in the preparation process. 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 expiration, recommended storage conditions, and any additional warning or advisory notes. Intrathecal cytotoxic drugs should be labelled "For intrathecal use only." The integrity of the seal of the product should be checked. The pharmacist must sign that the final check of the product has been performed.

Before release from the pharmacy, the product should be checked against the medication prescription by a pharmacist. This pharmacist should not be the same pharmacist who clinically verified the prescription.

### 11.2.4 Non-pharmacist staff

Non-pharmacist staff involved in the preparation and/or checking of cytotoxic drugs may include qualified pharmacy technicians and pre-registration graduate pharmacists. Different countries will have different requirements for the certification of technicians. At the least, they should have completed some in-house training or credentialing to the satisfaction of an experienced pharmacist (see Section 4). Unqualified technicians and pharmacy assistants and pharmacy undergraduates should not be permitted to prepare or check these agents.

## 11.3 Validation

### 11.3.1 Validation of the product

Validation of the product is used to confirm that the processes used consistently result in a product having 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) because each preparation is specific to the patient and the final volume is usually too small to reach 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 a media fill test.

Validation of the concentration of the final product is 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 extra volume for sampling is added to the preparation, there is a risk of error in the dosage given to the patient. Methods should be developed during the preparation process to ensure the correct concentration of the final product. Double checking during withdrawing and injecting the drug must be implemented. Weighing procedures during the preparation process and on final product check could help guarantee the correct final concentration. Dosage of extra preparations could also be checked 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 the following into consideration:

- (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 lack of cross-contamination

Cross-contamination can be defined as the contamination of one drug with another during the preparation process.

For cytotoxic drugs prepared in the hospital setting, many different drugs are simultaneously prepared. However, the risk of cross-contamination is low if the process is performed without opening vials by using disposable transfer devices. The checking of all routinely used cytotoxic drugs is extremely difficult due to the diversity of analytical methods required. One method to check cross-contamination would be to choose one cytotoxic drug commonly used, simulate the process with the drug chosen, then search for the drug inside placebo preparations that are simultaneously prepared. Another method would be to use a tracer instead of the cytotoxic drug and simulate the process in the same way.

### 11.3.3 Validation of computer program

Computer program validation confirms that computer hardware and software systems perform to the required standards, delivering an output that is accurate and free of error (see Section 27).

## References

1. Institute for Safe Medication Practices. (ISMP) List of Error-Prone Abbreviations, Symbols, and Dose Designations. Horsham, USA; 2015. Accessed June 2021 [www.ismp.org/tools/errorproneabbreviations.pdf](http://www.ismp.org/tools/errorproneabbreviations.pdf)
2. Clinical Oncology Society of Australia. Guidelines for the safe prescribing, dispensing and administration of systemic cancer therapy. <https://www.cosa.org.au/publications/guidelines/> (2019, accessed 2019).
3. British Oncology Pharmacy Association. Standards for pharmacy verification of prescriptions for cancer medicines. <https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Hospital%20Pharmacy%20Hub/bopa-standards-for-clinical-pharmacy-verification-of-cancer-medicine-prescriptions.pdf> (2 April 2013, accessed 2019).

## Section 12 – Safe administration of cytotoxic drugs and monoclonal antibodies

### 12.1 Overview

The safe handling of cytotoxic drugs and monoclonal antibodies (mAbs) is the joint responsibility of all departments in the healthcare facility. A multi-disciplinary approach should be taken to reduce workplace contamination and exposure to cytotoxic drugs and mAbs.

Standard operating procedures (SOPs) and guidelines should be developed to facilitate the safe administration of all hazardous drugs and monoclonal antibodies. These drugs should only be administered by nursing, medical, and pharmacy staff with adequate training, competency, and credentialing.

These drugs require safe handling precautions by staff as there is a risk of internalisation of drugs through ingestion, aerosol inhalation, or absorption into mucous membranes. Exposure may occur from solid (particulate) or liquid aerosols, liquid spills or splashes, and needle stick injuries.

The choice of products and devices used will have an impact on reconstitution and administration practices. For example, the use of closed system transfer devices (CSTDs) for preparation can have implications in the compounding process and administration (compatible administration sets) (see Section 7).

The pharmacy has an important role to play in the choice of these products and devices in assessing safety, usability, and costs. All professionals involved in cytotoxic and mAb compounding and administration should participate in the selection of devices used within the institution.

Despite best practice, the external surfaces of a manufactured product can be contaminated with cytotoxic drugs. If bags or syringes prepared in the pharmacy are contaminated on the outer surfaces, nurses are at risk of exposure. Any process undertaken during the preparation of cytotoxic drugs in the pharmacy which may result in contamination outside the pharmacy must not be permitted (see Section 6).

Any equipment used for parenteral, oral, or topical administration of cytotoxic drugs should be immediately discarded into a cytotoxic bin.

In the event of a spill, cytotoxic spill procedures should be followed (see Section 14).

If cytotoxic drugs are administered outside the hospital, sufficient information should be made available to nurses

about the products and safe handling requirements. Additional written protocols about administration should also be made available.

Nurses should be given education and training for using electronic or mechanical pumps, what to do in the case of alarms, and dealing with incidents or accidents.

The excreta of the patient should be treated as a cytotoxic contaminant. Anything (such as the treatment chair) that comes into contact with the patient's skin can be contaminated and should be treated with the same precautions.

### 12.2 Parenteral administration

Exposure to monoclonal antibodies may occur via ingestion or contact with mucosa. Although unlikely, exposure may occur during administration of the product via splashes.<sup>1</sup> Personal protective equipment (PPE) should be worn during administration of monoclonal antibodies (refer to Section 22).

During the connection and disconnection of cytotoxic bags or syringes to the administration set, nurses are at risk of exposure. Nurses should therefore don personal PPE beforehand. CSTDs have been shown to reduce environmental contamination. Their use is recommended for administration of cytotoxic drugs.<sup>2-5</sup>

Administration sets should not be removed from an IV bag containing a cytotoxic drug. Administration lines should only be disconnected after the IV drug has been thoroughly flushed with a compatible non-cytotoxic solution. The IV bag should be removed with the tubing intact whenever possible.

After connection or disconnection of administration lines, nurses should remove their gloves and wash their hands with soap and water.

### 12.3 Oral administration

It is advisable that oral forms, such as tablets and capsules, be packed in individual packages (unit-dose). Patients should self-administer where possible.

If coated tablets or capsules are to be administered, chemotherapy-resistant gloves should be worn. If the

tablet is uncoated or an oral cytotoxic liquid is to be administered, full PPE should be worn.

Oral formulations of cytotoxic drugs should not be crushed, dissolved, or otherwise altered without the advice of the pharmacy department. See Section 9 for pharmacy-based compounding and alteration of oral dose forms.

## 12.4 Topical administration

Topical applications such as creams or lotions may be covered with bandages to protect clothing and linen. Occlusive bandages may increase the dermal absorption of the drug. Pharmacists should provide advice to other staff on the use of appropriate dressings.

### References

1. Alexander M, King J, Bajel A, et al. Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel. *Intern Med J* 2014; 44: 1018–1026.
2. Wick C, Slawson MH, Jorgenson JA, et al. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. *Am J Health Syst Pharm* 2003; 60: 2314–2320.
3. Siderov J, Kirsa S and McLauchlan R. Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device. *J Oncol Pharm Pract* 2010; 16: 19–25.
4. Sessink PJ, Trahan J and Coyne JW. Reduction in surface contamination with cyclophosphamide in 30 US hospital pharmacies following implementation of a closed-system drug transfer device. *Hosp Pharm* 2013; 48: 204–212.
5. Simon N, Vasseur M, Pinturaud M, et al. Effectiveness of a closed-system transfer device in reducing surface contamination in a new antineoplastic drug-compounding unit: A prospective, controlled, parallel study. *PLoS One* 2016; 11: e0159052.



## Section 13 – Cleaning procedures

Cleaning procedures are part of the administrative controls for safe handling of cytotoxic drugs. These procedures control and reduce environmental contamination in areas where cytotoxic drugs are handled.

Cleaning procedures include deactivation, decontamination, cleaning, and disinfection. These procedures must be based on legislative requirements. Refer to USP or PIC/S guidance and the recommendations of the manufacturer of the equipment to be cleaned.

In this section, the term “disinfectant” includes antimicrobial agents and sanitising agents.

### 13.1 Cleaning the C-PEC, including automatic equipment for aseptic preparation

The cleaning, disinfection, and organising of the ventilation tool is the responsibility of trained pharmacists and technicians following written procedures.

#### 13.1.1 Personal protective equipment (PPE) (also see Section 6)

PPE includes 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, N95 in North America), and disposable hair cover. Refer to local and authoritative cytotoxic safe handling guidelines.

PPE must be worn for all cleaning procedures. Gloves must be chemically resistant to the detergent, cleaning, disinfection, and deactivation agents used. Face shields must be worn if splashing is possible. Hands must be washed thoroughly with soap and water immediately after removing gloves.

#### 13.1.2 Cleaning agents

Cleaning agents include surfactants, chlorine-based products, and alcohol. The choice of products should be related to the bio-burden, time and application of the product, the equipment used, and eventual resistance problems.

Consideration should be given to compatibility, effectiveness, and inappropriate or toxic residues. Isopropyl alcohol (IPA) 70% may harbour resistant microbial spores. Therefore, IPA used in the clean room should be passed through a 0.2 µm filter to render it sterile. Alternatively, sterile IPA or ethanol 70% may be able to be sourced directly from a supplier. In some some compounding aseptic containment isolator (CACI – refer to glossary) applications, IPA 70% may not be used due to an incompatibility with attached neoprene gloves. Refer to CACI manufacturer’s guidelines for more information, however IPA concentration of greater than 60% should be used. Sterile IPA should be checked periodically for microbial contamination.

Chlorine-based products have been shown to be highly effective decontamination agents for a variety of cytotoxic products. They are useful for the cleaning of cytotoxic spills and for decontamination. However, they are corrosive: their use on metals such as those in biological safety cabinets (BSCs) and CACIs is not recommended.

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

#### 13.1.3 Cleaning materials

Cleaning materials for use in the clean room, such as wipers, mops, and disinfectants, should be made of materials that generate a low number of particles. Disposable cleaning materials are recommended. After use these should be disposed of with other cytotoxic waste.

#### 13.1.4 Timing of cleaning

*Beginning of session or after liquids are spilled.* At the beginning of each compounding session and after liquids are spilled, all items should be removed from the ventilation tool. All surfaces should first be cleaned with sterile water

for irrigation and detergent to remove loose material and water-soluble residues. The same surfaces should then be 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 runs continuously.** A Class II BSC that 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 to 3 times during the day.

**BSC is turned off.** If the BSC is turned off between aseptic processes for routine maintenance or any other reason, it should be operated for at least 30 min to allow complete purging of room air from the critical area, then cleaned and disinfected before use. If the CACI has been turned off for less than 24 h, a 2-minute start-up time is sufficient. For periods greater than 24 h, the chamber should be disinfected. The CACI should not be used for at least 10 min after application of the disinfectant.

The time required for purging will depend on the design of the ventilation tool and determined during performance qualification or validation.

### 13.1.5 Procedure for cleaning BSC

The procedure for cleaning the BSC is as follows:

- (a) Wipe the surfaces of the ventilation tool including front, sides, and bottom in the direction of the groove of each surface.
- (b) Clean from upstream, closest to the HEPA filter, to downstream.
- (c) Start with the rear wall of the BSC and move down.
- (d) Wipe in a continuous motion working parallel to the HEPA filter.
- (e) When a corner is met, 'S' curve and return to the opposite side while overlapping the previous stroke.
- (f) Continue with fixtures (e.g. gas or vacuum valves, bar and hooks, if present), the sides, and lastly the work surface.
- (g) After completing the cleaning, do not use the hood for at least 5 min. This allows the alcohol to dry.
- (h) 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 or voluntary

interruption, and when the ventilation tool is moved. Ideally, the process and its frequency should be validated.

Detergent, sterile water for irrigation, and disinfectant bottles should be placed on a plastic-backed disposable liner outside 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.

The procedure for decontamination is as follows:

- (a) Wipe from top to bottom, starting with the top grill (controversial – see Section 13.1.10) and following airflow.
- (b) Repeat using sterile water for irrigation until residue is removed.
- (c) Finish by disinfecting. An alcohol dampened towel may be used to wipe the top grill (see Section 13.1.10) and front grill.
- (d) Pull the viewing window down and decontaminate both sides with detergent solution, rinse with sterile water for irrigation, then disinfect.
- (e) Discard the outer pair of gloves and used wipers in the sealable bag.
- (f) Decontaminate the perimeter of the opening into the BSC with detergent solution, then rinse with sterile water for irrigation.
- (g) 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 should be allowed to run for 30 min to purge before using it for aseptic preparation.

**Decontamination after biological product.** The use of one cabinet to prepare both cytotoxic drugs and BCG vaccine is NOT recommended. If a biological product such as 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 centers dedicate one BSC solely to the preparation of BCG and prepare chemotherapeutic drugs in a separate pharmacy location.<sup>1</sup> Other centers prepare BCG on the ward using a containment device. The latter two options are preferred.

**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 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 contamination.

The fan motor (blower) should not be turned off 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 this.

The sump decontamination procedure is as follows:

- (a) Raise the work tray.
- (b) Rather than removing it from the BSC, lean on the back surface of the BSC, use a stainless-steel wire to suspend the work tray, or use a stainless-steel prop to hold it up. To prevent back strain when decontaminating a 1.8 m (6 foot) BSC, two people should lift and replace the work tray.
- (c) Decontaminate with detergent and rinse with sterile water for irrigation, then disinfect the work tray with alcohol before replacing.
- (d) A filter is located under the work tray. It is essential that care is taken not to wet the filter as it will render it ineffective.

*Decontamination of initial and prepared product.* Cytotoxic vials should be wiped before entering the cabinet or CACI where compounding will take place; avoid spraying the vials as this could result in transfer of the contamination to the air and adjacent surfaces.<sup>2</sup>

Additionally, the prepared product (infusion bag or syringe containing the hazardous drug) must be decontaminated before it is sealed in a plastic bag for transfer into the ward.

### 13.1.7 Waste handling

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

### 13.1.8 Documentation

Daily cleaning and disinfection, weekly decontamination, and monthly sump cleaning should be recorded in the quality control log.

### 13.1.9 Gas sterilised CACIs

The above procedures for cleaning and disinfecting should be implemented for CACIs. Compatibility with structural components (e.g. the plastic wall, CACI gloves, sleeves, half suit) must be checked before use. The cleaning procedure must take care never to disrupt the sealed enclosure. For example, the CACI attached gloves should be removed following a "safe change" procedure (without breaking the integrity of the system) in accordance with ISO14644-7<sup>3</sup> annex C. If for maintenance reasons the CACI integrity is disrupted, PPE must be used appropriate for the chemical

risk. Cleaning and disinfection of the workstations should be performed daily. Sterilisation of the enclosure should be performed 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 using detergent. Some references suggest cleaning in place while others caution not to wipe it with detergent. The concern is that if the HEPA filter becomes wet, this may affect the integrity of the filter and compromise its function.

*Alternating germicides.* The ASHP guidelines on quality assurance for sterile products describe the need to alternate germicides as controversial. According to Akers and Moore,<sup>4</sup> the data do not support alternating germicides. A literature search<sup>5</sup> 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. Microbial resistance might be due to the use of ineffective disinfectants, sub-effective dosages, or sub-effective contact times.<sup>6</sup>

In general, the disinfectant need not be changed unless there is a problem. The source of the problem should be identified before making a change.

*Residues left by disinfectants.* There are two opinions on residue left by disinfectants. One opinion is that residue from the use of formulated germicidal detergents may have beneficial bacteriostatic properties. The other opinion is that no residue is acceptable in a clean room, and the residue should be removed with an alcohol or water irrigation rinse.<sup>7</sup>

*Sporicidal disinfectants.* Because routine disinfectants will not be effective against bacterial endospores such as Bacillus, a sporicidal agent should also be applied periodically (e.g. weekly or monthly). Since most sporicidal disinfectants are highly toxic or corrosive, they should not be considered for daily use.<sup>8</sup>

*Deactivation agents.* The NIOSH Alert<sup>9</sup> recommends that work surfaces be cleaned with a deactivation agent 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 react with some cytotoxics. For example, the material safety data sheet for mitoxantrone notes that chlorine gas may be liberated when the drug is degraded with bleach. Other drugs are deactivated by hydrolysis. These issues have been reviewed recently.<sup>10</sup>

No single product is capable of decontaminating all hazardous products.

## 13.2 Cleaning rooms

For the purposes of this standard, the terminology in the USP 797<sup>11</sup> will be used to describe the cleanroom (the area designated for preparing sterile products). The ventilation tool is located in the buffer zone/area adjacent to the anteroom/area.

### 13.2.1 Buffer zone

**Personal protective equipment.** PPE must be worn as per Section 13.1.1.

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

**Carts, tables, stools, and chairs.** Large pieces of equipment used in the cleanroom, such as carts and tables, should be made of materials that can be easily cleaned and disinfected. Stainless steel is recommended. Stools and chairs should be cleanroom quality. Carts, tables, stools, and other hard surfaces should be cleaned and disinfected weekly and after any event that could increase the risk of microbial contamination.

**Storage shelving.** Storage shelving should be emptied of all supplies, cleaned, and disinfected at least weekly using approved agents.

**Nonporous and washable surfaces.** The floors of the cleanroom should be nonporous and washable to enable regular disinfection. Carpeting and porous floors, walls, and ceiling tiles are not suitable for cleanrooms. These surfaces cannot be properly cleaned and disinfected.

**Floors.** Floors in the cleanroom should be cleaned by mopping at least once daily when no aseptic operations are in progress. Floor mops may be used in both the buffer zone and the anteroom, but only in that order. Trained supervised custodial personnel using approved agents described in the written procedures may perform the 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 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 performing 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 to prevent microbial contamination. Careful consideration should be given to compatibility, effectiveness, and inappropriate or toxic residues. The schedule of use and methods of application should be in accordance with written procedures. Diluted solutions should be kept in cleaned containers. They should not be stored for long periods unless they are sterilised and chemical stability has been established. Partly emptied containers should not be topped up. The cleaning solution should be applied to the wiper while avoiding contamination of the cleaning solution.

**Cleaning materials.** Cleaning materials for use in the clean room, such as wipers, mops, and disinfectants, should be made of materials that generate a low number of particles. Disposable cleaning materials are recommended. After use these should be disposed of with other cytotoxic waste.

All cleaning tools should be non-shedding and dedicated to use in the clean room. Most wipers should be discarded after one use. If cleaning tools are reused, they should be cleaned and disinfected after use and stored in a clean environment between uses.

**Waste handling.** A method of disposing of waste, including needles, should be established that does not allow accumulation in the cleanroom. Trash should be collected in suitable plastic bags and removed with minimal agitation.



### 13.2.2 Anteroom

**Supplies and equipment.** In the anteroom, supplies and equipment removed from shipping cartons should be wiped with a disinfectant. 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 individual items. No shipping cartons should be taken into the cleanroom.

**Custodial personnel.** Trained, supervised custodial personnel should perform cleaning and disinfection of the anteroom at least weekly in accordance with written procedures.

**Floors.** Floors should be cleaned and disinfected daily, always proceeding from the buffer zone to the anteroom.

**Storage shelving.** Storage shelving should be emptied of all supplies and cleaned and disinfected at least monthly.

## 13.3 Cleaning of equipment and material used for oral and topical drugs (nonsterile)

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. Commonly associated with cytotoxic drugs given by parenteral routes, exposure can also occur with drugs prepared for administration by oral or topical routes.

All items used for the preparation of oral or external-use cytotoxic drugs should be identified for that use and reserved solely for these activities. These items should not be used for non-cytotoxic preparations. Examples include mortars, pestles, glass plates, spatulas, mixing devices, and tube fillers. These items should be cleaned separately from all non-cytotoxic equipment.

### 13.3.1 Preparation in a BSC

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

**Written procedures.** Class I BSCs should be cleaned and decontaminated following written procedures.

**Personal protective equipment.** PPE must be worn as per Section 13.1.1.

**Beginning of session or after liquids are spilled.** At the beginning of each compounding session and after liquids are spilled, all items should be removed from the BSC. All surfaces should first be cleaned with sterile water for irrigation

and detergent to remove loose material and water-soluble residues.

**Procedure for cleaning.** Refer to Section 13.1.5.

**Decontamination.** Refer to Section 13.1.6.

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

**Documentation.** Cleaning, disinfection, and weekly decontamination should be recorded in the quality control log.

**Class II BSC also used for sterile compounding.** A Class II BSC that 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 should be undertaken with care.

### 13.3.2 Preparation outside a BSC

**Personal protective equipment.** PPE must be worn as per Section 13.1.1.

**Work surfaces.** Work surfaces should be cleaned with an aqueous high-pH detergent solution diluted in water then rinsed with water before and after each activity.

**Equipment.** Contaminated equipment should be cleaned initially with gauze saturated with water, decontaminated with detergent, then rinsed. The gauze should be 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 of validation is to confirm that microbiological, chemical, and other contaminants have been removed or inactivated during the cleaning process.

### 13.4.1 Microbiological validation

Microbiological validation of the cleaning process uses contact plates or swabs before and after the cleaning operation. For sterile CACIs, the efficiency of the sterilisation process must be validated using Biological Indicators (BIs).



### 13.4.2 Chemical validation

Due to the diversity of drugs used simultaneously in a controlled area, chemical validation of the cleaning process is complex when handling cytotoxic drugs. One approach is to investigate the most commonly used cytotoxic drugs (e.g. fluorouracil, methotrexate, ifosfamide, cyclophosphamide) by wipe sampling of the surfaces before and after cleaning. If an analytical procedure is available, investigation of lipophilic drugs (e.g. carmustine, paclitaxel) should also be done. The cleaning should not degrade the cytotoxic drug into more toxic components.

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## Section 14 – Cytotoxic spills, extravasation, and other incidents

### 14.1 Cytotoxic spills

A standard operating procedure (SOP) 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 toward the center. All personnel involved in handling cytotoxic drugs must be trained 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 cytotoxic drug safety cabinet (CDSC) or compounding aseptic containment isolator (CACI – refer to glossary)

When a cytotoxic spill occurs within a CDSC or CACI, 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, then wiped with sterile isopropyl alcohol (70%) or other agent.

#### 14.1.2 Spills within cleanroom and anteroom

Cytotoxic cleanrooms that 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 contamination of the external environment. The switch should also be fitted with an audible alarm to alert other staff working in the immediate area. 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 the following:

- (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) Personal protective equipment (PPE) (e.g. single use chemoprotectant gown, boots or overshoes, head cover, goggles or face shields, respirator mask).
- (d) Two pairs of gloves manufactured specifically for handling cytotoxics (with proven resistance).
- (e) Small scoop to clean up any broken glass.
- (f) Spill mat (alginate impregnated) to absorb small volumes of spilled liquid.
- (g) Spill pillow to absorb large volumes of liquid (this may be an integral part of the spill kit or may be supplied separately).
- (h) Large quantities of swabs.
- (i) Concentrated alkaline detergent solution.
- (j) Bottled water in the correct quantity for dilution of detergent.
- (k) 2 plastic bags clearly identified for cytotoxic waste.
  - (l) Clearly labelled cytotoxic waste container.
- (m) Spill report or incident form.

If BCG is being transported/used, tuberculocidal disinfectant for BCG live vaccine spills should be included in the spill kit.

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

#### 14.1.6 Spill cleanup procedure

In the event of a cytotoxic spill in any area other than the CDSC or CACI, the following cleanup procedure should be followed.

1. Alert other staff in the area to the potential hazard and limit access by placing the warning sign in a prominent position. Do not leave the area unattended.
2. Immediately remove unaffected personnel from the environment to avoid increased exposure.
3. Request assistance with managing the spill. Send an assistant to gather the spill kit, detergent, and cytotoxic bin and bring them to the area.
4. Remove the contents of the spill kit and put them on in the following order:
  - (a) respiratory mask;
  - (b) protective eyewear;
  - (c) headcover;
  - (d) first pair of chemoprotectant nitrile gloves;
  - (e) long sleeved gown with cuffs over the gloves;
  - (f) overshoes;
  - (g) Second pair of chemoprotectant nitrile gloves, covering over the top of the cuffs.
5. For a liquid spill, wait a few seconds for aerosols to settle, then carefully place a sufficient quantity of swabs, alginate impregnated mat, or spill pillow over the liquid. Take care to avoid splashes. If the spill involves a powder, carefully place sufficient swabs over the powder, then carefully wet the mat with water so that the powder dissolves and is absorbed by the swab. Cleaning should begin from the outside of the spill area and gradually work toward the center.
6. Using scoop and scraper, scoop up any contaminated swabs, mats, and pillows and carefully clean up any broken glass. Discard all of this waste into the first waste bag.
7. Pour detergent solution to cover the spill and clean the area of the spill thoroughly using absorbent cloths, wiping in a circular motion from the outside of the spill to the centre point of the spill.
8. Pour water to cover the spill, then wipe with absorbent cloths in a circular motion from the outside of the spill to the centre point of the spill. Repeat 3 times. Discard all waste generated into the waste container.
9. Dry the area using absorbent cloths completely to prevent accidental slippage on wet floor.
10. Discard all used items into the second waste bag. Seal the bag and discard into a cytotoxic waste container. Do not compact waste.
11. Once the spill has been adequately managed, remove PPE in the following order and discard in the cytotoxic waste container:
  - (a) outer gloves;
  - (b) overshoes;
  - (c) gown;
  - (d) protective eyewear;
  - (e) hair cover;
  - (f) respirator mask;
  - (g) inner gloves.
12. Arrange for collection of waste according to institution policy.
13. Wash hands thoroughly with soap and water.
14. Arrange for hospital cleaning staff to re-clean the area.
15. Complete the spill report card and forward to the pharmacy (or record incident as required by institutional policy).
16. Arrange for a replacement spill kit to be obtained.

Note: Some spill kits may require diluting detergent to water and using this to clean the spill.

#### 14.2 Contamination of staff and patients

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

1. Immediately call for assistance. Do not leave the person unattended.
2. Arrange for the spill to be managed by a qualified staff member while a second staff member attends to the contaminated person.
3. Remove all contaminated clothing and, if heavily contaminated, discard it into the cytotoxic waste container. Clothing with a minimal amount of contamination should be bagged and laundered separately in soapy water with a thorough rinse.
4. If potential exposure to skin has occurred, wash using an emergency shower. If one is not available, wash the contaminated area of skin with soap and rinse with large amounts of water.
5. If exposure to the eyes occurs, thoroughly irrigate contaminated eyes with sodium chloride 0.9% or other suitable ophthalmic solution for at least 15 min. It is not recommended to irrigate the eye directly under running water from a 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.
6. If the skin is broken, irrigate the affected area with water and control bleeding.
7. Seek medical attention as soon as practical if exposure is not limited to clothing (e.g. skin, inhalation, eyes).
8. Complete an incident report if this is institution policy.
9. Arrange for a replacement spill kit to be obtained if one is used.

#### 14.3 Extravasation

Each institution should develop a policy on dealing with the extravasation of vesicant and irritant 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 and measures (cold/heat packs) to use

for each extravasation. An institution may choose to use a specific antidote for the drug which has extravasated. Commonly used agents to treat extravasation include dimethyl sulfoxide (DMSO), dexrazoxane, and hyaluronidase. A formulation of dexrazoxane is available in some countries for the management of extravasation. This is usually used if extravasation is large and involves an anthracycline. Cooling and DMSO should not be used during treatment with dexrazoxane.

DMSO may be used in the management of amsacrine, dactinomycin, daunorubicin, epirubicin, idarubicin, mitomycin, and doxorubicin extravasation (**NOT** with liposomal doxorubicin). DMSO is thought to accelerate the systemic distribution of the extravasated drug through its vasodilating and anti-inflammatory effects and has free radical scavenging properties.

Hyaluronidase is recommended for the management of extravasation of vinca alkaloids and may be used for the management of extravasation of paclitaxel. It is thought to act by rapidly promoting the dispersion of extravasated drug.

DMSO and hyaluronidase should be available in an extravasation kit and applied as soon as possible after extravasation has occurred, ideally within 10–25 min.

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

A list of vesicant and irritant cytotoxics should be maintained by the pharmacy. “Vesicant” should be on the label of any admixtures prepared by the pharmacy containing a vesicant.

General recommendations for handling extravasation include the following:

1. Stop the injection or infusion immediately.
2. Leave the venous access device (VAD) in place.
3. Aspirate any residual drug from the VAD using a sterile syringe.
4. Make a plan.
5. Call for assistance. Notify a medical officer, pharmacist, or senior nurse.
6. Collect the extravasation kit.
7. Assess the affected area for signs and symptoms such as redness, swelling, burning, or pain and trace the affected area with a marker pen.
8. Photograph the area.
9. Remove the IV device or port needle. Do not apply pressure. If a central line is in situ this should remain in position.
10. Refer to a medical officer for further instructions.
11. Elevate the limb if it provides comfort to a patient.
12. Initiate appropriate drug-specific management measures as per protocol.
13. Administer pain relief if indicated.

14. Refer to a plastic surgeon or other specialist surgeon according to individual case and site of extravasation if clinically indicated.
15. Avoid applying direct pressure to the extravasation site.
16. Document the extravasation in the patient medical record. Complete institution specific documentation or an incident report as required by the institution.
17. Inform and instruct the patient and relatives.
18. Perform aftercare. Plan the follow-up/patient monitoring.

It is important for patients and families to be aware of the aftercare procedures at home.

- (a) Monitor the affected area for any change.
- (b) Touch the area as little as possible. Wear loose clothing around the area where possible.
- (c) Protect the area from sunlight.
- (d) Raise the injured area if this helps with comfort.
- (e) Exercise and move the injured area gently.
- (f) Do not use any creams on the area apart from those prescribed.

Some protocols may require a drastic approach, particularly products known for tissue damage.

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

An incident report which reflects the institution’s policies should be completed whenever a case of 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. Consideration should be given to having both an extravasation kit and an anaphylaxis kit available in areas where chemotherapy is administered so they are immediately available when required.

#### **14.4 Inadvertent intrathecal administration of vinca alkaloids and bortezomib**

Vincristine and other vinca alkaloids are neurotoxic and must only be administered by intravenous infusion. If given intrathecally, 85% have a fatal outcome and survivors may have devastating neurological effects. 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 mini-bag of at least 50 ml.

Vinca alkaloids must be clearly labelled with the intended route of administration. For example, "FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES." The use of negatively worded labels such as "Not for Intrathecal Injection" must 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 in time.

Bortezomib has resulted in fatalities when inadvertently administered intrathecally. Bortezomib should only be administered intravenously or subcutaneously. As bortezomib is presented in a syringe for subcutaneous administration, it is essential that it is clearly labelled with the intended route of administration.

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

Health professionals who prescribe, prepare, or administer intrathecal chemotherapy must complete any compulsory institutional training before handling it. They should be educated on the published case reports of fatal intrathecal administration of vincristine.

## 14.5 Documentation of incidents

Procedures should be developed for documenting spills and other incidents that occur with cytotoxic drugs. Such records should be maintained indefinitely. Regular reviews should take place to ensure that any procedural changes are implemented as required. In the case of cytotoxic spills, a pharmacist should be involved in any changes to procedures.

The institution may have electronic systems for recording Occupational Health and Safety incidents and clinical incidents. If so, these should be used to record spills and incidents as appropriate.

### 14.5.1 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 a spill report card:

- (a) date and time of spill;
- (b) location of spill;
- (c) persons involved and their titles;
- (d) drugs involved;
- (e) brief description of incident;
- (f) whether medical attendance was 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 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 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.

Some institutions may want to use a diagram for marking the extent of extravasation.

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## Section 15 – Waste handling and patient excreta

### 15.1 Handling of cytotoxic waste

Waste handling strategies cover identifying, segregating, containing, transporting, storing, and disposing of waste, patient excreta, and contaminated personal protective equipment (PPE). Cytotoxic contaminated waste is a hazard. Workers should be protected from the risk of exposure through the entire waste handling process, from generation to destruction. Institutions should develop and periodically review policies for waste handling. These should be in accordance with all relevant federal, regional, and municipal regulations and legislation.

The policies should define safe systems of work such as standard operating procedures (SOPs) and spill management and include training and information for all those involved in the handling of contaminated waste.

#### 15.1.1 Contaminated waste

Some countries differentiate between cytotoxic and contaminated waste. Contaminated waste includes any device used by patients who have undergone chemotherapy, such as syringes, needles, catheters, and serum bags. These contaminated items should be placed in separate chemotherapy waste containers that are separate from general waste to protect workers from injury and exposure.

Contaminated waste containers should be collected by the environmental services staff and sealed so that they are airtight before being transported on wheel-driven carts. The carts should be easy to clean and disinfect to offer protection for handling personnel. They should not be used for any other type of waste.

Some countries do not differentiate among wastes based on concentration of contamination. In this case, all cytotoxic waste is disposed of in the same cytotoxic waste container.

The remainder of this section uses the term “cytotoxic waste” to cover all cytotoxic and contaminated waste.

#### 15.1.2 Cytotoxic waste

Cytotoxic waste is any material contaminated with residues or preparations that are cytotoxic.

Cytotoxic waste includes the following:

- (a) Unused cytotoxic drugs such as expired drugs, contaminated stock, and cytotoxic drugs returned from patients.
- (b) Contaminated waste from preparation processes.
- (c) Syringes, needles, and empty or partially used ampoules and vials.
- (d) Disposable drug administration aids and devices such as used medicine cups.
- (e) Contaminated PPE such as gloves, respirator masks, gowns, and shoe covers.
- (f) Materials from the cleanup of cytotoxic spills.
- (g) Contaminated body substance receptacles such as disposable vomit bags.
- (h) Ostomy bags, catheters, and catheter bags.
- (i) Contaminated dressings and bandages.
- (j) Heavily contaminated linen and patient clothing that is unable to be cleaned.
- (k) Contaminated patient body waste (excreta) following treatment with a cytotoxic drug.
  - (l) Contaminated specimens from laboratories.
- (m) Contaminated sharps.
- (n) Air filters from C-PECs (CACIs and CDSCs).

Untreated waste should be collected in clearly marked dedicated containers made from hard, robust material that is shock-resistant and can withstand external pressure during transport. These containers should be puncture-resistant, leak-proof, and of a dedicated colour. They should display a recognisable symbol for cytotoxins, such as a purple symbol depicting a cell in late telophase. All cytotoxic waste should be placed in secondary packaging and sealed to ensure that leakage cannot occur. Cytotoxic waste should be segregated, double-bagged (the first bag being sealable), and discarded into specifically labelled cytotoxic waste containers with sealable lids. Waste containers should not be overfilled.

Untreated waste should be segregated, packaged, and disposed of in such a way that healthcare personnel, home caregivers and the environment are not contaminated.

All regulations of the relevant country concerning the disposal of cytotoxic waste should be followed.

Personnel involved in transporting cytotoxic waste should receive instruction on procedures for safe transport and dealing with spills.

### 15.1.3 Labeling

Cytotoxic waste should be clearly marked as cytotoxic and identifiable to all staff handling it. Bins and containers should be identified by color coding and marked "cytotoxic waste." Containers and wheel-driven carts should be marked with the same label. A second label may be used on each container giving the date of waste production.

### 15.1.4 Transport and storage

Cytotoxic waste collection bins should be located as close as practical to the site of generation and transport corridors. Bins should be rigid-walled, puncture-resistant, and dedicated for use only with cytotoxic waste. They should be sealed prior to collection and should not be reopened or reprocessed on site.

In a hospital setting, cytotoxic waste containers should be collected by environmental services staff. Collection should be scheduled at times that avoid peak work hours. The waste should be taken to a temporary storage area within the hospital. This should be a dedicated secure area with adequate lighting and ventilation, located away from drains. It should be appropriately signed to indicate it contains cytotoxic waste. It should not be accessible to animals or unauthorised persons.

If waste is to be stored for more than 72 h before disposal, consideration should be given to refrigerating the waste, particularly where waste could be subject to decomposition. A specialised company should be used to transport cytotoxic waste from the temporary storage area to an approved destruction facility. Any operators handling, transporting, or destroying cytotoxic waste should be familiar with emergency procedures to be followed in the event of a spill. Spill kits should be available in all waste storage and loading areas. The spill kits should contain all items necessary to clean up spills of cytotoxic waste. Records should be maintained for each spill documenting the specific waste involved and the causes and corrective actions for the spill.

### 15.1.5 Disposal

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

Many countries have their own guidelines and regulations for the disposal of cytotoxic waste. These guidelines and regulations should be followed in addition to those in this document.

### 15.1.6 Education

Ongoing education should be provided to staff who handle (or may handle) cytotoxic drugs to ensure safe handling and spill or leak management. Training should conform to best-practice standards in place. Annual training for the safe handling of cytotoxic drugs and related wastes should be documented in a staff register.

Training and education should cover the following:

- (a) Workplace hazards that may lead to exposure to cytotoxic drugs and waste.
- (b) Risks of exposure.
- (c) Legislative requirements for health and safety.
- (d) Legislative requirements for waste management.
- (e) Risk management.
- (f) Control measures and work practices for handling cytotoxic drugs and related waste.
- (g) Maintenance of equipment.
- (h) Selection, use, cleaning, and disposal of PPE.
- (i) Procedures for accidents, injuries, or spills, including reporting and recording each incident.
- (j) Access to first aid resources.
- (k) Storage, transport, treatment, and disposal of cytotoxic waste.
- (l) Health monitoring and reporting.
- (m) Standard operating procedures (SOPs).

Training records should be kept for a minimum of 5 years.

### 15.2 Handling excreta from patients receiving cytotoxic waste

Cytotoxic drugs are primarily eliminated from the patient in urine and faeces. However, all body substances may be contaminated with either the unchanged drug or active drug metabolites. These include bile, sweat, saliva and semen. These should all be handled as cytotoxic waste.

Exposure to contaminated patient excreta may occur through the following:

- (a) Contact with vomit, blood, excreta, semen and fluid drained from body cavities.
- (b) Contact with bedpans and urinals.
- (c) Emptying urinary catheter bags, colostomy or urostomy bags, and vomit bowls.
- (d) Handling bed linen or clothing soiled with patient waste or contaminated with hazardous drugs.
- (e) Touching or handling contaminated surfaces or equipment.
- (f) Cleaning body fluids from the floor and other surfaces (this should be considered a hazardous drug spill).

**Table 1.** Excretion rates for selected cytotoxic drugs.

Reproduced with kind permission from Cass and Musgrave.<sup>1</sup> Modifications and additions to data made in 2020 on basis of studies below. If not specified for a drug, excretion is at least 48 h.

Cytotoxic agent	Excretion rate	Duration after therapy for which PPE is recommended when handling excreta	
		Urine	Faeces
5-Fluorouracil	Urine: unchanged up to 15% over 24 h	2 days	5 days
Azacitidine			
Bleomycin	Urine: unchanged up to 68% over 24 h	3 days	
Bortezomib			
Busulfan			
Cabazitaxel			
Capecitabine			
Carboplatin	Urine: up to 60% over 24 h	1–2 days	
Carmustine	Urine: 55–65% over 24 h	4 days	
Chlorambucil		1–2 days	
Cisplatin	Urine: unchanged plus metabolites up to 75% over 5 days	7 days	
Cladribine			
Cyclophosphamide	Urine: unchanged up to 25% over 48 h; unchanged plus metabolites up to 62% over 48 h	3 days – in urine, sweat, and saliva	5 days
Cytarabine	Urine: up to 90% in first 24 h	1 day	
Dacarbazine		1 day	
Dactinomycin			
Daunorubicin		7 days	7 days
Docetaxel	Urine: up to 60% within 24 h	1 day	2 days
Doxorubicin	Urine: unchanged and metabolites up to 15% over 5 days	6 days	7 days
Epirubicin	Urine: unchanged up to 11% over 24 h Faeces: unchanged and metabolites up to 85%	3 days	
Etoposide	Urine: unchanged 40–50% over 24 h	3 days	5 days
Fludarabine	Urine: 40–60% over 24 h	3 days	
Fotemustine			
Gemcitabine		1 day	
Idarubicin		3 days	2 days

(continued)

**Table I.** Continued.

Cytotoxic agent	Excretion rate	Duration after therapy for which PPE is recommended when handling excreta	
		Urine	Faeces
Ifosfamide		2 days	
Irinotecan			
Lomustine			
Melphalan	Urine: 30–60% over 24 h	2 days	7 days
Mercaptopurine	Urine: unchanged 10–20% over 24 h; metabolites 10–40% over 24 h	2 days	5 days
Methotrexate	Urine: unchanged and metabolites 40–50% (low doses) and up to 90% (high doses) over 48 h Faeces: up to 9%	3 days	7 days
Mitomycin C		1 day	
Mitoxantrone	Urine: unchanged up to 6.5% over 5 days	6 days	7 days
Oxaliplatin	Urine: 40–50% over 24 h	3 days	
Paclitaxel	Urine: unchanged up to 13% over 24 h Faeces: more than 13% over 3 days	3 days	5 days
Pemetrexed			
Procarbazine	Urine: unchanged 5% over 3 days; metabolites 25–70% over 3 days	3 days	
Raltitrexed			
Temozolomide			
Teniposide		3 days	
Thioguanine		1 day	
Thiotepa		3 days	
Topotecan		2 days	
Trastuzumab emtansine			
Vinblastine	Urine: unchanged and metabolites 13–33% over 3 days Faeces: unchanged and metabolites 10–41% over 3 days	4 days	7 days
Vincristine	Urine: unchanged 8% over 3 days; metabolites 4% over 3 days Faeces: unchanged 30% over 3 days; metabolites 40% over 3 days	4 days	7 days
Vindesine		4 days	4 days
Vinorelbine		4 days	7 days



### 15.2.1 Contamination period

The period during which patient excreta may be contaminated with cytotoxic drugs differs for individual drugs and patients. The majority of cytotoxic drugs will be excreted within 7 days. Care should be taken during risk assessment to identify drugs that have longer excretion periods (see Table 1 for more information).

To simplify policy, health services may opt to consider contaminated all excreta from patients who have received cytotoxic drugs for 7 days with care taken to identify drugs with extended excretion.

To assist in determining whether body waste may be contaminated, the following should be documented in the patient's medical record for each cytotoxic drug:

- (a) Drug name(s), including common protocol name if used.
- (b) Route of administration.
- (c) Date and time of administration.
- (d) Length of time and end date for use of PPE for patient excreta.

### 15.2.2 Risk to caregivers

Caregivers including relatives should be educated about the risk of handling contaminated excreta. Trained staff should provide caregivers involved in administering cytotoxic drugs in the home with education and a process for the disposal of cytotoxic waste, including leftover drugs and human waste. Spouses and significant others should be provided with information regarding the risks associated with intimate contact.

### 15.2.3 Precautions during the contamination period

For the specified time indicated by a specific drug (or 7 days if the health service has chosen to adopt this policy) following chemotherapy, PPE should be worn when handling excreta or cleaning bathrooms and toilet facilities used by the patient. PPE should include chemotherapy-tested gloves, a face shield or goggles, and a non-permeable gown.

### 15.2.4 Disposable and re-usable 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 Toilets

If possible, there should be one or more toilets dedicated to the use of the chemotherapy patient. To reduce the risk of

splashing and aerosolisation, men should sit when urinating. The patient should close the toilet lid before flushing and use a full flush. When a lid is not present, covering the toilet with a plastic-backed liner before flushing should be considered. The liner should be disposed of as cytotoxic waste.

### 15.2.6 Collection of body fluids

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

### 15.2.7 Contaminated linens

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

### 15.2.8 Patient protection

Incontinent patients should protect their skin from their excreta by cleaning with soap and water and applying a barrier cream to the perineal area. Disposable incontinence pads should be used and disposed of as cytotoxic waste.

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## Section 16 – Laundry

Risk of contamination exists when a person comes into direct or indirect contact with urine, faeces, vomit, blood, or other secretions from a patient treated with cytotoxic drugs. These include antineoplastic, non-antineoplastic, and investigational drugs.

Indirect contact includes via clothing, bedding, bath linens, or other items that have been in direct contact with the patient. The following measures are recommended to minimise contamination risk (following the ALARA principle – As Low as Reasonably Achievable) when handling these items. These measures are valid for both the hospital and the home.

Every healthcare organisation must develop its own SOPs, and if applicable, obtain certification from the Healthcare Laundry Accreditation Council (HLAC) or equivalent national or regional organisation.

### 16.1 Gloves and personal protective equipment (PPE)

Gloves and other PPE must be worn when handling linens and clothing of a patient receiving cytotoxic drugs. Gloves should meet the requirements of the American Society for Testing and Materials or other relevant national or regional standards. PPE should include the following:

- (a) Gowns (back-closing without seams and with closed cuffs).
- (b) Head, hair (including beard and moustache), shoe, and sleeve covers.
- (c) Face and eye protection.
- (d) Respiratory protection (such as masks).

Disposable PPE should be discarded after use as cytotoxic waste. This should continue for several days after a patient has completed treatment. In the absence of any specific

detailed information, general recommendations should be followed for up to 7 days (see Section 15).

### 16.2 Linens and clothing

Consider that the middle of the bed linens and especially the pillowcase, the feet, and the pelvic area could be highly contaminated. To avoid the generation of dust, linens and clothing should not be stirred up. If possible, disposable linen should be used.

Linens should be changed every day. Mattress cleaning should follow OSHA standards or equivalent national or regional standards.

### 16.3 Patient hygiene

Patients who need to be washed in bed should be washed with disposable moist tissues to avoid spilling water.

### 16.4 Laundry

Linens and clothing should be considered contaminated materials. Contaminated laundry should be put into sealable plastic bags, placed inside a rigid container, and labeled “Cytotoxic Contamination.” Contaminated laundry after bagging should be transported by carts or chutes.

Contaminated laundry should be kept and washed separate from other laundry.

All laundry should be placed directly into a single-batch washer without pre-sorting to avoid aerosolising the contents. Laundry and bedding should be rolled and not shaken. Faeces should be put into a commode for disposal.

Wash the contaminated laundry twice. First start the washing process with water at a temperature of 71 °C for 25 min, with agitation. Start the second cycle with the normal washing process.

## Section 17 – Warning staff of the presence of cytotoxic drugs

All staff should be made aware of the presence of cytotoxic drugs and the potential for contamination in any situation. This applies when cytotoxic drugs are being stored, reconstituted and compounded, transported, and administered, and when cytotoxic waste is being handled. Staff must be warned to avoid an area where a cytotoxic spill has taken place. Areas where cytotoxic drugs are usually stored or handled must have a cytotoxic spill kit.

### 17.1 Storage

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

### 17.2 Reconstitution and compounding

The area where cytotoxic drugs are reconstituted and compounded should be restricted to authorised personnel and should be clearly labelled to alert staff to the presence of cytotoxic drugs (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 drugs are transported both within the institution and externally (see Section 2). Transport staff must also be given instructions in case of emergency. Cytotoxic spill kits should be readily available if needed.

### 17.4 Administration

Staff members must be made aware that a patient is receiving cytotoxic drugs. The drugs will be labelled with a prominent warning. Nursing staff should attach stickers to IV

lines indicating that the infusion is cytotoxic. This is particularly important if the cytotoxic drug must be protected from light and labels may therefore be hidden. In this scenario, labelling the outside bag as cytotoxic or the use of translucent/transparent photoprotector bags may additionally reduce risk.

Whenever patients are transported around the hospital during administration, it is important that all staff are aware that a cytotoxic infusion is running. This should also be communicated to staff who will assume care of the patient.

Staff in areas that do not usually handle cytotoxic drugs or do not have credentialed staff must be supported by staff knowledgeable and credentialed in handling these drugs. This may involve handover with pertinent points of management and provision of a contact number depending on the organisational policy.

Patients who are under cytotoxic precautions (i.e. have contaminated excreta) must also be identifiable to hospital staff. This may be achieved by attaching a warning sign or sticker to the patient's bed, bed card, or ID band, with consideration made for both patient privacy and clarity for staff. Alerts may also be used in the medical record to inform staff. Staff will then be aware that the patient's excreta may have to be handled as contaminated waste (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 these purposes and dedicated temporary storage areas within the institution.

### 17.6 Spills

Staff must be warned whenever a cytotoxic spill occurs. This will usually be achieved using a specific warning sign provided in the spill kit (see Section 14).

### **17.7 Home care**

Patients receiving chemotherapy at home and their care-givers must be made aware of the importance of warning other people in the household and visitors about the use of cytotoxic drugs in the home. 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 and specimens as potentially dangerous, blood samples and specimens taken from a patient having received chemotherapy in the preceding 7 days must be labelled as cytotoxic to alert laboratory personnel.



## Section 18 – Home care

Patients may receive cytotoxic drug therapy at home or in a residential care facility. Nursing, medical staff, other health-care professionals, and informal caregivers such as family members may participate in home care.

Home care may consist of oral or parenteral drug therapy. Oral anticancer drugs are delivered as tablets or solutions at home, provided with careful instructions (see Section 24).<sup>5</sup> Infusions or syringes may be administered at home under direct medical supervision<sup>9</sup> or may be ambulatory.<sup>1,4,8</sup>

In ambulatory therapy, an intravenous solution contained in an infusion device is connected to the patient through a central venous access device (CVAD) connected at the hospital. The patient is then discharged and free to ambulate for a specified number of days (usually 2–7) before disconnection.

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. These patients should receive treatment in a hospital or other healthcare center under direct medical supervision.

Information on handling cytotoxic drugs in the workplace can be found in Section 15 and may provide additional help to caregivers.

### 18.1 Home care by nursing staff

Home chemotherapy should be administered only by appropriately trained and credentialed nurses or health practitioners with documented knowledge and experience with cytotoxic drugs.

The institution providing the home care service should 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 home care must be prepared under the same conditions as all other chemotherapy in the hospital pharmacy department, approved external compounding, or community pharmacy complying with the same requirements.

Nursing staff must not reconstitute cytotoxic drugs in the patient's home. Before proceeding with chemotherapy in

the home, nursing staff must verify that the following facilities are available:

- (a) hand washing facilities;
- (b) laundry facilities;
- (c) access to appropriate toilet;
- (d) secured waste storage.

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

- (a) strong alkaline detergent (pH 10);
- (b) approved container for sharps;
- (c) cytotoxic waste container;
- (d) personal protective equipment.

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

### 18.2 Home care by the patient or relatives: Ambulatory and oral anticancer therapies

If the home care is to be provided by the patient or relatives, this care should be organised and coordinated in advance. With close cooperation among hospital staff, all aspects of the treatment should be explained and full education and training provided. Caregivers 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. Caregivers should be advised about special requirements of the specific drugs used.

Detailed written information, instructions, and training should address the following:

- (a) Treatment the patient is to receive.
- (b) Drug side effect profiles and possible drug interactions (including OTC drugs).
- (c) Storage and stability of the prepared drugs.
- (d) Route and schedule of administration.
- (e) Care of infusion lines, catheters, port systems, and any other venous access devices likely to be used.

- (f) Contained transfer devices, elastomeric infusion devices, ambulatory electronic pumps, and spill kits for patients connected to an infusion device.
- (g) Personal protective equipment (PPE).
- (h) Safety precautions required in the handling of cytotoxic drugs, waste handling, excreta, and laundry.
- (i) How to proceed in the event of an emergency or other incident such as extravasation, hypersensitivity reactions, electronic device alarms, and spills.
- (j) Disposal of drugs that are no longer required.
- (k) Contact details for home caregivers and hospital staff.
- (l) Precautions to be taken when a caregiver is pregnant or breast feeding.

For oral anticancer medications, caregivers should do the following:

- (a) Avoid cutting, crushing, chewing, or opening tablets or capsules unless otherwise instructed.<sup>7</sup>
- (b) Wear gloves to hand drugs to the patient or pour pills into a disposable medication cup, later discarded as cytotoxic waste.<sup>2</sup>
- (c) Wash hands before and after touching the drugs.

Unused or expired chemotherapy drugs should be returned to the local pharmacist or hospital for adequate disposal, not discarded with domestic waste or flushed down the toilet. Disposable pumps should be returned in a sealed plastic bag if disconnected at home.

### 18.3 Handling bodily fluids

Because anticancer drugs are excreted through the urine and faeces, patients should be advised to use a dedicated toilet and flush twice after use. Good hygiene should be practiced during and after toilet use, including sitting to avoid splashing and washing hands after use.

If disposable undergarments are used, gloves should be worn to remove and discard them. They should be put in a double bag before disposal and the surrounding skin gently washed and dried before putting on a clean undergarment. Caregivers should also wear gloves when handling contaminated clothes, linens, and towels. These items should not be washed by hand: they should be machine washed twice in hot water with regular laundry soap separate from other laundry. Contaminated garments or linens must be kept in a sealed plastic bag until adequately washed.<sup>7</sup>

### 18.4 Liability

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

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## Section 19 – Risk management

Cytotoxic drug risk management consists of hazard identification, risk assessment, risk control, and review of risk control.

### 19.1 Hazard identification

Occupational exposure to antineoplastic drugs was first brought up as a concern in the 1970s. Over the years, there has been an increasing number of alerts related to other drugs with hazardous characteristics. The National Institute for Occupational Safety and Health (NIOSH)<sup>1</sup> in the United States identifies approximately 210 drugs that fit its definition of hazardous drugs, including drugs that have adverse effects primarily on reproduction. The classification was based on a six-point definition modified from the American Society of Hospital Pharmacists (ASHP) definition of what constitutes a hazardous drug.<sup>1</sup> About half of these drugs are antineoplastic drugs.

The first step in hazard identification is to generate a list of all drugs used in the facility and to identify drugs that are listed as cytotoxic drugs. This list should be made available to anyone who has the potential to come in contact with these drugs. These people may include pharmacists, 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.

### 19.2 Risk assessment

Once the cytotoxic drugs in a facility have been identified, an exposure assessment should be completed by identifying the path the drugs follow from entering the facility to leaving it. They may leave as patient waste, contaminated laundry, IV bags, contaminated medical equipment, or other forms. The path may include receiving, transport within the facility, storage (including refrigerators and freezers), drug preparation and administration, operating rooms, and laundry and waste handling. All potential sources of exposure, internal or external, should be identified. It is also important to identify all individuals who may come into contact with the cytotoxic 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 cytotoxic drugs are used will most likely be contaminated with those drugs. Because only six to eight drugs are commonly used so far as “markers” of exposure, this approach can only estimate the overall exposure from the dozens of drugs that may be in use.<sup>2</sup>

### 19.3 Risk control

Frequently, exposure in the workplace occurs due to failure or violation of control measures. Thus, it is important to identify basic components in a hierarchy of control and apply different strategies at different levels of the hierarchy (see Section 5).

### 19.4 Implementation and review of risk control

Before implementing risk control in a facility, a risk control plan must be prepared. The risk control plan may include a history of health and safety activities involved in the process and immediate and long-term control measures. Priorities of putting controls in place must be recognised to ensure the plan will be successfully executed. Maintaining this control plan requires regular inspection and compliance to audit. In the case of any incident related to cytotoxic drugs, a thorough investigation must be done to identify the root cause and ways to prevent it in the future.

Risk control strategies may include the following:

- (a) Work organisation (rotation of staff to reduce fatigue, proper identification of cytotoxic drugs).
- (b) Medical surveillance (see Section 26).
- (c) Appropriate management of spills involving personnel (see Section 5).
- (d) Review of incident reports.
- (e) Regular monitoring and review of control measures, with changes implemented as needed.

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## Section 20 – Medicines management

### 20.1 Procedures for drug selection

Drug selection should be a multidisciplinary process overseen by the institution's Drug and Therapeutics Committee (DTC) or other oversight group. Selection should involve oncologists, hematologists, pharmacists, nurses, management, and administrative staff.

#### 20.1.1 Drug and Therapeutics Committee (DTC)

Written policies and procedures should be developed to define the functioning of the DTC or other oversight group.

#### 20.1.2 Drug selection

Written policies and procedures about the process of drug selection in an institution should be developed that include the following:

- (a) How to request additions, changes, or deletions to and from the formulary, which is a list of drugs approved for use in the institution.
- (b) Evaluation process.
- (c) Dissemination of information about DTC decisions.
- (d) Mechanism for updating the formulary or list at least annually (including consideration of external procurement arrangements if they exist).

#### 20.1.3 Drug evaluation

Drug evaluation should be based on efficacy, safety, harm minimisation, cost, and convenience (e.g. easier route of administration, reduced dosing frequency) and should be in accordance with current legislation. Comparison should be made with alternatives (antineoplastic drugs or protocols already available at the institution). The evaluation process should be guided by evidence-based bibliography search/revision, evaluation report/monograph format, and interdisciplinary input and deadlines.

#### 20.1.4 Criteria for requests

Criteria should be developed to evaluate requests, including the following:

- (a) *Efficacy*: clinical outcomes, absolute risk reductions.

- (b) *Safety*: adverse events, contraindications, precautions, potential for errors (sound-alikes, look-alikes, labeling).
- (c) *Pharmacotherapeutic criteria*: dosages, administration route, premedication regimens, interactions.
- (d) *Pharmaceutical criteria*: strength of doses available, stability and compatibility, convenience of drug presentation to usual doses, ease of manipulation, unit-dose packaging, bar-codes, potential for drug errors.
- (e) Cost per course, incremental cost-efficacy, institution budget impact.
- (f) Availability of scientific evidence and documentation.
- (g) *Manipulation safety*: unbreakable containers, surface contamination protection, material safety data sheets.

#### 20.1.5 Procuring non-formulary drugs

Requests for approving medication on a patient by patient basis for extraordinary circumstances (rare disease or patient circumstance) must be submitted to a DTC or equivalent for approval. The institution should have a policy where an application for a medication to be added to the formulary is requested if there are multiple applications for the same medication and indication on an individual patient basis.

#### 20.1.6 Drug selection decisions

Drug selection decisions (additions, deletions, changes) and recommendations must be disseminated to healthcare professionals involved in patient care.

#### 20.1.7 Updates

An updated hospital formulary or pharmacotherapeutic guide (preferably online to ensure currency) should be distributed to all healthcare staff. This should discuss drug selection, policies and guidelines of drug use, and enhancement of rational drug use.

### 20.2 Procedures for drug purchasing

All drugs should enter the hospital through the hospital pharmacy, including clinical trial medicine, drugs available through drug access programs, and samples.



### 20.2.1 Purchasing decisions

Purchasing decisions are based on the drug selection process.

### 20.2.2 Criteria to evaluate purchasing process

Criteria should be developed to evaluate the purchasing process and should include (but not be limited to) the following:

- (a) Usage.
- (b) Generic policies.
- (c) Economic offers (industry promotions, flexible pricing, public tenders).
- (d) Pharmaceutical criteria (unit-dose packaging, strength of doses available, bar-coding).

### 20.2.3 High-cost and high-use drug review

High-cost and high-use drugs should be reviewed regularly to ensure appropriate use of resources and compliance with formulary guidelines. Deviations should be analysed and corrective measures implemented. Contracts for drug purchase by the institution or group purchasing organisation should be honoured.

### 20.2.4 Purchase approvals

Purchase of drugs from wholesalers or manufacturers must be approved by a pharmacist or designate such as a pharmacy technician and must follow all local regulatory laws and regulations. Products with similar packaging should be avoided whenever possible.

### 20.2.5 Purchase history

A computerised system should be used to track purchase history and use for all drugs managed by the pharmacy. This system should be used to assist in the drug purchasing process (stock limits, purchasing proposals).

### 20.2.6 Purchasing updates

Periodic updates on purchasing and use of drugs should be made available to the hospital administration, directors of clinical units, and DTC (to be used in their review process).

## 20.3 Procedures for stock control

### 20.3.1 Drug security

Drugs must be secured in storage areas in accordance with local laws, regulations, and organisational policies.

### 20.3.2 Discrepancies

Drugs received should be checked against the delivery invoice and the pharmacy order form. Discrepancies should be reconciled by the responsible pharmacist or designate.

A quality control process should be established. Products should be quarantined if nonconformity is detected.

### 20.3.3 Updated drug inventory

An updated, ideally computerised, drug inventory should be available that includes batch and expiration data. Information technology (radiofrequency, bar code, image identification) should be used to assist in stock control.

### 20.3.4 Drug inventory

Written policies and procedures should be developed for regularly comparing drug inventory with actual stock. Discrepancies should be analysed and corrective action taken. Drug traceability should be guaranteed from entering the pharmacy to patient administration.

### 20.3.5 Discrepancies

Written policies and procedures should be developed for handling drug shortages, outages, and recalls.

This is mandatory for shortages in case an alternative commercial product should be temporarily included in the guide or formulary. In the event that the change to formulary needs to be permanent, an application to the DTC should be made.

### 20.3.6 Expiration dates

There should be a manual or automated procedure for checking expiration dates throughout the institution and for removing expired stock.

### 20.3.7 Disposal

Policies and procedures must be established for disposal of expired or damaged stock that complies with local laws and regulations.

### 20.3.8 Drug storage

Written policies and procedures should be developed for the drug storage system (alphabetical order, pharmaceutical forms) and labelling (generic, brand names, expiration, and appropriate warnings).

### 20.3.9 Error prevention

To prevent errors, drugs that can be easily mistaken for others (sound-alikes, look-alikes, similar labelling) must be separated in all areas of the healthcare organisation. Safe practices such as tall man lettering and bar codes must be used to prevent errors of confusion.

### 20.3.10 Storage guidelines

Drugs should be stored according to the manufacturer's recommendations. Storage conditions (temperature, moisture, light protection) should be monitored periodically to ensure effectiveness and safety.

### 20.3.11 Cytotoxic drugs

Policies and procedures for cytotoxic drugs should be developed. Special handling requirements should be identified. Personal protective equipment (PPE) and separate storage areas employing measures to minimise breakage should be available. Storage areas should each have an extraction fan that can be used in an emergency. Cytotoxic spill kits should be available where appropriate.

## 20.4 Procedures for reuse of drugs

### 20.4.1 Responsible parties

The pharmacy department is responsible for the management of all unused drugs returned that were compounded or dispensed for cancer patients.

### 20.4.2 Drug returns

Written policies and procedures for drug return to the pharmacy should be developed.

### 20.4.3 Quality control

A quality control policy for returned drugs should be developed to address patient safety, including technical aspects (integrity, packaging, labelling, defective devices, expiration dates considering both chemical and microbial factors) and physicochemical aspects (colour, precipitation).

### 20.4.4 Drug disposal

Written policies and procedures for the safe disposal of returned drugs should be developed. This is mandatory for pharmacy-prepared sterile products. These should consider stability and compatibility under actual handling conditions, including storage or transportation when outside the pharmacy and microbial risk level.

Drugs unused and in their original sealed packaging can be returned and reused if they comply with quality criteria.

### 20.4.5 Causes for drug return

Causes for drug return should be documented and recorded and the pharmacotherapy history updated as needed. This information should be analysed periodically to identify opportunities for improvement in the pharmacotherapy process.

### 20.4.6 References for accepted expiration dates

A table or chart of accepted expiration dates for common pharmacy-prepared sterile products should be maintained, taking into account stability in the actual environmental conditions. Consideration needs to be given to the environmental characteristics of preparation and their effect on maximal expiry date for the product for microbial stability (refer to section 8).

### 20.4.7 Drug reuse

Written policies and procedures for safely re-dispensing and recycling returned drugs must be developed that include the following.

- (a) Process of new expiration date assignment.
- (b) Identification and labelling as recycled.
- (c) Re-dispensing process.
- (d) Dose banding.

Healthcare professionals involved in drug reuse processes should be recorded. A computerised application may assist in optimal reuse of sterile preparations and management of expiration. Traceability should be guaranteed throughout the drug reuse process.

### 20.4.8 Returned drug storage

Returned drugs should be placed in optimum storage conditions (strictly adhering to temperature, light, and other criteria) and their reuse prioritised over normal stock.

### 20.4.9 Disposal

Policies and procedures for the disposal of expired or other unusable returned drugs must follow all local laws and regulations.

### 20.4.10 Bibliographies

Bibliographic sources (product approved labelling and reliable published stability data) used to establish criteria should be referenced, available, and periodically updated.

## 20.5 Procedures for partial vials

### 20.5.1 Final concentration

To avoid drug preparation errors and facilitate stability concentration limits, the final concentration should be the same irrespective of different available dosages of a drug.

### 20.5.2 Maximal accepted expiration dates

A table or chart should be available in 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 diluent, microbial risk level, and optimal storage conditions (light protected, refrigerated).

### 20.5.3 Drugs in solution

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

### 20.5.4 Labelling

Residual volume in multidose vials generated during anti-neoplastic compounding should be re-labelled with the reconstitution and first-used dates and times and the expiration according to recommended storage conditions.

### 20.5.5 Use of partial vials

Partial vial use should be prioritised. Partial vials that are beyond determined expiration should be discarded.

### 20.5.6 Storage

Residual volumes in vials should be stored adhering to temperature, light, and other criteria.

### 20.5.7 Disposal

Policies and procedures for the disposal of expired or other unusable vials should follow all local laws and regulations.

### 20.5.8 Bibliographies

Bibliographic sources used to establish that criteria are referenced (product approved labelling and reliable

published stability data) and available and basic information (tables, charts) should be regularly updated.

## 20.6 Procedures for unlicensed, foreign, compassionate, and off-label use drugs

Use of these drugs is covered in Section 25.

### 20.6.1 Unlicensed drugs

Written policies and procedures should be in place regarding rational, safe use of unlicensed drugs in accordance with regulatory laws, patients' rights, and ethics. Unlicensed drugs include drugs not approved or licensed but available in a foreign country, off-label use of licensed drugs, and investigational drugs in the setting of clinical trials or drug access programs.

### 20.6.2 Foreign and compassionate use drugs

A procedure for purchasing, storage, and stock control of foreign and compassionate use drugs should be developed. Written policies and procedures for the effective and safe use of foreign drugs should include selection, prescription, preparation, dispensing, administration, and monitoring.

### 20.6.3 Off-label use drugs

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

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## Section 21 – Documentation

### 21.1 Overarching policy and SOPs

#### 21.1.1 Policies

Each institution should have written policies covering all aspects of the safe handling of cytotoxic and other hazardous drugs, including prescribing, management, preparation, and administration. The policies should include the roles and responsibilities of staff working within the oncology pharmacy service and identify the staff responsible for the implementation and governance of these policies.

#### 21.1.2 Standard operating procedures (SOPs)

Each institution should develop and maintain a manual of SOPs detailing the following:

- (a) Receipt, storage, transport, preparation, dispensing and administration of cytotoxic drugs.
- (b) Disposal of drugs and other contaminated waste.
- (c) Actions to be taken in the event of an extravasation, spill, needlestick, or other accidental exposure.
- (d) Engineering controls including cleaning, environmental monitoring and servicing.
- (e) Medical surveillance programs.

SOPs should contain a full description of all PPE and special containment devices used in the preparation and administration of cytotoxic drugs. SOPs must be regularly updated and available to staff at all times.<sup>1,2</sup> Policies and procedures should be reviewed and updated regularly. There should be a policy in place defining the responsibility for writing, verifying, approving, and archiving all documentation used within the oncology pharmacy service. This should include a version control process to ensure outdated documents are removed from use.<sup>2,3</sup>

#### 21.1.3 Electronic documents

Protocols, procedures, and other documentation templates that are stored electronically should be in a read-only format to avoid unapproved or undetectable alterations that could lead to errors. Access to original clinical protocols and templates should be restricted to authorised named staff.<sup>4</sup> Printing copies of procedures and protocols

that are available electronically should be minimised to prevent out-of-date information being accessed and incorrect procedures being used. Consider adding a statement<sup>4</sup> such as the following to each electronically stored document.

All printed copies of this document are considered uncontrolled copies. Printed copies are only valid for the day printed.

### 21.2 Staff

#### 21.2.1 Occupational health monitoring

All staff involved in the direct handling of cytotoxic or other cytotoxic drugs should have a baseline health assessment and medical history to identify potential risks to the staff member and any health issues that may affect their suitability for work in the aseptic preparation area or clinical area before commencing work. A record of this assessment must be kept in the employee's health record.<sup>2</sup>

Staff may be asked to confirm in writing that they understand the risks of handling cytotoxic drugs. If an institution offers employees routine blood testing or any other test relating to the exposure to cytotoxic drugs, a baseline measurement should be taken, followed by routine measurements at regular intervals with results documented in the health record. Any abnormal test result should be documented with the follow-up action taken. These health records should be retained for the duration of employment plus 30 years and may be transferred if the employee moves to a different institution (see Section 26).<sup>1</sup>

#### 21.2.2 Education and training

A training record should be created for each staff member upon hiring to document initial training and accreditation (see Section 4). The record should be updated to reflect subsequent training, education, and competency assessments.

The training record should include the following:

- (a) Dates of the training sessions.
- (b) Contents or a summary of the training sessions.

- (c) Names and qualifications of the persons conducting the training.
- (d) Copies of any certificates issued.<sup>1</sup>

The training record should be maintained throughout employment and archived for a reasonable period of time after employment ceases.

A log should be kept of staff trained in the clean-up of cytotoxic spills. This should include staff working in a pharmacy store where cytotoxic drugs are kept, involved in the operation of a robot, involved in the transport of cytotoxic drugs in or outside the hospital and cleaning staff. A signature of the staff member and the date training was completed should be recorded.

### 21.2.3 Exposure to cytotoxic drugs or other hazardous drugs

A log of all operators preparing cytotoxic drugs should be maintained indefinitely.<sup>5</sup> At a minimum, this log should reflect daily reconstituting activities. The specific CDSC or CACI – refer to glossary used should be noted. For staff operating manufacturing robots, details of work shifts should be recorded.

In the event of a spill or accidental exposure (direct skin or eye contact, needlestick injury), additional details should be documented in the log, including the following:

- (a) Name of the operator.
- (b) Name of each drug involved.
- (c) Number of products of each drug involved.
- (d) Estimated drug exposure (e.g. mg).
- (e) Location and duration of exposure.
- (f) Specific CDSC, CACI, or robot involved (if the institution has more than one).
- (g) Details of any follow-up action, including the clean-up process and any medical treatment required by the operator.

This information should also be recorded in the employee's health record.<sup>1,2,6</sup>

## 21.3 Facilities

Records must be kept of initial and routine validation work carried out in the preparation area and regular environmental monitoring results, cleanings, and maintenance.<sup>3,7</sup>

### 21.3.1 Validation

Details of process validations, equipment validations or calibrations, and validations of individual operators should be maintained in accordance with SOPs.

### 21.3.2 Microbiological monitoring

The results of microbiological testing performed in the aseptic suite should be maintained for a period of 3 years or other time dictated by local or institutional requirements. Microbial testing may include settle plates, finger dabs, broth inoculations, and end-product testing.

### 21.3.3 Contamination monitoring

The results of chemical contamination monitoring should be maintained for a period of 10 years or other time dictated by local or institutional requirements.

### 21.3.4 Cleaning log

A record should be kept of daily, weekly, and monthly cleaning activities, including the staff member performing the cleaning and the cleaning agents used (if two cleaning agents are used in rotation). Cleaning should be documented whenever an unusual event occurs requiring the shut-down and cleaning of an appliance or if a major spill occurs.

### 21.3.5 Maintenance log

An equipment maintenance log should be maintained. This should include the dates and results of all routine maintenance and certification relating to cytotoxic facilities, CACI, CDSC, and robots. If equipment fails any test, follow-up action should be included. Details of any repairs, filter replacements, and technical problems with equipment should be recorded.

### 21.3.6 Pressure differentials

Pressure differentials within the cytotoxic suite should be checked and recorded in a log daily. This includes pressure differentials between any cleanrooms, airlocks, and external environments. Pressure readings on a CACI should be checked and documented daily.

### 21.3.7 Temperature logs

Refrigerator, freezer, and room temperatures should be recorded in a log daily. Follow-up actions taken as a result of temperature excursions should be documented. There may be additional temperature monitoring requirements for investigational drugs stored within the department. Refer to the clinical trial protocol to ensure the requirements are followed (see Section 25).



### 21.3.8 Particle counts

The results of any particle counts performed should be documented and retained for a period of 3 years or other time dictated by local or institutional requirements.

## 21.4 Operational records

### 21.4.1 Risk assessments (also see Section 19)

A risk assessment should be undertaken and documented to evaluate the risks to staff handling cytotoxic and other hazardous drugs within the institution, including oral dosage forms.<sup>2</sup> This risk assessment should be reviewed annually (or more frequently in response to a change in practice) to ensure current practice is reflected. Policies and procedures must be put in place to minimise risk as much as practically possible.

### 21.4.2 Safety data sheets (SDSs)

A list of all cytotoxic drugs used within the institution should be kept up to date. A SDS must be available for each drug included on the list. SDS should be readily available in all areas where cytotoxic drugs are stored or used.

### 21.4.3 Manufacturing records (also see Section 11)

Drug preparation worksheets (also referred to as work cards or admixture or compounding logs, sheets, and cards) should identify the drug products prepared for each patient and the staff who prepared and checked them.<sup>7,8</sup> These worksheets should be retained for an appropriate length of time.

### 21.4.4 Cytotoxic spills (also see Section 14)

A log of cytotoxic spills should be maintained for a period of 10 years or other time dictated by local or institutional requirements. The log should include the information 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 staff involved in the spill and clean-up.

### 21.4.5 Transport of product within the institution (also see Section 2)

An institution may wish to maintain a record of any cytotoxic being transported. Details may include the destination, contents of the package, date and time of delivery, and identity of the person transporting and receiving the items.

The supply and transport of doses intended for intrathecal administration require special attention (see Section

14). Details should be recorded of all deliveries of intrathecal doses. The institution may wish to adopt a policy of requiring a signature on receipt of intrathecal preparations.

### 21.4.6 Transport outside the institution

A record should be kept of any cytotoxic preparations transported out of the institution by courier to another institution or a patient's home. The details should include the destination (address), contact details at destination, person collecting the item, package contents, storage conditions, date and time of collection, and person packing the items. Signature logs should be used to record successful delivery.

### 21.4.7 Error and incident reporting

A system of error and incident reporting should be in place to allow institutions to investigate serious incidents and identify areas where procedures could be improved if a recurring pattern becomes evident to reduce the risk of errors. The error reporting tool should focus on why errors occur rather than blaming or censuring staff.<sup>8</sup>

### 21.4.8 Workload statistics

Each institution should keep statistics characterising the workload of the cytotoxic preparation suite. These statistics should reflect the quantity and complexity of the items prepared. They should be reviewed on a regular basis to optimise staffing level and mix of staff working in the area.

## 21.5 Clinical documentation

### 21.5.1 Standard treatment protocols and pro forma prescriptions

Experienced oncology pharmacists should participate in developing treatment protocols for standard treatments and clinical investigations. These should be used to develop standardised preprinted paper or electronic medication-order forms or pro forma prescriptions for requesting systemic anticancer treatments and treatment-related services. Well-designed standardised, regimen-specific medication order forms reduce errors by organising treatment information in a clear, consistent, and uniform format.<sup>8</sup>

Clinical protocols, standard order forms, and pro forma prescriptions must be regularly reviewed, updated, and document controlled.

### 21.5.2 Patient health records

The pharmacist responsible for the oncology pharmacy service should ensure there are policies and procedures for the documentation of pharmacy patient care activities

in the patient's health record. These may include the following:

- (a) Drug monitoring plans.
- (b) Patient allergies.
- (c) Identification and management of potential drug interactions.
- (d) Documentation of required recommendations or modifications to drug prescriptions.
- (e) Patient counselling on appropriate drug use to support optimal patient care.

Where an electronic prescribing system is used, it should provide an audit trail of all prescriptions entered and changes made, including the date, time, and author of each change. The system may also collect reasons for changes of schedule, dose, or drug modification that can be reviewed retrospectively to monitor clinical practice.<sup>9</sup>

### 21.5.3 Documentation and monitoring of medication errors and adverse events

The institution should have a policy for reporting errors, adverse events, and near misses relating to the use of systemic anticancer medicines. There should be a formal process for collecting and evaluating the data at a defined frequency. This process should allow data from previous incidents to be used to implement measures that will prevent future events.

### 21.5.4 Extravasation

A log of episodes of extravasation should be maintained for a period of 10 years or other time dictated by local or institutional requirements. Details of follow-up action taken and patient outcome for each extravasation incident should be recorded. This may be either a pharmacy or nursing responsibility.

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## Section 22 – Monoclonal antibodies

### 22.1 Evaluating potential health hazards of monoclonal antibodies (MABs)

There is little information available to aid in the evaluation of the potential health hazards of MABs.<sup>1,2</sup> This lack of information coupled with the ever-increasing number of monoclonal antibodies added to hospital formularies each year has made it difficult to propose recommendations for their safe handling. Recommendations have varied considerably among countries and even within a single country. Questions raised about the risks to workers based on exposure pathways and bioavailability in occupational settings is mostly unanswered.

Research on occupational exposure to antineoplastic drugs has focused on low molecular weight compounds. Reports have associated workplace exposures to these cytotoxic drugs with acute health effects such as hair loss, headaches, skin and mucous membrane reactions, and hypersensitivity.<sup>3</sup> Adverse reproductive outcomes, including infertility, spontaneous abortions, and congenital malformations, have also been reported.<sup>4,5</sup>

Many safety provisions such as ISOPP [2007] have been advanced to reduce exposure. Safety improvements, including the use of CSTDs, have been introduced. Despite these measures, workplaces continue to be contaminated and workers continue to suffer exposures.<sup>6,7,8–10,11,12,13,14–16</sup>

MABs, on the other hand, have molecular weights several orders of magnitude higher than most traditional antineoplastic drugs. This may limit uptake via some exposure routes, thus reducing the potential for adverse health effects in workers.

Some MABs used to treat cancer are conjugated with radioactive or chemical moieties. Two drugs that possess a radioactive moiety are ibritumomab tiuxetan and tositumomab.<sup>17</sup> As radiopharmaceuticals, these monoclonal antibodies fall into a separate class of hazards that are under the control of nuclear regulatory agencies and require special handling due to their radioactivity.<sup>18</sup> Specialised commercial radiopharmacies often perform radiolabeling prior to shipment.

Three MABs that are conjugated to toxic compounds have been approved by the European Medicines Agency<sup>19</sup> and the U.S. Food and Drug Administration (FDA).<sup>20</sup> Brentuximab vedotin incorporates three to five molecules of monomethyl auristatin. These molecules inhibit the

polymerisation of microtubules. Trastuzumab emtansine is conjugated with a single molecule of mertansine, a microtubule inhibitor. Gemtuzumab ozogamicin is a drug-linked monoclonal antibody attached to a derivative of N-acetyl gamma calicheamicin.<sup>21</sup>

Because these moieties are highly toxic, the manufacturers recommend that they should be handled as would other antineoplastic drugs.<sup>22</sup> Whether or not a healthcare facility considers monoclonal antibodies to be hazardous drugs, antineoplastic conjugated antibodies such as these require special handling to protect workers from the antineoplastic moiety.

According to manufacturer recommendations, most MABs fall into a low-risk category for pregnant patients.<sup>23</sup> However, NIOSH recently listed pertuzumab as a potential occupational hazardous drug based on the manufacturer's black box warning for embryo-fetal death and birth defects.<sup>22</sup> This is the only non-conjugated monoclonal antibody that NIOSH has included in its list of hazardous drugs. However, NIOSH has also proposed adding three MABs as hazardous drugs: bevacizumab, blinatumomab, and trastuzumab.<sup>24</sup>

Newly approved monoclonal antibodies are each unique in structure, molecular weight, biological activity, availability, formulation, and other characteristics. Each drug should therefore be evaluated on an individual basis for its potential as an occupational hazard.

In the US, NIOSH uses six criteria to evaluate drugs for the potential to be occupational hazards.<sup>3,22</sup>

- (a) carcinogenicity,
- (b) genotoxicity,
- (c) mimicking existing hazardous drugs in structure or toxicity,
- (d) teratogenicity or developmental toxicity,
- (e) reproductive toxicity in humans,
- (f) organ toxicity at low doses in humans (>10 mg/day) or animals (> 1 mg/kg/day).

Of these, only the last three criteria can be used to evaluate potential occupational hazards of MABs due to their unique characteristics. Therefore, little information is available on these criteria for many MABs. If the European CMR classification scheme (carcinogenic, mutagenic, reprotox) is

applied to monoclonal antibodies, little data will be available to evaluate these agents as potential occupational hazards.

## 22.2 Routes of exposure to MABs

Exposure of healthcare workers to traditional antineoplastic drugs varies based on recommendations and work practices in different countries. Exposure is typically through dermal uptake or inhalation. Oral exposure has also been reported.<sup>25,26</sup>

Overall, the potential for occupational exposure of healthcare workers to MABs is minimal during most routine handling activities. Physical and chemical properties of MABs further suggest that the risk of health hazards resulting from exposure is low. Exposure scenarios that apply to lower molecular weight antineoplastic drugs do not apply to protein-based molecules with the molecular weights of MABs.

Long-term, low-dose exposures of healthcare workers to MABs may result in sensitisation. Sensitisation could limit treatment of workers who may subsequently develop cancer or other illnesses.

### 22.2.1 Dermal exposure

Dermal exposure occurs when workers touch contaminated drug vials and other surfaces that are contaminated with drugs during their preparation, administration, or disposal.<sup>6-9,11-14,16</sup> Exposure can also result from contact with surfaces contaminated with the waste products of patients treated with these drugs or metabolites of the drugs.

In most cases, there is limited information available on the dermal absorption of MABs.

Given their large molecular weight (> 140 kDa), the potential for dermal uptake of MABs in the occupational setting is very low. Research has postulated the upper limit for dermal absorption of compounds at 500 Da,<sup>27</sup> although some slightly larger drugs may have the potential for dermal uptake. Local irritation or allergic reactions in damaged skin may facilitate dermal uptake.<sup>28</sup>

Healthcare workers, especially nursing personnel, have an unusually high incidence of dermatitis, which could contribute to dermal uptake. One study reported that 72% of the nurses surveyed had some form of dermatitis.<sup>29</sup> Routine uses of gloves when handling MABs is recommended and would prevent possible dermal uptake, especially by damaged skin. Dermal uptake of MABs is minimal in the occupational setting and the risk of contact allergy is similar to that of other pharmaceuticals that contain excipients such as surfactants (Table 2).<sup>1</sup>

### 22.2.2 Inhalation exposure

Workers may be exposed by inhalation via particulates or when droplets and vapours escape containment. Inhalation hazards may result from aerosols, dust generated when crushing tablets, and cleaning up spills and bodily wastes.

It is argued but not proven that the normal preparation and administration practices used by healthcare workers for MABs do not result in the formation of aerosols that pose inhalation hazards.

The bioavailability of high molecular weight substances (> 100 kDa) has been estimated at a maximum of 5% by inhalation.<sup>30,31</sup> Given the high molecular weight of MABs, the absorption rate may be quite low.

Despite a probable low absorption rate, researchers are exploring methods to deliver MABs directly into the lungs for the treatment of cancer.<sup>32-35</sup> If MABs are to be administered to patients by aerosolisation, this could increase the potential for occupational exposure by inhalation and nasal mucosa absorption and possibly lead to respiratory sensitisation.<sup>36</sup> Special precautions are usually taken for drugs, such as ribavirin, that are administered by inhalation.<sup>37</sup> Inhalation is a possible but unlikely route of occupational exposure to aerosolised liquids or powders during preparation of MABs (Table 2).<sup>1</sup>

### 22.2.3 Other forms of exposure

Oral or mucosal exposure from hand-to-mouth or hand-to-nose contact and accidental injection with an antineoplastic drug are reported rarely.<sup>3,22</sup>

Exposure to MABs by the oral route would result in denaturation and digestion in the gastrointestinal tract,<sup>28</sup> severely limiting exposure by this route. However, animal studies suggest mucosal absorption may be a viable route of exposure.<sup>2</sup> Although the study authors considered oral ingestion a possible route of exposure, they felt that occupational exposure by this route was highly unlikely (Table 2).

## 22.3 Risk of handling MABs

Four approaches have been published for characterising the occupational risk of handling MABs.

Langford et al.<sup>38</sup> developed a risk assessment tool based on the antigenic properties and toxic potential of MABs. These authors recommended that most MABs available in the United Kingdom at that time should be considered high to moderate risk and should only be prepared in the pharmacy. A smaller group of MABs was considered low to moderate risk and could be prepared in the clinic if need be. However, many new MABs have been approved after this review was published and were not included in this assessment. Because of the complex nature of preparation for some MABs and the need for aseptic preparation

**Table 1.** FDA approved monoclonals (as of March 12, 2018).

Generic name	Brand name	Year approved	Administration	Activity	Antibody against
Abciximab	Reopro	1993	IV	Anticoagulant	Platelet GP2b/3a
Adalimumab	Humira	2002	SQ	Immunosuppressant	TNF
Adalimumab-atto	Amjevita	2016	SQ	Immunosuppressant	TNF
Adalimumab-adbm	Cyltezo	2017	SQ	Immunosuppressant	TNF
Ado-trastuzumab emtansine/ trastuzumab Amtanise	Kadcyla	2013	IV	Intineoplastic	HER2
Alemtuzumab	Campath	2001	IV	Immunosuppressant	CD-52
Alemtuzumab	Lemtrada	2014	IV	Immunosuppressant	CD-52
Alirocumab	Praluent	2015	SQ	Lipid regulator	PCSK9
Arcitumomab (discontinued)	CEA-Scan	1996	IV	Imaging (radio-Tc 99m)	Carcinoembryonic antigen
Atezolizumab	Tecentriq	2016	IV	Antineoplastic	PD-L1
Avelumab	Bavencio	2017	IV	Antineoplastic	PD-L1
Basiliximab	Simulect	1998	IV	Immunosuppressant	IL-2R-alpha
Belimumab	Benlysta	2011	IV	Immunosuppressant	B-cell stimulation
Benralizumab	Fasenra	2017	SQ	Antiasthma	CD-125
Bevacizumab	Avastin	2004	IV	Antineoplastic	VEGF
Bevacizumab-awwb	Mvasi	2017	IV	Antineoplastic	VEGF
Bezlotoxumab	Zinplava	2016	IV	Antibiotic	C. diff toxin B
Blinatumomab	Blinicyto	2014	IV	Antineoplastic	CD-19, CD-3
Brentuximab vedotin	Adcetris	2011	IV	Antineoplastic	CD-30
Brodalumab	Siliq	2017	SQ	Immunosuppressant	IL-17
Canakinumab	Ilaris	2009	SQ	Immunosuppressant	IL-1-beta
Capromab penetide	Prostascint	1996	IV	Imaging (radio-Indium 111)	PSMA
Catumaxomab (clinical trials?)	Removab (Proximium)	2005	Intraperitoneal	Antineoplastic	EpCAM
Certolizumab	Cimzia	2008	SQ	Immunosuppressant	TNF
Cetuximab	Erbix	2004	IV	Antineoplastic	EGFR
Daclizumab (discontinued)	Zenapax	1997	IV	Immunosuppressant	CD-25 (IL-2)
Daclizumab	Zinbryta	2016	SQ	Immunosuppressant	IL-2
Daratumumab	Darzalex	2015	IV	Antineoplastic	CD-38
Denosumab	Prolia, Xgeva	2010	SQ	Osteoporosis, Antineoplastic	RANKL
Dinutuximab	Unituxin	2015	IV	Antineoplastic	GD-2
Dupilumab	Dupixent	2017	SQ	Immunosuppressant	IL-4-alpha
Durvalumab	Imfinzi	2017	IV	Antineoplastic	PD-L1
Eculizumab	Soliris	2007	IV	Antianemia	Complement (C5)
Efalizumab (discontinued)	Raptiva	2003	SQ	Immunosuppressant	CD-11a
Elotuzumab	Empliciti	2015	IV	Antineoplastic	SLAMF7
Emicizumab-kxwh	Hemlibra	2017	SQ	Antihemophilia A	Activated coag Factor IX and Factor X
Evolocumab	Repatha	2015	SQ	Lipid regulator	PCSK9
Gemtuzumab ozogamicin	Mylotarg	2000 (discontinued) 2017 (re-approved)	IV	Antineoplastic	CD-33
Golimumab	Simponi	2009	SQ	Immunosuppressant	TNF
Guselkumab	Tremfya	2017	SQ	Immunosuppressant	IL-23
Ibalizumab-uiyk	Trogarzo	2018	IV	Antiviral	CD-4
Ibritumomab tiuxetan	Zevalin	2002	IV	Antineoplastic (radio-Y 90)	CD-20

(continued)



Table 1. Continued.

Generic name	Brand name	Year approved	Administration	Activity	Antibody against
Idarucizumab	Praxbind	2015	IV	Antidote	Dabigatran (anticoagulant)
Imciromab pentetate (discontinued)	Myoscint	1996	IV	Imaging (radio-indium 111)	Myosin
Infliximab	Remicade	1998	IV	Immunosuppressant	TNF
Infliximab-abda	Renflexis	2017	IV	Immunosuppressant	TNF
Infliximab-dyyb	Inflectra	2016	IV	Immunosuppressant	TNF
Infliximab-qbtx	Ixifi	2017	IV	Immunosuppressant	TNF
Inotuzumab ozogamicin	Besponsa	2017	IV	Antineoplastic	CD-22
Ipilimumab	Yervoy	2011	IV	Antineoplastic	CTLA-4
Ixekizumab	Taltz	2016	SQ	Immunosuppressant	IL-17a
Mepolizumab	Nucala	2015	SQ	Antiasthma	IL-5
Natalizumab	Tysabri	2004	IV	Immunosuppressant	Integrin receptor
Necitumumab	Portrazza	2015	IV	Antineoplastic	EGFR
Nivolumab	Opdivo	2015	IV	Antineoplastic	PD-1
Nofetumomab (discontinued)	Verluma	1996	IV	Imaging (radio-Tc 99)	NR-LU-10
Obiltoxaximab	Anthim	2016	IV	Antianthrax	Anthrax PA
Obinituzumab	Gazyva	2013	IV	Antineoplastic	CD-20
Ocrelizumab	Ocrevus	2017	IV	Immunosuppressant	CD-20
Ofatumumab	Arzerra	2009	IV	Antineoplastic	CD-20
Olaratumab	Lartruvo	2016	IV	Antineoplastic	PDGFR-alpha
Omalizumab	Xolair	2003	SQ	Antiasthma	IgE
Palivizumab	Synagis	1998	IM	Antiviral	RSV-F
Panitumumab	Vectibix	2006	IV	Antineoplastic	EGFR
Pembrolizumab	Keytruda	2014	IV	Antineoplastic	PD-1
Pertuzumab	Perjeta	2012	IV	Antineoplastic	HER2
Ramucirumab	Cyramza	2014	IV	Antineoplastic	VEGF
Ranibizumab	Lucentis	2006	Intravitreal	Macular degeneration	VEGF
Raxibacumab	ABThrax	2012	IV	Antianthrax	Anthrax PA
Reslizumab	Cinqair	2016	IV	Antiasthma	IL-5
Rituximab	Rituxan	1997	IV	Antineoplastic	CD-20
Rituximab/ hyaluronidase	Rituxan Hycela	2017	SQ	Antineoplastic	CD-20
Sarilumab	Kevzara	2017	SQ	Immunosuppressant	IL-6
Secukinumab	Cosentyx	2015	SQ	Immunosuppressant	IL-17a
Siltuximab	Sylvant	2014	IV	Antineoplastic	IL-6
Tocilizumab	Actemra	2010	IV, SQ	Immunosuppressant	IL-6
Tositumomab (discontinued)	Bexxar	2003	IV	Antineoplastic (radio- I 131)	CD-20
Trastuzumab	Herceptin	1998	IV	Antineoplastic	HER2
Trastuzumab-awwb	Ogivri	2017	IV	Antineoplastic	HER2
Ustekinumab	Stelara	2009	SQ	Immunosuppressant	IL-12, IL-23
Vedolizumab	Entyvio	2014	IV	Immunosuppressant	Integrin receptor

conditions, preparation outside the pharmacy was not recommended.

Another approach by Halsen and Krämer<sup>28</sup> evaluated MABs based on reproductive and developmental toxicity and fertility effects. For most MABs, these authors reported that significant data were lacking for these endpoints. However, they concluded that all the MABs they evaluated had the potential for some level of reproductive toxicity in patients and potentially in workers exposed to them. They also concluded that possible oral and dermal exposure to

these agents could be high due to the amount used, but worker exposure may be minimal. They speculated that exposure by inhalation of aerosols would also result in minimal exposure.

In 2014, Australian consensus guidelines were published for the safe handling of MABs for cancer treatment by healthcare personnel.<sup>1</sup> These guidelines were informed by a survey of current practice and synthesis of evidence cited previously in these standards. Recommendations were assigned appropriate levels and grades, and guidelines

**Table 2.** Australian Consensus Guidelines for handling monoclonal antibodies (Alexander et al., 2014).

Route of exposure	Recommendation
Dermal	Based on physiochemical (molecular size) and pharmacokinetic (permeability profile) properties, dermal absorption of MAB was not considered to be a viable mechanism of internalisation.
Inhalation	Based on demonstrated internalisation in therapeutic animal models, inhalation was considered to be a viable route of internalisation with unquantified and indeterminate effects at long-term low-dose exposure levels. Exposure risk was considered to be the greatest during the preparation of doses for administration where staff may be exposed to powdered or aerosolised liquid particles.
Oral	Based on demonstrated stability in preclinical studies and internalisation in therapeutic animal and human models, oral ingestion was considered a viable route of internalisation with unquantified and indeterminate effects at long-term low-dose exposure levels. Although viable, internalisation required idealistic conditions and occupational exposure at levels required for systemic bioavailability was considered to be highly unlikely.

endorsed by major Australian pharmacy, nursing, medical, and, oncology societies. Definitive recommendations were given for the minimum safe handling requirements to protect healthcare personnel. The seven recommendations covered the following:

- (a) Appropriate determinants for evaluating occupational exposure risk.
- (b) Occupational risk level compared to other hazardous and non-hazardous drugs.
- (c) Stratification of risk based on healthcare personnel factors.
- (d) Waste products.
- (e) Interventions and safeguards.
- (f) Operational and clinical factors.
- (g) Handling recommendations.

The seventh recommendation included a risk assessment model and flowchart for institutions to consider and evaluate clinical and operational factors unique to their own healthcare service.

Most recently, Bauters and Vandenbroucke<sup>39</sup> developed a flowchart for risk assessment and allocation of preparation of MABs. It provides recommendations for the

classification of MABs according to their toxicity profile and takes practical and financial issues into account. It allows oncology pharmacists to define which MABs may or must be prepared in pharmacy aseptic facilities and which MABs can be prepared on the ward.

Many non-conjugated MABs do not meet the current criteria for hazardous drugs or have insufficient information to evaluate as a hazardous drug. As new post-marketing information becomes available, their hazard potential should be re-evaluated. Many MABs are under development or are being approved, requiring the continual evaluation of MABs as potentially hazardous to healthcare workers. At present, testing MABs for carcinogenicity or genotoxicity is not required by regulatory agencies.

## 22.4 Recommendations for handling MABs

Given the uncertainties surrounding the safe handling of most MABs, the following recommendations should be followed:

- (a) A MAB that contains a radioactive component should be handled and disposed of according to the local regulations for radioactive substances where it is being used.
- (b) A MAB that has recommendations from the manufacturer to handle it like other antineoplastic drugs should be handled accordingly during preparation, administration, and disposal.
- (c) A MAB that requires multiple steps or other complex procedures for its preparation should be handled to ensure a sterile product (unrelated to occupational exposure risks).
- (d) When required, preparation should be done aseptically using proper procedures and personal protective equipment (unrelated to occupational exposure risks).
- (e) If a MAB is administered by aerosolisation, precautions like those used for other inhaled drugs need to be in place to protect both the work environment and healthcare workers.

For non-conjugated MABs and those not considered hazardous, no additional precautions are required. Workers can follow standard operating procedures for administration.

Following these procedures will protect both the integrity of the MAB and the health of the worker.<sup>3,22,40</sup>

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## Section 23 – Automation

### 23.1 Background

In oncology pharmacy, each admixture has traditionally been tailor-made for the individual patient based on the physician's orders, real-time lab results, and medication availability. In many facilities, just-in-time production is used for expensive and short-expiration items. Sterile, accurate chemotherapy doses must be prepared while the patient is waiting.

The pressures of modern healthcare create strain on pharmacies to deliver efficient service and maximise capacity. Pressures include rapid turnover of patients, high cost of medications, the need for timely and accurate information, and the hazardous nature of antineoplastic drugs. These pressures make it difficult to consistently maintain high quality in manual preparations. Efficiency, accuracy, and safety need to improve constantly.

Manual preparation of both parenteral and oral antineoplastic drugs has always been considered a high-risk activity for personnel compounding these drugs due to prolonged exposure to carcinogens. The personalisation and complexity of therapies also increases the chances of error.

The type of production influences the pass-through time of a preparation and the quality assurance activities that can be performed. In hospital pharmacies, three different types of production can be used.

1. Tailor-made or individualised production creates a different preparation for each combination of drug, diluent, final concentration, and container. One batch corresponds to one preparation.
2. Series production is the repeated preparation of the same drug at the same final concentration and same final volume. One batch corresponds to one preparation.
3. Batch production is the production of a bulk solution in a "big bag" for transfer to small-volume containers ready to administer. The composition of the final product is the same as that of the bulk solution. Each batch corresponds to several identical preparations. This method is used in pharmaceutical production.

Automation can improve the quality and efficiency of all these production methods.

### 23.2 Definitions

#### 23.2.1 Identification systems

An identification system uses bar codes, data matrices, radio-frequency identification (RFID), or picture recognition to identify drugs, infusions, and devices.

A bar code is an optical, machine-readable representation of data. The data usually describes the drug that carries the barcode.

RFID identifies drugs using electromagnetic or electrostatic coupling in the radio-frequency portion of the electromagnetic spectrum.

Picture recognition identifies drugs by their physical features, such as colour or shape.

#### 23.2.2 Automation

Automation performs a process or procedure with little or no human intervention. Automation applied to the production of chemotherapy products reduces errors and risk of exposure of personnel to carcinogenic substances while ensuring accurate dosage and sterility of the drugs.

#### 23.2.3 Semi-automated compounding devices

Semi-automated compounding devices are peristaltic or volumetric pumps used for the preparation of sterile solutions. They can accurately transfer a volume of drug or diluent from a vial or bag to final containers. These include mini-bags, syringes, and portable elastomeric pumps.

Semi-automated compounding devices function without continuous input from an operator. This often reduces labour requirements.

To comply with regulations (Good Manufacturing Practices, PICs guidelines, USP 800), these devices must be run in ISO 5 controlled areas.

#### 23.2.4 Robots for sterile drug compounding

Robots minimise human interactions with a process. Robots are always operated within an ISO 5 controlled area with total air exchanges. These may be biosafety cabinets (BSCs) or isolators, in accordance with ISO 14644.



The use of robots is growing to allow hospital pharmacies to increase workload with minimal increases in human resources. Robots can do the following:

- (a) automatically identify products;
- (b) weigh active ingredients and solutions;
- (c) reconstitute powdered drugs;
- (d) prepare syringes, bags, and other final containers;
- (e) label the prepared product;
- (f) safely load and unload materials and preparations.

Robots have been designed to produce syringes, IV bags, or both. Not all robots have designs capable of dissolution of powder forms of drugs. Some are designed for repeated preparation of standard preparations in syringes or bags. Others can produce both patient-specific and standard doses.

In-process controls improve process safety and guarantee the quality of the preparation. In-process controls include bar coding, data matrix and picture identification of drug vials and diluent bags, and weight checks during liquid transfers.

Robots can be used for hazardous drug compounding. However, the risk of contamination in the workplace must be assessed before putting such an operation in place.

### 23.3 Evaluation of automation

Automation and measurement are valuable tools for increasing efficiency and safety. The introduction of automation will alter workflow. To make the best use of automation, the entire production system should be analysed and adjusted after implementation. This requires assessments of the following:

- (a) workflow impact;
- (b) financial impact;
- (c) project management requirements;
- (d) vendor assessment and service level agreements;
- (e) requirements for new quality control measures;
- (f) integration and interoperability with existing information systems and technology.

Careful evaluation and planning are required to ensure the safety of operators and the reconstituted drugs.

### 23.4 Validation of automation

Validation of semi-automated systems and robots is achieved through monitoring or measuring the following:

- (a) correct identification of drugs;
- (b) dosing precision;
- (c) identification of intermediate and final products;
- (d) product exposure to operator and environment;
- (e) execution times and productivity;

- (f) validation of performance and reliability of technical devices and computer systems;
- (g) integrity of HEPA filtration and sterility;
- (h) contamination of the preparation area, materials used, and final preparations;
- (i) ease of cleaning;
- (j) waste management.

Rigorous validation is a delicate and time-consuming effort necessary before starting live production.

#### 23.4.1 Interfacing automation to the electronic order system

The communication and automated translation of the preparation order from the electronic chemotherapy order system to a preparation protocol for the automated device must be checked and validated. Without proper communication and transmission, orders to be executed by the automated device may need to be introduced manually. This can lead to errors of transcription and calculation.

#### 23.4.2 Physical testing

Physical testing assesses contamination risk, versatility, chemical combination, accuracy, calibration, leakage, and smoke.

The ability of the robot system to prevent chemical contamination of surfaces inside and surrounding the robot and surfaces of the end products should be assessed at the qualification step. All steps of the process should be simulated using a tracer that can be quantified by analytical control or semi-quantified by fluorescence or UV detection.

Versatility should also be assessed at the qualification step. The versatility assessment will identify the brands of devices, vials, syringes, bags, and needles that can be used by the robot.

The capacity of the identification system to properly identify all drugs and diluents should be checked.

Accuracy must be checked for all ranges of volumes to be withdrawn and transferred. Assessment should use standard aqueous solutions and worst-case solutions. These are solutions able to physically modify the quality (alcoholic, foamy, viscous) of the withdrawal and transfers. The worst-case assessment should yield a blacklist of drugs that should not be used by the robot.

Periodic calibration and certification of the robot should be performed. For robots claiming containment enclosure, a leak or smoke test should be performed where relevant.

#### 23.4.3 Microbiological testing

Microbiological validation of the process is conducted using a media fill test. All processes to be implemented in the robot are performed using culture media. The

maximum workload per cycle should be repeated on at least three consecutive cycles on 3 consecutive days. The desired outcome is no microbial growth of the media fill preparations.

Surfaces and air should be sampled to determine the steps of the process vulnerable to microbiological contamination. Pre- and post-processing steps run manually by an operator should be included and glove prints performed.

For self-cleaning robots, the efficacy of the cleaning process on microbial contamination should be assessed. The surface sampling should include contact plates and swabs to assess contamination of areas of difficult access and frail areas (such as a robot's arm). Active air sampling should be used for the qualification step. Passive air sampling with contact plates can be used alternatively with active air sampling during routine processing. The results should conform to accepted limits for a grade A ISO 5 environment according to international regulations (CGMPs, USP800, PICs) and should be set at < 1 colony-forming unit (CFU).

Parts of the procedure that need to be done by an operator, such as loading and unloading the robot, should be validated using media fill tests for each operator.

Sterility testing on the final products will depend on the process (batch production, series, or individualised preparation) and should be performed during the qualification step.

#### 23.4.4 Cleaning and disinfection validation

This validation assesses the efficacy of cleaning and disinfection in minimising cross-contamination and microbial and chemical contamination on surfaces. The compatibility of the cleaning and disinfection products used must be provided by the robot's manufacturer.

In areas where multiple drugs may be handled simultaneously, cross contamination should be assessed by simulation using tracers or placebos.

The microbial contamination validation counts challenge or other microorganisms before and after each cleaning and disinfection process.

The chemical contamination validation should at a minimum visually assess cleaning agent residue after each cleaning process. UV lamps and fluorescent tracers may improve sensitivity.

### 23.5 Automation versus manual preparation

#### *Pros of manual preparation*

- (a) No expensive investment and maintenance cost.
- (b) Easy planning.
- (c) Flexibility in preparation format and final container.

#### *Cons of manual preparation*

- (a) Patient-specific dosing and variability increases the possibility of error.
- (b) Risk of wrong patient label placed on the final container.
- (c) Risk of data omissions and transcription errors.
- (d) Variation in preparation technique among operators.
- (e) Manual tasks can lead to repetitive stress and workplace injuries.

#### *Pros of automation*

- (a) Limits direct human exposure to cytotoxic drugs during compounding process.
- (b) In-process controls are always in place.
- (c) Lower risk of errors.
- (d) Improved dosage accuracy.
- (e) Assurance of the sterility of the finished product.
- (f) Electronic audit trail.
- (g) All drugs, supplies and fluids are identified ensuring that the correct drug has been loaded.
- (h) Waste disposal performed without human intervention.

#### *Cons of automation*

- (a) Costly initial investment.
- (b) Longer preparation times.
- (c) Continuous preventive maintenance, remote assistance, and on-site intervention required.
- (d) Long-term benefits and risks not fully defined.
- (e) Drugs for which specific gravity is not available cannot be reconstituted.
- (f) Specific brands of supplies may be required.
- (g) Higher costs of ventilated non-coring needles for the preparation of compounds.
- (h) Limitations in preparation of odd-shaped vials and ampoules.

One study found that the average time spent per preparation was 14.2% higher with automated versus manual preparation. However, this increase may reflect numerous quality checks that are not carried out during the manual process.

Another study comparing the effects of manual antineoplastic and adjuvant drug preparation with automated preparation on staff safety events, medication accuracy, drug preparation time, cost of materials, and personnel time. The study focused on accuracy during drug preparation, working conditions, and costs. Automation delivered measurable and meaningful value across many dimensions. These included patient and operator safety, pharmacist

efficiency, peace of mind, physician satisfaction, nursing confidence, inventory management, cost reduction, automated record-keeping, and risk management.

Future studies are needed to investigate the overall effectiveness and efficiencies of robotic implementations compared with traditional manual preparation.

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## Section 24 – Oral anticancer therapies

### 24.1 Introduction

This policy pertains to cytotoxic and non-cytotoxic oral anticancer therapies, including targeted therapies, endocrine therapies, and immunotherapy.

Processes for ensuring the safety of the ordering and supply of oral anticancer therapies should mirror those for parenteral therapy. However, oral anticancer therapies offer special challenges.

- (a) Accidental exposure to oral anticancer therapies may occur during transport, unpacking, storage, handling, administration, and disposal.
- (b) Contrasted with parenteral chemotherapy, oral anticancer therapies carry a risk of non-adherence, since patients may misinterpret directions or doses or may decide not to follow prescribed instructions.
- (c) Because oral anticancer therapies are usually taken in an outpatient setting, monitoring for toxicity and patient compliance is challenging.

### 24.2 Prescribing guidelines

Oral anticancer therapies are prescribed by physicians in many specialties. Most have had extensive specialty training and credentialing in cancer diagnosis and treatment. Restricting oral anticancer therapy prescription to a selected group of credentialed healthcare professionals could limit access to treatment unintentionally or inappropriately. However, it is reasonable to require that prescribers have formal training in oncology and experience in treating the condition for which oral anticancer therapy is prescribed.

Compliance with best practices is required when patients have difficulty swallowing or require administration via feeding tube. This applies both to delivery of appropriate dosage and ensuring minimal environmental contamination. Pharmacists are best placed to offer this advice.

Doses and schedules of oral anticancer therapies should be adjusted, with the least rounding possible, to match the commercially available strengths with the most appropriate patient outcomes.

For intermittent or cyclical therapy, the quantity of tablets or capsules prescribed and dispensed for ambulatory patients must be the exact quantity required for a specified timeframe, determined by cycle length and next review. For

example, capecitabine is available as 500 and 150 mg tablets. One cycle of treatment is ordered for capecitabine 1250 mg/m<sup>2</sup> (BSA = 1.6 m<sup>2</sup>) twice a day for 2 weeks; that is, 2000 mg twice a day for 2 weeks or 112 tablets in 500 mg strength. For continuous therapy, the quantity supplied must not exceed that required until the next review.

Computerised Prescriber Order Entry (CPOE) systems reduce prescribing errors, thereby also reducing patient harm. They are considered the gold standard in safe prescribing. Where CPOE is not available, the minimum prescribing standard for oral anticancer therapies requires pre-printed orders (PPOs). Jurisdictions should discontinue the use of hand-written orders.

Verbal or telephone orders for oral anticancer therapies are not permitted, apart from instructions to hold or cancel a prescription.

The order set must include dosing information (mg/kg or mg/m<sup>2</sup> or concentration, if appropriate) to facilitate dose verification by the pharmacist. Additional information may include requirements for laboratory values, supportive care, dose reductions, or dose-limiting parameters. Warning messages to prevent route and frequency of administration and other errors may also be included.

The prescriber should determine whether the patient is taking any other prescribed, complementary, or over-the-counter medications that may interact with the oral anticancer therapy.

Patients' medical records should be organised and made readily accessible to all providers who prescribe, dispense, and administer oral anticancer therapies to enable independent confirmation that all prerequisites have been met before starting treatment.

### 24.3 Content of the oral anticancer therapy prescription

The following information should be included on every oral anticancer therapy prescription. If comprehensive electronic health records are readily available, data may not need to be transcribed into the prescription.

- (a) Name of prescriber, registration and prescribing number, and contact information.

- (b) Date of prescription, treatment start and stop dates, duration of therapy, and any rest period.
- (c) Three patient identifiers (such as name, address, date of birth).
- (d) Full generic name of prescribed drug, which may be written with tall-man lettering but without abbreviations.
- (e) Drug doses, route and frequency of administration, quantity, and any specific administration instructions, including effect of food on absorption (such as “Drug A for 21 days followed by a 7-day break with no tablets. Do not restart until advised by doctor”).
- (f) Patient’s drug allergies.
- (g) Drug regimen or protocol being followed, including drug dosages and how they are to be calculated (for example, by patient height and weight, or renal and hepatic function).
- (h) Reason for and percentage of any dose reduction or deviation from a standard protocol, with supporting data.

The following information should be included for the benefit of the dispensing pharmacist if it is not otherwise available.

- (a) Diagnosis or disease-specific indications for treatment (such as diagnosis = breast cancer, disease specific indication = HER2+).
- (b) Cycle number, including total number of cycles.
- (c) Lab data required to calculate dose, confirm drug eligibility, or determine appropriateness of the prescribed regimen (such as BRAF 600 mutation status prior to dispensing vemurafenib).
- (d) Constraints on maximum dosages and administration routes and schedules.

It is highly desirable that “no refills” or “no repeats” be the default standard. If the intention is to allow for refills to accommodate limited access to a pharmacy, financial limitations, or travel plans, the prescriber should write the total quantity and specify the amount to be dispensed and any parameters that should be monitored.

In providing clear dosing instructions, phrases such as “use as directed” should be avoided. In consultation with the patient, the prescriber should choose a specific day of the week when the medication is to be taken and include it in the prescription. Monday should not be chosen, as this word has been misread as “morning.”

## 24.4 Dispensing guidelines

Only suitably trained and experienced pharmacy staff should be involved in the supply of oral anticancer therapies. This includes taking a medication history on receipt of

the prescription, verifying the prescription, dispensing, and patient counselling.

### 24.4.1 Prescription verification

A pharmacist, preferably one with formal training in oncology, should verify the clinical appropriateness of the prescription. This will require a review of the protocol or regimen name (including cycle number), drug names, drug dosage and dosage modifications, administration instructions, start date, duration of treatment, laboratory data, body surface area calculation, and other data.

A minimum of two licensed health professionals should verify that the prescription includes three patient identifiers, drug names, drug dose, quantity to be dispensed, route and frequency of administration, and dose calculation.

The pharmacist should consult with the treating medical oncologist to clarify unclear or confusing instructions regarding the dosage, regimen, or monitoring requirements.

The pharmacist should ascertain whether an oral anticancer therapy regimen or dosage should be altered in the case of significant changes in patient parameters, such as weight, blood tests, or side effects.

### 24.4.2 Dispensing

All dispensing of oral anticancer therapies should be checked by another pharmacist or designated technician.

The quantity to be dispensed should be for one cycle of treatment only, or for the amount required until the next clinic visit. Drug packaging and government-reimbursed quantities should not be factors in dispensing. Multiple cycles may only be supplied in extenuating circumstances.

The indication for all supportive care medications, such as antiemetics and antiepileptics, should be on the label of the dispensed medication. The pharmacist is responsible for ensuring that all supportive care medications are provided.

The pharmacist who counsels the patient should verify and document the patient’s comprehension of treatment and safe drug handling. Each patient must receive both verbal and written information. Information leaflets must be reviewed to ensure that content is accurate, appropriate, and up-to-date.

In some community and hospital pharmacies, only one pharmacist may be available to manage all pharmacy-related activity. Pharmacists who work in community pharmacies typically dispense very few oral anticancer therapies, so their knowledge and comfort with dispensing them may be limited. It may be difficult for these pharmacists to verify all components of the prescription. It may also be difficult to ensure that independent checks are conducted. Bar coding technology may enable automated independent double checking. Audiovisual computer equipment



may enable remote access to a healthcare professional with formal training or experience in oncology.

### 24.4.3 Fill policy

Given the limited interaction between providers and patients during treatment with oral anticancer therapy, policies, and approaches that limit the quantity of medication dispensed initially and in all subsequent refills should be considered. When limited quantities have been established, these should be documented on the PPO and embedded within the CPOE system. There needs to be institutional agreement about the quantities that will be supplied by the pharmacy.

Exceptions to a limited fill policy should be explicitly described in an institution-wide policy and considered on an individual basis. Larger initial fill quantities may be appropriate for those who live in remote communities if alternative arrangements can be made for monitoring adherence, lab work, toxicities, and side effects. Patient immobility, inclement weather, and other obstacles to picking up medications might also need to be considered. When an exception to the limited initial and subsequent fill approach is warranted, a risk assessment must be performed by a member of the patient's care delivery team to address any patient safety risks.

Institutions may wish to take into account the individual safety profiles of each oral anticancer drug and develop policies specific to the anticipated appearance of side effects or toxicity. A drug-by-drug approach may help to reduce the likelihood that increasing the frequency of dispensing will affect pharmacy workload and wait times while improving patient safety.

### 24.4.4 Use of personal protective equipment

Pharmacy staff who dispense oral anticancer therapies must follow all appropriate PPE recommendations for each step of the medication circuit. Healthcare providers should be trained and follow all applicable handling guidelines.

### 24.4.5 Labeling, packaging, storage, and disposal

Oral anticancer therapies should be dispensed with auxiliary labels (such as "Chemotherapy" or "Cytotoxic – Handle with Care") on the primary container and the transport container so that drugs are easily identified and understood as being cytotoxic.

For oral anticancer therapies intended to be taken weekly, such as methotrexate, the label must specify this as well as the day the dose is due.

All medication labels must specify temperature requirements for storage.

Cancer patients must often travel long distances to receive care, so guidance and support, such as coolers and

ice packets for refrigerated medications, must be provided to properly store medications when in transit.

Containers for oral anticancer therapies should have child-proof caps.

Appropriate packaging by manufacturers can reduce the need for repackaging at the healthcare site and reduce the need for healthcare providers and patients to handle chemotherapy drugs. A label should be placed on the outside of the package indicating that the agent is cytotoxic. Manufacturers should package only the number of tablets or capsules needed for one cycle of therapy or use unit-of-use packaging.

Oral anticancer therapies should be safely stored in a separate designated area of the pharmacy with appropriate signage to warn of hazards.

An oral anticancer therapy that needs to be manipulated from its original form (crushed, split, opened, or dissolved) should first be checked against a published reference, such as a Do Not Crush list. Many oncology patients have difficulty swallowing and cannot take solid dosage forms. A liquid formulation, or information on how to compound a liquid formulation, should be provided by the manufacturer. For best practices, compounding should be performed inside a hood.

Any unused medication should be returned to the pharmacy for appropriate disposal.

### 24.4.6 Patient counseling

Patients should be encouraged to become active participants in their own care. During counseling sessions, it is important to ensure that patients understand the information provided by asking them to describe their understanding of that information.

## 24.5 Monitoring

A high degree of adherence to prescribed cancer treatment is essential for optimal outcomes. For intravenous treatment, lack of adherence is obvious and there are opportunities to intervene quickly if toxicity or side effects appear. In contrast, oral anticancer therapy is self-administered at home, making it harder for providers to assess adherence or gauge the patient's tolerance of the therapy.

As part of a comprehensive approach to monitoring adherence and establishing opportunities for routine assessment, individualised, proactive monitoring plans must be established before each new oral anticancer therapy begins. These should be reviewed with each dose modification, or as otherwise needed. Pharmacists should check compliance on each dispensing. This is easily achievable when only one cycle of therapy is dispensed at a time.

When necessary, new tools and mechanisms should be developed to ensure appropriate patient assessments, the accurate relay of information from providers to prescribers,

and the coordination of a patient's needs with healthcare providers' schedules.

In some circumstances, constraints on traditional drug distribution system are appropriate. A primary safety concern is that restricted distribution may adversely affect continuity of care. Delays in therapy could result when patients must wait for medications to be shipped to their homes from a specialty pharmacy. In addition, receiving prescriptions by mail does not allow for face-to-face interaction between the patient and pharmacist during which patient concerns and educational deficits may be identified.

## 24.6 Training and education

Patients, caregivers, and specialty and community healthcare professionals have distinct training and education needs. Patients and their caregivers should be offered culturally sensitive information about the oral anticancer therapy they have been prescribed before the medication is initially dispensed. This should be reviewed by the dispensing pharmacist.

Verbal instructions should be supplemented with written take-home instructions. Topics should include safe handling, storage, administration, monitoring and adherence, disposal, the effect of food on absorption, the potential on drug–drug interactions, and expected side effects their and management. Information about safe handling of oral anticancer therapy by pregnant and breastfeeding mothers should also be included. Specialty and community healthcare professionals should be aware of, and apply, the current best practices related to safe handling of oral anticancer therapies in their work settings. They should also be encouraged to participate in education programs that will allow them to learn about newly-approved oral anticancer therapies.

A process should be in place to specify who provides what information and how patient comprehension will be evaluated. The teach-back method is the preferred approach, but given the time and training required this may only be an appropriate expectation of specialised oncology healthcare providers. Consumer information or locally developed information should be provided to supplement verbal instructions. Information should be presented in the primary language of the patient.

Patients on oral anticancer therapy receive care in a variety of practice settings, including ambulatory clinics, hospitals, long-term care facilities, and the home. Members of the healthcare team involved in prescribing, handling, dispensing, administering, and monitoring oral anticancer therapies, regardless of setting, must undergo periodic standardised competency evaluations of knowledge and skills related to safe practices.

This may be particularly important and relevant for healthcare professionals in non-oncology settings where formal training may be more limited. In these situations,

where the opportunity to dispense oral anticancer therapies is relatively low, the value of in-depth education about oncology may have little lasting impact. Access to drug-specific information about indication, dosing, and safety precautions should be available as close to the point of dispensing as possible.

Oral anticancer therapies normally should not be filled in a dose-administration container (such as a Dosette-Webster pack) with other medications. If a dose-administration container is necessary, the cytotoxic medication must be filled in a separate container and clearly labeled “cytotoxic.” The container must be well-sealed to avoid accidental opening.

If oral anticancer therapies are to be administered by caregivers or staff, instructions must be supplied to use protective gloves (powder-free nitrile or latex gloves) when handling them to avoid occupational exposure.

Caregivers and staff should also be instructed that cytotoxic exposure can occur through exposure to body fluids and waste. Appropriate instructions must be available for handling bodily fluids (vomit, blood, and excreta), linens, diapers, and clothing. Precautions should continue for up to 7 days after the completion of a treatment cycle.

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## Section 25 – Investigational drugs

### 25.1 Background

An investigational drug (ID), or investigational medicinal product (IMP), is a chemical or biological substance that has been tested in the laboratory and approved in the country or region for use in clinical trials or studies.

Pharmacists and pharmacy personnel play an important role in ID clinical trials and research studies across the life cycle of a protocol. Pharmacist contribution to quality assurance in clinical trials with a focus on ID therapy management is crucial. The Institute for Safe Medication Practices (ISMP) has reported errors in pharmacy manuals, often not reviewed by the trial's scientific review committee (SRC). As a drug advances through phases of a clinical trial, protocol updates are frequently needed. ISMP found many were disorganised or unavailable. ISMP also observed that there is limited regulation and standardisation of ID nomenclature, labeling, and packaging. These are of lower priority for many sponsoring companies.

In the oncology setting, investigational agents involve high-risk and hazardous drugs with complex protocols and trial designs. Therefore, consideration for additional safe practices in drug use processes is required. An interdisciplinary team should implement a plan to address all the ID drug use processes involved.

All safeguards and quality controls applied to the anti-neoplastic medication use process in place in an institution should be applied to the ID use process. Examples include information systems, computerised physician order entry (CPOE), barcoding, and smart pumps.

Clinical oncology and haematology expertise is often needed when evaluating investigational or research protocols or drug process risks involved with antineoplastic agents, such as blinding and investigational drugs commercially available in cooperative groups.

The pharmacist's role in investigational drugs or protocols includes clinical, logistic, operational, and investigational activities.

- (a) Clinical activities include reviewing and evaluating protocols, monitoring and assessing drug usage or areas of improvement (such as stability, compatibility,

and premedication), assessing drug use risks, and medication therapy consultation.

- (b) Logistic and operational activities include acquisition, shipment, storage, preparation, dispensing, pharmacy manufacturing, parenteral unit workload assessment, distribution, traceability, documentation, and disposal.
- (c) Investigational activities include clinical research and drug development.

This section focuses on oncology pharmacist roles and responsibilities. It is not intended to summarise clinical trials legislation, which will vary by country and jurisdiction. All laws that apply to practice in a specific jurisdiction take precedence over these standards.

### 25.2 Good clinical practice principles and requirements

An institutional review board (IRB), ethics review committee (ERC), or independent ethics committee (IEC) is a group formally designated to protect the rights, safety, and well-being of the people involved in a clinical trial. These groups review the clinical trial protocol (ethics of research and methods), the risks and benefits to study participants, and study materials, such as informed consent documents and investigator brochures. They ensure, both in advance and through periodic review, that the trial's risk/benefit ratio is favourable and seek to maximise the safety of participants. These groups have the authority to approve or disapprove research.

Pharmacist participation in investigational protocol review is usually regulated by legislation. Where this is not the case, a pharmacist should participate in the SRC/IRB/ERC whenever possible, including review of the informed consent document.

If the participating pharmacist is not the institution's oncology or haematology pharmacist, the latter should be consulted to assist in the prospective review and evaluation of the drug information section, medication use, and investigational protocol. The oncology pharmacist should also provide information about premedication and regimes available in the institution.

The institution should establish and regularly update policies and procedures to address the review, approval, supervision, and monitoring of ID protocols.

An investigational drug service (IDS) should be formed to perform the logistical tasks of ID procurement, manufacturing, and dispensing. A close collaboration is needed between the research pharmacy and the oncology or haematology pharmacy. All local legislation, regulatory requirements, and good manufacturing practices (GMP) should be followed in compounding and manufacture of preparations by the pharmacy.

Early phase, combined phase, and blinded trials add complexity and can require specialised procedures. Interactions between unblinded and blinded personnel should be minimised.

Policies should be in place to manage continuum of care of patients on investigational protocols. These are especially important for participants discharged for home therapy or admitted to a hospital or other care institution that is not participating in the trial.

## 25.3 Before the trial

### 25.3.1 Protocol evaluation

The clinical research pharmacist must participate in the sponsor's site initiation meeting and pharmacy training session. These meetings provide opportunities to discuss ID dispensing logistics and provide information needed by sponsors and the research or study team. This is especially important for research protocols from non-sponsored cooperative groups or institutional researchers.

The clinical research pharmacist provides a specialised perspective on review and evaluation and contributes expertise to the medication use section of the protocol. An accurate and complete drug information section is critical to ensure that investigational drugs are appropriately prescribed, prepared when required, dispensed, and administered.

During protocol review prior to approval, protocol feasibility, ID information and handling, and dosing strategy should be reviewed and evaluated.

#### Feasibility of the protocol

- (a) Institutional policies and procedures.
- (b) Impact on hospital and pharmacy workload and workflow.
- (c) Compounding and manufacturing requirements.
- (d) Implications for pharmacy formulary and pharmacotherapy guide.
- (e) Randomisation, blinding, and masking.

- (f) Kit/lot/bottle assignment method.
- (g) Compatibility with institution policy and information systems (dose banding, dose rounding, assisted tools).
- (h) Costs for the institution.
- (i) Medication error risk evaluation.

#### ID information and handling

- (a) Drug procurement
  1. Supplied by investigation sponsor or commercial sources?
  2. Drugs provided, including placebo by monitors and those used from hospital stocks, clearly indicated.
- (b) Pharmaceutical dosage forms (such as tablets, vials) and strengths.
- (c) Packaging and labeling.
  1. Request from the sponsor if not provided with the protocol.
  2. Contents of the label (name, identifier, appearance, strength, lot number).
- (d) Dose range and schedule.
- (e) Storage requirements.
- (f) Compounding/manufacturing instructions.
  1. Reconstitution, dilution.
  2. Blinding requirements.
  3. Hazardous classification.
- (g) Stability and compatibility issues
  1. Original package, reconstituted, diluted (vehicle, containers, and materials).
  2. Expiration date and time.
- (h) Dispensing and transportation requirements.
- (i) Route and administration instructions.
- (j) Administration recommendations (filters, infusion times, fasting conditions, tissue damage risk).
- (k) Special handling recommendations/requirements (spills, extravasations).
  1. Correct disposal methods for used and unused doses.
- (m) Treatment regimen/plan section.

#### Dosing strategy

- (a) Dose calculation formulae and parameters, if applicable.
- (b) Dose schedule (periodicity, cycles, days of cycle, maximum number of cycles).
- (c) Dose limiting toxicity (DLT).
- (d) Dose escalations, delays, and modifications (adverse effects, re-escalation, renal or hepatic function).
- (e) Regimen (combination oral/parenteral drugs, sequence/order of administration).
- (f) Treatment plan (arms, evaluations, rescue regimens, re-inductions).



- (g) Potential drug adverse events (prevention and treatment regimens).
- (h) Concomitant medications (premedication) and supportive care recommendations.
- (i) Drug, herbal, and food interactions.
- (j) Concurrent medication restrictions (permitted or prohibited).
- (k) Rescue therapy.
- (l) Contraindications.
- (m) Surveillance and study cancellation.

This information should be available from the CT or RS protocol document (ID handling manual or package insert for investigational agents). Additional information (usually container compatibility, devices, infusion sets, or stability issues) should be obtained from the sponsor before starting recruitment and ideally before trial approval by SRC and IRB/ERC. All additional data provided should be signed and recorded with the protocol documentation, in hard copy or electronically.

Premedication and supportive treatment chosen at investigator discretion or as per local clinical practice should be discussed and fixed in advance before starting recruitment and before activating a template or introducing the regimen into the information system. Any decisions should be recorded in the protocol, the sponsor informed, and conformity signed if required.

Any minor changes suggested to fulfil institutional requirements and procedures should receive signed sponsor approval and be recorded in the protocol documentation. Pharmacists can provide institutional policies and procedures and standard operating procedures (SOPs) to sponsors for review and approval.

After protocol approval, pharmacists can prepare specific guidelines or reference sheets that summarise key aspects of the protocol clinical trial information to aid in the safe and efficient management of the ID and regimen before implementation. The data sheet should be developed specifically for each ID and protocol. This summary should be linked to the investigational protocol. A process should be established to update these, with version control, as the protocol changes. The clinical research pharmacy should facilitate access by and dissemination of key information to personnel involved in the ID drug use process.

This summary drug data sheet information can follow the ASHP Guidelines for Clinical Drug Research.<sup>6</sup> The following information should be included.

Pharmacists can develop supportive documents, such as drug guidelines or charts, information supplements, administration tables and instructions, patient diaries, and other adherence documents.

- 
- |  |   |
|--|---|
| • Medication designation   | • Expected therapeutic effect   |
| • Common synonyms (names to be used in prescribing and labeling the investigational agent) | • Expected and potential adverse events   |
| • Dosage forms and strength  | • Potential toxicity prevention   |
| • Pharmacology   | • Symptoms of toxicity and their treatment as per protocol  |
| • Pharmacokinetics   | • Drug, herbal, and food interactions   |
| • Usual dosage range   | • Contraindications   |
| • Dosage schedule  | • Special handling precautions  |
| • Preparation information  | • Names and telephone numbers of authorised investigators and institutional contact points for patients |
| • Route of administration  | • Correct disposal methods for unused doses   |
| • Storage information  |   |
| • Dispensing information   |   |
| • Administration instructions  |   |
| • Appropriate monitoring   |   |
- 

All these aspects and activities should be considered when defining remuneration by the sponsor for the pharmacy services provided.

### 25.3.2 Practicalities and legal aspects

Investigational studies and clinical trials are regulated by law, with well-defined structures, committees, and duties and activities of all professionals involved. Pharmacist tasks and activities should comply with all applicable laws and regulations.

A pharmacist should be included on the SRC to provide expertise on drug use processes and to evaluate the following:

- (a) feasibility;
- (b) appropriateness of drug information;
- (c) administration and dosing strategy;
- (d) accuracy and completeness of the informed consent;
- (e) pharmacological effects;
- (f) anticipated risks and benefits;
- (g) adverse reaction reporting process;
- (h) applicability of safe handling standards and GMP for ID (such as gene therapy, hazardous drugs);
- (i) any additional regulatory requirements.

Institutions conducting numerous or complex ID clinical trials could consider establishing an IDS with dedicated, specialised personnel.

The oncology pharmacist, when not included in the SRC, IRB/ERC, or IDS, can act as an expert consultant and liaison among all professional participants in the ID drug use process.

SRC and IRB/ERC approval is needed before activating an investigational protocol. This should include preparing a regimen model and label templates.

The clinical research pharmacy or equivalent should have SOPs and annual training to ensure compliance with applicable laws and requirements.

The most recent approved versions of the study documents (study protocol, investigational handling manual, pharmacy manual, summary data sheets, and practice guidelines) should be available to pharmacy personnel involved in dispensing.

### 25.3.3 Education and training

The research pharmacy pharmacists, IDS, or equivalent unit should train pharmacy and study team personnel with a focus on ID medication management.

All pharmacy staff involved in activities related to medications used in clinical research should receive standard information and training on institutional policies and procedures. This includes but is not limited to the following:

- (a) How to access the most recent version of all investigational documents (protocol, study-specific summary drug data sheets, dispensing and compounding guidelines, checklists related to the drug use process).
- (b) Duties and responsibilities.
- (c) ID storage, circuits, and workflow in the pharmacy department.

All personnel with delegate responsibilities should be trained to refer to the most recent version of the summary drug data sheets, specific checklists, and guidelines, which should be readily available printed or on-line. These key documents should be added or linked to the investigational protocol documentation.

Minimum qualifications should be established for pharmacy technicians. Duties should facilitate IDS operations, such as IMP dispensing and compounding and medication distribution and control.

Records of education sessions, training, and competency assessments should be maintained in each individual's personnel file.

### 25.3.4 ID regimen templates

The development of a computerised or printed protocol prescription template for each ID regimen is a key to assuring compliance with the research protocol and avoiding drug-related errors.

In the development of a new regimen, it is mandatory to involve all the members of the multidisciplinary team (oncology, haematology, pharmacy, and nursing).

Oncology pharmacists should participate in translating the investigational regimen to the information system that

manages the ID use process or the development of protocol prescription templates. ID profile and regimens should be built by an expert in the information system, as recommended by ASHP guidelines.

Protocol- and regimen-specific electronic alerts, reminders, and assistance tools should be developed to assist during prescribing, pharmacist verification, compounding, dispensing, and administration. This includes dose-rounding policies, dosage weight calculation, automated calculations, drug adjustments in renal or hepatic failure, dose capping, and dose limiting.

Integration of clinical decision support systems (CDSSs) with electronic health records is recommended to reduce medication-related errors and miscommunication. Pharmacists should lead efforts to integrate information technology into the ID medication-use process.

ID regimen templates should follow the same safety recommendations as all antineoplastic regimens used in the institution. A draft version should be prepared to identify information that needs to be obtained, clarified, or agreed upon before enrolling participants.

Cancer studies can use multiple regimens or arms for the same protocol and different regimens for different cycles or age ranges. Policies and procedures should clearly differentiate investigational protocols and investigational agents from standard practice and commercial agents. One strategy is to use the protocol code, number, alias, or name registered in clinical trial register databases, such as CT XXXX25 induction A arm. It is recommended to match all the regimens in a protocol with the corresponding institutional acronym to facilitate the prescription process and prevent medication errors.

The development of new ID regimen templates involves phases of design, revision, approval and signed validation, and activation or implementation. Recommendations below are adapted from the Best Practice Recommendations for Regimen Development and Maintenance.

**Template design.** The following data should be included at a minimum following institutional policies and procedures:

- (a) Protocol name or acronym (multidisciplinary research team consensus).
- (b) Medication/drugs, investigational drugs, and medication-specific supportive care (both parenteral and oral).
- (c) Dosing options and calculations, formulations, and capping if necessary, including titrations and tapers, dose modification per protocol, biometric deviation allowed (include provision for recording reasons for dose modification).
- (d) Schedule (cycle, days of cycle with administration, maximum number of cycles, cycle interval).
- (e) Sequence of administration of ID and premedications.
- (f) Assisted checklists, electronic alerts, reminders for each protocol.

- (g) Preparation instructions and labeling.
- (h) Label template.
- (i) Administration instructions (e.g. route of administration and duration of administration).
- (j) Other specific instructions (use real weight or adjusted body weight in obese patients, dose capping).

**Template review.** All members of the team should independently check the final template and provide feedback before approval. The review is mandatory for the principal investigator.

**Template approval and signed validation.** All variables of the template should be discussed and consensus reached by the research team before the template is made available. The template must be approved and validated by the principal investigator and signed off by all professionals involved, with approvals documented. All template changes, updates, and amendments require new validation. It is recommended to keep a historical record of the process and decision-making.

**Template activation or implementation.** After interdisciplinary consensus has been reached and approval issued, the template should be made available for prescribing.

A process should be in place to retire outdated printed templates and inactivate templates in the information system when they are no longer in use.

All protocol documents should be secure, preferably electronically and on intranet servers rather than on paper. A contingency protocol should be developed to avoid loss of information.

## 25.4 During the trial

The main researcher and the interdisciplinary team involved should agree on the workflow of ID dispensing. It should follow the usual practice of the institution and be in accordance with the organisation's requirements.

### 25.4.1 Risk management

ISMP recommends assessing the potential for medication errors with each new protocol during SRC or IRB/ERC review. Safety concerns should be discussed with sponsors before approval.

Protocol complexity and the necessity to maintain blinding in controlled studies may contribute to risks associated with product appearance, labeling, packaging, storage, ordering, and dispensing. If labeling and packaging information has not been provided with the protocol, it should be requested from the sponsor.

Characteristics of ID that increase the risk of medication errors include the following.

There is limited regulatory guidance to promote safety related to investigational drug nomenclature, labeling, and

Characteristics of ID	Description and examples
Look-alike product labels	Long numbers truncated on label/screen, similar labels shared by sponsor
Drug name changes in labels and protocols	As investigation advances in the different phases of clinical trials, the alpha-numeric identifier moves to assigned generic names based on sponsor discretion and may change without notice. These changes may not be reflected on labels and protocols.
Labelling: lacking, different languages, peel-off labels	Clinical product information (name and strength) hidden, not provided, or underneath peel-off label
Blinding	Similarity of appearance or lack of imprint markings due to blinding
Expiration/retest dates	May be absent or inaccurate on label, often updated during course of investigation
Lack of or incomplete relevant information from the pharmacist's perspective	Stability and compatibility with different containers
Documentation	Missing content in protocols, pharmacy manuals, drug information sheets, and investigator brochures

packaging. Error mitigation strategies have been proposed by IMPS for sponsors, regulatory agencies, and clinical sites. These can be consulted at <https://www.ismp.org/resources/investigational-drugs-strategies-sponsors-fda-and-clinical-sites-prevent-product-related>.

If available, an electronic information system should be used to manage all data and store all documents linked by protocol to improve processes and documentation access. This should be integrated with the system managing the ID drug use process. Automated storage systems can be used if compliant with regulations and guidelines.

### 25.4.2 ID ordering and receiving

The research pharmacy or IDS should ensure that enough ID is ordered in advance of each CT study participant's needs.

After reception, ID deliveries should be checked against the shipping invoice: CT or RS identifier (protocol code/number/name), IDs and strength, amounts, batch/serial/lot numbers and expiry dates, and integrity and maintenance of optimal environmental conditions during transport

(temperature/humidity). If temperature monitoring devices are included during transport, instructions should be provided for reading them, acknowledging receipt, and returning them.

All validation checks and receipts should be recorded in the protocol documentation and log and communicated to monitors as required by protocol.

Any deviation or discrepancy should prompt quarantine in optimal environmental conditions in a separate area. Monitors should be informed, and the ID should be held until instructions to move to active inventory or waste are received. Deviations and notifications from monitors and sponsors should be documented.

ID received should be recorded in the accountability log. Data should include study identifier, name of the supplier, order number, ID name and strength, quantity received, batch/serial/lot number, expiration/re-evaluation date, receipt date, and total in stock.

Invoices should be filed in the protocol documentation. Minimum stock levels should be established to trigger ordering of additional supplies.

### 25.4.3 ID inventory and storage

ID must be stored in a restricted access area, available only to authorised staff in accordance with standards and regulatory requirements. Off-hour access may require on-call support.

Storage criteria should be developed to facilitate locating ID and reducing the risk of incorrect ID selection. ID should be clearly separated by protocol or study, arm, numerical order identification kit or number, lot/batch, and expiry date.

Storage should comply with environmental range values, standards, and regulatory requirements. Hazardous ID should be stored in a dedicated place under negative pressure in optimal storage conditions (such as light-protected). Depending on the space needed, semi-automated medication storage and retrieval systems can be used if compliant with guidelines and regulatory standards. Expired, damaged, or returned ID should be stored separately from active inventory.

Temperature, relative humidity, and other required environmental conditions should be monitored and recorded, with deviations investigated and notified to sponsors. In case of deviations, ID should be quarantined or not dispensed until instructions from monitors or the sponsor are received. Actions taken and instructions should be documented and recorded in the study file.

Calibration and preventive maintenance should be implemented following SOPs.

A perpetual inventory should be maintained. If retest expiration dates are provided, labels should be periodically updated. Visible warnings should be attached to alert staff to short-dated stock.

If available, an electronic information system should be used to manage inventory. This should be integrated with the system managing the ID drug use process.

### 25.4.4 ID labeling

All ID containers and packaging must be identified as for investigational use. For example, in the United States, the label should include "Caution: New drug—Limited by federal or United States law to investigational use." This may require the research pharmacy to re-label or repackage the ID.

The ID containers must also be labelled to ensure safe and effective use. In addition to information required by the specific study protocol, the following details must appear on the ID container label.

- (a) protocol number/clinical trial number;
- (b) dispensing date;
- (c) investigator's name;
- (d) participant initials and identification number;
- (e) ID name, strength, and formulation;
- (f) quantity of tablets/capsules/solution/suspension/applicators;
- (g) lot/batch number and expiration date;
- (h) directions for administration;
- (i) name, address, and telephone number of the research pharmacy or contact information to aid in coordination of care when outside institution.

Special instructions, such as storage conditions or food intake recommendations, should be included on the dispensing label or provided as auxiliary labels.

Oral medication and ID directly dispensed and administered by patients or caregivers should also include name, address, and phone/contact number of the dispensing location, instructions for dosing, quantity dispensed in container, and specific administration instructions. Sponsors should leave space on the package to permit additional labelling. As with dispensing any other oral chemotherapy drug, an auxiliary label should be added to the ID packaging with the warning "Chemotherapy drug/Cytotoxic."

Commercially available medications not provided by monitors in an investigational regimen (as in some cooperative-group-driven studies or CT) should be labeled as investigational products. This should differentiate them from others at the pharmacy (such as by re-labeling using the protocol code/name or ID alphanumeric code) and should follow the recommendations above. ID used for compassionate use should also be labeled differently from ID used in investigational studies.

It is highly recommended to sponsors that information be included on the primary (external) containers to be handled. This should include data-matrix or barcode



Clinical Trial 12345678
<b>XYZulumab (XYZ-123)</b>
<b>500 mg/50 mL (10 mg/mL)</b>
Solution for IV infusion
Batch/Lot Number: _____
Expiration/Retest Date: _____
Medication Number: _____ (required for blinded studies)
<b>Investigator:</b> _____
<b>Patient Number:</b> _____
Store at 2-8° C, Protect from Light, Keep Vial in Outer Carton
<b>Do Not Freeze, Do Not Shake</b>
Caution: New Drug – Limited by Federal (or US) law to investigational use
Sponsor: Name and Address

**Figure 1.** Example of an injectable investigational drug label (required elements in black, optional elements in red).

labeling to facilitate traceability and increase safety during compounding and dispensing.

#### 25.4.5 ID drug use process

It is highly recommended that at least the standard safety measures in place in an institution (electronic prescribing and clinical decision support alerts) for non-investigational antineoplastic medications are used for antineoplastic ID and the investigational regimens. This enhances protocol compliance and prescribing, validating, checking, and dispensing processes.

All recommendations and clinical practices guidelines on safe handling of oral chemotherapy should be implemented for oral antineoplastic ID.

SOPs should address the workflow from prescribing to dispensing to patients, care givers, hospital wards, or the pharmacy aseptic compounding unit.

When dispensing ID, the following data must be recorded in the study and patient profile: date, patient identifier, ID, identification numbers and lot numbers, amount dispensed, and expiration dates.

Dispensing guidelines should include protocol-specific functions and responsibilities to help manage and train pharmacy staff as recommended by ASHP guidelines.

Dispensing guidelines should be available and updated in print or electronic form to any pharmacy personnel with responsibilities in the dispensing process. It is recommended that only trained, authorised pharmacy personnel dispense ID.

#### 25.4.6 Prescribing

The prescribing step has been associated with the highest risk of medication errors during the ID drug use process.

Prescribing ID in clinical trials and studies should be limited to clinicians who meet legislated and study criteria

for participation in the clinical trial or study (authorised prescribers). If CPOE is used, data access should also be restricted to authorised users. An up-to-date list of authorised prescribers for each study or protocol should be available to professionals involved in the ID drug use process.

Only the latest versions of template sets printed or in information systems approved by the multidisciplinary clinical research team should be available.

Prescribing guidelines or checklists should be available and updated to guide and assist during prescription. These should include the institution's designated acronyms and names for regimens. When a computerised information system is used, a protocol should be developed and incorporated into the CDSS in the prescribing module to assist during prescription. Considerations for CDSSs should include at least the following:

- (a) alerts to confirm patient registration;
- (b) automated dose calculations and protocol-directed dose modifications and limits;
- (c) drug–laboratory value checks;
- (d) drug–drug interaction checks;
- (e) protocol remainder-specific checks.

All professionals involved in this process should sign or be recorded into the system, identified by user code and date. Sign-in should be required for any modification or deviation of the investigational protocol, such as dose reductions, regimen delays, dose individualisations for organ failure, and reasons to override alerts. When possible, all adverse effects should also be recorded.

If available, an electronic information system should be used to manage all data and store all documents linked by protocol to improve processes and documentation access. This should be integrated with the system managing the ID drug use process. Automated storage systems can be used if compliant with regulations and guidelines.

If multiple information systems are in use, system integration is recommended to facilitate traceability and avoid duplication of effort.

#### 25.4.7 Prescription validation

Prior to dispensing investigational drugs or treatments compounded, pharmacists should verify that informed consent is done and validated.

Wrong medication kit number, dose, and diluent are the most frequent prescribing errors involved in ID prescribing. Most of these errors are intercepted by a pharmacist before the drug reaches the patient.

The clinical research pharmacy or equivalent should establish policies and procedures to ensure adequate pharmacist review, validation, and verification of all ID prescriptions before dispensing. All clinical checks in place for



the antineoplastic drug use process should be implemented for the ID drug use process.

For safety and accuracy, each institution should have a policy that identifies medications that require verification prior to dispensing. Verification may be performed by a second pharmacist or delegated professional or by object recognition technology, particularly useful when ID is dispensed directly to patients or caregivers.

ID is considered high-risk. ID prescriptions must be reviewed each cycle, day, or new regimen in the context of the protocol and patient treatment assignment (treatment arm, stage and dose). Medications, dosages, calculations, routes, schedules, and treatment plans should be checked, manually or electronically, against the approved protocol or regimen. When investigational regimens differ by cycle (testing infusion reactions or maintenances cycles), reminders and alerts should be implemented to consistently maintain dose adjustments across the treatment plan.

CDSS specific to each protocol should be developed and incorporated in the pharmacist's validation module to assist during the prescription verification process.

Any adjustment or deviation from a standardised protocol should be analysed as a potential medication error. If found to be appropriate and justified, the reasons for accepting the deviation should be documented.

Documentation of the verification process, deviations, and pharmacists' interventions to prevent or correct drug-related problems should be analysed periodically to identify general or protocol-specific strategies to improve the prescribing and validation processes.

### 25.4.8 Preparation

**Assembling raw materials.** Policies and workflow should be established for distributing ID, other medications, samples, devices, containers, and ancillary materials to the aseptic compounding unit (ACU).

ID name and code, strength, kit number, and patient identification must be checked before compounding. The investigational product should be added to the information system to manage lots and generate traceable data matrix labels. Unit-dose, unit-of-use, and injectable drug packaging should employ newer technologies, such as barcode or radio frequency identifiers.

**Compounding.** For most parenteral ID, compounding by the pharmacy is required. Compounding carries a risk for error (tall man lettering lacking, sound-alike or look-alike vials with different strength or ID). Both the drug compounder and receiver should double-check the product.

Labelling and compounding should be in accordance with safe handling standards for hazardous drugs and should include all recommended validation checks.

During compounding, any incident of deviation should be analysed as a potential medication error and the

responsible pharmacist contacted to validate or correct the incident. Interventions to prevent or correct drug related problems should be documented. These should be analysed periodically to help improve the process.

All drug manufacturing safety policies should be available at the pharmacy compounding unit. These policies should be clarified with the sponsor or monitor before activating the regimen or entering data in the information system.

Preparation sheets should include all information needed for safe and efficient compounding. This may include solvents, diluents, reconstitution instructions, containers, and filtration requirements. If compounding is manual, all calculations and labels should be double-checked before compounding. If compounding is computer-assisted, alerts or support systems should be implemented for each protocol to inform of any deviations from the approved protocol.

If the compounding process is complex, an auxiliary document with compounding instructions may need to be developed, approved, and made available at the ACU.

The final labeling should include the following:

- (a) patient identifier;
- (b) ID identifiers;
- (c) final dose;
- (d) diluent type and volume;
- (e) special administration instructions (such as use filter, administer 30 min after, vesicant risk);
- (f) hazardous/cytotoxic labeling as required;
- (g) expiration date;
- (h) optimal storage conditions.

For blinded studies, the active ID and placebo must be identical in appearance, including the following:

- (a) light protection;
- (b) tubing;
- (c) colour;
- (d) labeling (identical information);
- (e) preparation times;
- (f) expiration date (if different, ASHP guidelines recommend using the shorter of both);
- (g) administration/dispensing times.

Spent and partially used vials after dose preparation of hazardous ID should be destroyed according to the institutional policies and procedures as recommended by ASHP guidelines.

Preparation sheets should record number of kits used and lots or batches. All professionals involved in this process should sign or be recorded into the system, identified by user code and date.

**Final checks.** Pharmacists or delegated professionals should check the finished product and verify the following:

- (a) amount used to reconstitute;
- (b) amount of medication withdrawn;
- (c) amount added to the bag;
- (d) type and final volume of diluent;
- (e) container;
- (f) labeling;
- (g) optimal storage conditions.

Pharmacists should ensure that all required checks have been completed prior to dispensing, especially when directly dispensed to the patient or caregiver. All checks should be recorded into the system, identified by user code and date.

### 25.4.9 Dispensing

When ID is directly dispensed to patients or caregivers, verification by a second pharmacist or delegated professional should be required before dispensing.

Sponsors should be encouraged to provide ready-to-dispense patient-specific ID to minimise repackaging errors. Newer technologies, such as barcodes, minimise dispensing errors and electronically double check and record the process.

The pharmacist should provide the participant or caregiver advice and counselling for oral or self-administered ID. This should include the following:

- (a) dosage and timing of administration;
- (b) special directions and precautions;
- (c) expected side effects;
- (d) interactions (drug, disease, food);
- (e) storage conditions;
- (f) what to do if a dose is missed or overdosed;
- (g) instructions to return ID containers to the research pharmacy at the next visit.

The pharmacist should also address questions a participant, caregiver, or clinic research member has regarding the ID.

The pharmacist can develop and provide supportive documents such as drug information supplements, patient diaries, or other adherence tools (diary cards, pill boxes, validated apps) according to protocol requirements or institutional practices.

The dispensing process should guarantee blinding (identical appearance) as required. Double blinded CT or RS by cooperative groups poses special challenges. Unblinding procedures should be defined in the CT or RS protocol.

The dispensing pharmacist or pharmacy staff member must sign and date this process. For oral or self-administered ID and ID directly dispensed to patients, dispensing documentation should also be signed by the patient or receiving caregiver.

Any adjustment or deviation from a standardised protocol should be analysed as a potential medication

error. The responsible pharmacist should be contacted to validate or correct the incident. Interventions to prevent or correct problems should be documented and periodically analysed to identify strategies to improve the dispensing process.

### 25.4.10 Administration

Parenteral administration is typically the responsibility of nursing. However, pharmacists collaborate in this process by providing administration-specific education, developing administration data sheets, and entering data in the information system that manages the ID drug use process.

Administration guidelines and data sheets developed for specific ID and protocols promote safe and effective administration. These instructions should deal with increasing administration rates by patient tolerance, adjusting administration rates for infusion reactions, complex procedures, expected adverse drug reactions, and extravasation risk. They should be readily available at administration sites when needed.

The administration process (times, sequence, stops, compatibility materials) and incidents should be recorded for all ID and other drugs included in the investigational protocol.

For oral ID directly dispensed to the patient or caregiver, adherence should be evaluated before the next cycle of dispensing. The patient or caregiver must be provided with oral and written information and counselling. The information can include handouts and adherence diaries and inform of situations that require contacting the research or provider team.

### 25.4.11 Accountability, returns, destruction

Accountability of ID should be documented in each CT or ST protocol profile and each patient profile. ID identification, amount received/dispensed/returned, batch/lot number, date, and professional involved should be recorded. Reasons for returning or discontinuation should also be recorded.

Segregating and destroying waste ID should be in accordance with procedures in the study manual. Waste includes non-conformed study products (ID shipped or stored improperly), samples returned, and expired samples in storage. Handling and disposing of hazardous waste should be in accordance with good pharmacy practice, sponsor requirements, and all applicable laws and legislation.

This wasting process should be documented in the CT or SC protocol. Monitors should verify quantities and details of destruction.

### 25.4.12 Expanded access to ID

After the ID clinical trial or study completion or termination and before regulatory agency approval and reimbursement, the ID could be made available to individual patients using expanded access or compassionate use programs when other therapy options are exhausted or not available.

Pharmacists involved in clinical trials should be familiar with expanded access resources, local SOPs, regulatory laws, and agency requirements for drug use in these situations, and use process documentation that mimics the ID drug use process.

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## Section 26 – Medical surveillance

### 26.1 Goal

Antineoplastic agents have a well-documented potential to cause chromosomal aberrations, congenital malformations, fertility issues, and cancers.<sup>1</sup> The goal of medical surveillance is to identify as early as possible any reversible consequences of exposure to hazardous drugs (HD) to minimise the risk of irreversible health effects.<sup>2</sup>

### 26.2 Systematic risk assessment

Medical surveillance procedures should be performed for each employee at the following times:

- (a) before employment, to establish a baseline;
- (b) periodically during employment;
- (c) after any acute exposure event;
- (d) when leaving employment.

Each of these is covered in a section following.

#### 26.2.1 Pre-employment screening

The United States Occupational Safety and Health Administration (OSHA) recommends that pre-employment health screening include a medical history, physical examination, and laboratory studies.<sup>2</sup> Pre-employment screening should include the following, at a minimum.

- (a) A history of hazardous drug handling, including dates of exposure and personal protective equipment (PPE) usage.
- (b) Laboratory studies, including a complete blood count and liver and kidney function tests.
- (c) A comprehensive medical history, including data from previous employment where an employee handled hazardous drugs.
- (d) A physical examination with emphasis on the skin, mucous membranes, cardiopulmonary and lymphatic systems, and liver.<sup>2</sup>
- (e) A history of reproductive and fertility issues, such as spontaneous abortion, congenital malformations, or other symptoms consistent with HD exposure.<sup>3</sup>

Biological monitoring tests, such as genotoxic markers, are not currently recommended for screening due to poor standardisation and high cost.

#### 26.2.2 Periodic medical surveillance

Periodic medical examinations are needed to identify early, reversible signs of HD exposure before they become irreversible health issues. Current international medical surveillance guidelines do not specify a timetable for these exams. The timeline should be agreed upon by employer and employee based upon institutional standards, the employee's history of HD exposure, and the degree of current exposure.

Annual physical examination and laboratory follow-up may be required. This interval may be extended to every two years or more upon the recommendation of an occupational medicine physician knowledgeable of the site's safety precautions.

Annual medical examinations may be conducted by the employee's personal physician or by an occupational medicine physician as directed by institutional policy. In either case, any issues of concern should be reported at the earliest possible time to the institution for analysis, and a plan should be written to address exposure risk.

#### 26.2.3 Acute medical surveillance

Physical examination with laboratory studies is recommended following any acute or accidental exposure where PPE was not used. All physical examinations should follow the format in Section 26.2.1.

#### 26.2.4 Post-employment medical surveillance

The post-employment medical examination documents the employee's health upon leaving a job that involved exposure to HD. It should include a physical examination, laboratory testing, and amounts and dates of drug exposures.

### 26.3 Reproductive concerns

Any employee who becomes or is attempting to become pregnant or is breast feeding should be provided with alternative job responsibilities and options for minimising

reproductive risks of HD exposure. The employee's physician and employer's healthcare and occupational medicine providers should assess the level of risk to the employee and take all appropriate precautions.

## 26.4 Employee training

All sites and employers should mandate instructional training for new employees, even those with significant prior experience in the handling of HD. Training should include institutional best practices, guidelines for safe handling, use of PPE, and appropriate disposal of hazardous compounds. Information should be provided about the expected level of exposure to HD, expectations for PPE, and mandated elements of the institution's medical surveillance program.

Education alone does not protect against the potential health consequences from prolonged exposure to these compounds. Each site should have a comprehensive program of medical surveillance consistent with national and international guidelines.

## 26.5 Surface testing

HD can enter the body through inhalation, accidental injection, ingestion of contaminated foodstuffs, mouth contact with contaminated hands, or absorption through the skin.<sup>4</sup> Airborne exposure is relatively rare.<sup>5-7</sup> Institutional standards should focus on identifying and sterilising surfaces from which HD may be absorbed. Surface testing recommendations may be determined by the volume of HD compounding and the availability and expense of testing. High-volume sites may consider monthly surface testing and thorough cleaning (see Section 10).

## 26.6 Institutional data collection

Each institution should periodically collect and report aggregate data regarding employee exposure to HD. The identification and assessment of any trends requiring acute health assessment and potential treatment of exposure-related symptoms should be used to improve the safety and welfare of all employees.

The United States Institute for Occupational Safety and Health (NIOSH) has issued guidance for the periodic use of HD-related aggregate employee data for the following purposes:

- (a) Evaluating existing PPE, such as biological safety cabinets and closed system transfer devices.

- (b) Evaluating policies for the use of PPE.
- (c) Assuring employee compliance with existing institutional policies and USP Chapter 700 (or 800).
- (d) Developing a plan of action to minimise future employee exposure.
- (e) Providing confidential communication between employees and employee healthcare providers.<sup>3</sup>

## 26.7 Medical surveillance alternatives

Implementing all medical surveillance recommendations may be cost-prohibitive for some institutions. The safety controls described here may not even be available in some countries or institutions. In these settings, medical surveillance should focus on encouraging and enabling employees to share health issues with healthcare providers as early as possible.

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## Section 27 – Computerised prescribing, dispensing and administration

### 27.1 Introduction

#### 27.1.1 Definition

Computerised prescribing, dispensing and administration systems, also referred to as computerised provider (also physician or prescriber) order entry (CPOE) or electronic prescribing systems (EPSs), allow a prescriber to enter and send medication orders and treatment instructions electronically.

CPOE and EPS are named for the prescribing function, but many of these systems also support dispensing and administration using the electronic system. CPOE will be used to refer collectively to these systems.

CPOE is an important tool that minimises prescription errors and improves patient safety. CPOE is especially important in chemotherapy prescribing, for which it is highly susceptible to errors due to complex regimens and narrow therapeutic indices. Research has established a knowledge base for successful CPOE implementation and ongoing use.

#### 27.1.2 Purpose and benefits

CPOE enhances patient safety and facilitates adaptation of protocols from clinical trials to practice through electronic integration of medication orders. Although CPOE typically includes all orders for patient care (laboratory tests, imaging, nursing orders, medications, and others), it can have particular benefits for chemotherapy prescribing. CPOE has been shown to save time and improve the quality and delivery of care by collating orders that are typically prescribed together, such as chemotherapy, premedications, laboratory tests, and nursing communication orders.

CPOE facilitates efficient order processing through instantaneous transmission of orders and avoiding the need for transcription. CPOE decreases medical errors by eliminating illegible and incomplete orders and improves compliance with clinical practice guidelines. CPOE can standardise practice, facilitate incorporation of clinical decision support, improve interdepartmental communication, and capture data for management, research, and quality

monitoring. In many cases, CPOE is part of a larger-scale integrated information system that includes an electronic health record (EHR), clinical decision support system (CDSS), and other clinical and business information systems. As a result, patient-specific data can be manipulated, organised, and presented in ways that are clinically meaningful during planning, ordering, and care processes.

#### 27.1.3 Challenges

Many implementation challenges have been reported from users of CPOE.

- (a) unfamiliarity with how to use the system;
- (b) integration of the CPOE system with typical user workflow;
- (c) persistence of paper-based tools;
- (d) clinician resistance to adoption of CPOE and perceived loss of autonomy;
- (e) requirement for new or upgraded hardware;
- (f) cost of continuous system upgrades;
- (g) introduction of new types of CPOE-related errors, such as alert fatigue or wrong drug selection from drop-down menus;
- (h) over-reliance on technology.

### 27.2 Pre-implementation phase

#### 27.2.1 Selection criteria for CPOE systems

CPOE is a major operational and financial decision for a healthcare institution. It requires a multidisciplinary planning and implementation team and support for the project at the executive level. Prescriber buy-in and acceptance is also crucial for success.

An important first step in selecting a CPOE system is to determine the vision, goals, and objectives for CPOE implementation. These fall into three main categories: clinical, operational, and financial.

A list of criteria should be developed for evaluation of candidate CPOE systems. The CPOE system must have the ability to interface with existing or planned information and inventory control systems. The CPOE criteria should

help identify what features are already in place and what functionality could be added. This might include chemotherapy dose calculation based on body surface area (BSA) and area under the curve (AUC) or chemotherapy preauthorisation tracking and billing.

Choosing a CPOE vendor may be based on considerations such as the following:

- (a) How long has the vendor been in business? The vendor should be well-established and financially stable.
- (b) How often is the system upgraded and updated? Is it responsive to changes in healthcare legislation and policy (such as updates in ICD codes)? The cost of upgrades and updates should be clearly stated and agreed upon before implementation.
- (c) Are interfaces available to integrate the CPOE with systems now in place?
- (d) Which oncology practices have successfully installed this system? The vendor should provide references and information about how other customers are using the system.
- (e) What type and availability of support is provided? If 24-hour support is not available, support should be available throughout the institution's business hours.
- (f) What will be the drug resource library? This should be a published reference from the institution's country, state, or province.
- (g) Is the software scalable and app-based? Is it available on smart phones and tablets?

### 27.2.2 Integration

A clear and realistic plan for integrating a new CPOE system is required. This should include how the transition will occur and how the system will be maintained. The impact of CPOE should be assessed with the goal of achieving ideal workflow. Because the changes in workflow will affect every clinician, project management and change management skills are vital for the conversion.

For a CPOE to be most useful, it must be deployed as part of an EHR. CPOE should include or interface with other systems that provide clinical information needed to provide patient care, including laboratory results, current medications, and allergies.

Essential baseline and post-go-live metrics should be developed to measure the success of CPOE implementation.

### 27.2.3 Training

All healthcare professionals, including prescribers, nurses, and pharmacists who majorly work with CPOE must be trained in the tasks required of them and their training records retained. User roles and responsibilities should be

clearly defined to ensure staff are trained to operate within their scope of practice.

Training should involve demonstrations of different types of prescriptions that may be encountered in various scenarios (e.g. dose reductions and how these are applied). Practicing with realistic patient scenarios will provide the best preparation.

Retraining should take place periodically according to local requirements and as appropriate following system upgrades. A healthcare professional trainee should not be enabled to act as a final signatory for a designated task until formally signed off as competent. Additional training should be undertaken if a new risk for error is identified.

## 27.3 Implementation Phase

The implementation of a CPOE system should involve key stakeholders and representatives from all types of end users. These include all health professionals that use or interact with the CPOE including prescribers, pharmacists, nurses, information technology professionals, decision support, clinical informatics, quality representatives, and patients.

### 27.3.1 Usability

CPOE usability will be determined by its ability to achieve specific clinical goals effectively and efficiently. Factors that can enhance usability include the following:

- (a) minimising the number of clicks to complete a workflow;
- (b) providing real-time alerts that are non-repetitive, patient-tailored, succinct, and non-disruptive to workflow;
- (c) ensuring that type-in fields are not punctuation sensitive (such as when searching);
- (d) minimising long menus and requirements for scrolling;
- (e) Well-designed visual cues and icons;
- (f) Pre-defined medication order sets (such as highly emetogenic chemotherapy premedications).

### 27.3.2 System access and permissions

Users must have individual, confidential, unique log-ins for the CPOE. Institutional log-ins are not acceptable. The system must be able to control access to personal health information to comply with information safety and security legislation, including the use of electronic signatures and secure passwords.

CPOE must have a secondary level of access permissions by role or individual that is consistent with organisational policy and professional scope of practice.

The system must enable user roles to be defined for access to order set management and restrict access to

individual order sets by user role or department. Order entry and regimen building should be restricted to individuals within their scope of practice or determined by local medical directives.

The system should permit restriction of medication orders by user type, individual order, or class of order. Each medication order should indicate the name and user level of the ordering party. The system should support the entry of unverified orders and the editing and verification of unverified orders. This function should be role-based and restricted. The system should also support the creation of reminders or inbox messages for orders that require a co-signature.

User actions taken within the system must be reportable.

### 27.3.3 Information display

The information display must be clear and organised in a way that minimises errors with look-alike and sound-alike drugs. Important information, such as drug name and dose, should stand out clearly, such as in bold, highlighted, larger font or tall-man lettering. All relevant information should be organised concisely and logically.

Chemotherapy regimens must be clearly named and identified to avoid confusing similarly named regimens. For clinical trials, the trial name and protocol number and the patient's trial arm or regimen must be clearly identified.

During order entry and review, the system should display information to accompany the chemotherapy order, such as laboratory values, current medication list, drug interactions, and allergy status.

The system must have the ability to customise printing and formatting of chemotherapy orders and take-home prescriptions to meet best practice recommendations and local regulations.

Medication order status should be clearly displayed. Pharmacist verification of every chemotherapy order should occur prior to dispensing and administration.

Once the chemotherapy order is processed, the CPOE system must have the ability to generate a label for each specific preparation based on local regulations. The label should include patient information, product name, dosage, concentration, diluent, total volume, route of administration, expiry date and any special information related to the preparation.

A verified order should populate as an active order in the pharmacy computer system and release the drug for dispensing followed by administration.

The CPOE system should be capable of storing and retrieving details from all previous patient orders.

### 27.3.4 Chemotherapy-specific considerations

The design and build of chemotherapy orders and order sets are key tasks that should have direct involvement by the

pharmacy department, by individuals with training and experience in oncology. Care should be taken in designing and building standard orders and order sets for chemotherapy and associated supportive care medications. Testing of order sets is vital to ensure proper medication management and workflow.

Whenever possible, calculations should be performed automatically by the system to reduce errors. The system should have a calculation tool for BSA, creatinine clearance, and medication dosing (including per kilogram, BSA, and AUC). Calculations should be built into the electronic ordering system using units consistent with jurisdictional standards (such as height in meters and weight in kilograms). Calculations should also take into consideration relevant pharmacological parameters (such as renal or hepatic function).

The system must have enhanced dosing logic and allow for complex instructions such as dose tapering, titrations, alternate day dosing, treatment interruptions, and dose capping.

The system should check ordered dose against local guidelines of best practice or other references. Alternatively, evidence-based protocols should be made available within the system for checking the following:

- (a) Medication dosage, frequency, and duration.
- (b) Cumulative lifetime medication dosage (such as for doxorubicin).
- (c) Minimum and maximum dose allowed per dose, per day, or per course for each route of administration.
- (d) Appropriate routes, units, and diluents for medications. Selection of other routes or units should be prohibited during the order process (such as intravenous route only for vincristine).

The CPOE system should prompt users to record reasons for deviations from protocol (such as dose, frequency, or substitutions) to ensure auditability. Reasons should be descriptive and clinical; non-specific reasons (such as "per clinical judgment") are not acceptable.

### 27.3.5 Workflow management

Workflow is typically reengineered as part of CPOE implementation. Therefore, the system should contain mandatory fields to enforce appropriate workflow. The system should be an integrated element in the interdisciplinary process of ordering chemotherapy with shared responsibility among the multidisciplinary team, including prescribers, pharmacists, and nurses.

All steps related to the chemotherapy regimen, including electronic prescription, verification, preparation, and administration, should be electronically tracked to document the workflow steps of each preparation.

The CPOE system must allow the patient to be uniquely identified across the continuum of care. The patient identifier must be unique, exclusive (only used for one patient), and eternal (never reused).

The system should allow unique identification of the healthcare provider and demographic information including name, role, gender, license number, and the locations where patient care is provided.

To prevent delays and transcription errors due to re-entry of medication information, prescribed orders should be electronically transmitted to pharmacy dispensing systems.

The system should have the ability to build conditional orders written with a hold status awaiting verification by pharmacy or nursing.

The system must require signed chemotherapy orders to be verified by an authorised user prior to preparation and administration. These orders should be locked while awaiting verification. Verification is required prior to dispensing and administration.

CPOE should have the ability to generate and display a daily worklist with all the information related to chemotherapy orders. These can be workflow-dependent. Examples include confirmed schedules, reimbursement conditions, need for any validation or pre-authorisation for medications, changes or updates in the patient regimen, and lists of patients awaiting treatment.

### 27.3.6 Alerts and error prevention

A CPOE system must present alerts with clear and concise messaging. The system should have fully customizable feedback features that alert the user to actions that may not have the desired effect, such as ordering too early or deleting essential adjuvant medications. Customizable warnings and hard-stops should be built in so certain actions cannot be taken.

CPOE must display alerts for allergies, drug interactions, and therapeutic duplications.

CPOE should have the ability to set customized alerts, such as threshold and expiry date for alerting based on height and weight or BSA changes.

CPOE should display alerts for drug-drug interactions in a highly specific and sensitive way, enabled through complete, accurate, current, and evidence-based clinical decision support. Consequences of over-riding the alert should also be included. The system should support categorization of drug interaction alerts based on severity and risk.

- (a) *Trivial*: no real-time alert required; could be included in batch reports sent to ordering clinicians or auditors at predetermined time intervals.
- (b) *Minor*: alerts can be overridden by prescriber.
- (c) *Moderate*: alerts can be overridden by prescriber but reason must be given.

- (d) *Serious*: alert cannot be overridden; unable to proceed with order unless appropriate changes are made.

Chemotherapy agents must have alerts that prevent order processing until physician confirmation and sign-off has been entered. Unsigned orders must be flagged to downstream staff including pharmacists and nurses.

Any prescriber changes to the chemotherapy regimen should have the option to be applied to the current cycle only or to current and subsequent cycles. The CPOE system must indicate any modifications to the standard order set, identifying the healthcare provider who initiated the changes and the reason for the modification.

CPOE should enable the ordering clinician and pharmacist to review and confirm all ancillary medications, hydration, and chemotherapy orders and doses.

To avoid infusion errors, CPOE must include at least three patient identifiers. Drugs to be infused should be labeled with those same identifiers.

### 27.3.7 Documentation and reporting

The system must maintain a record of the date and time for each entry, any change in recorded information, and the original content of the recorded information that was changed or updated. A record of any alerts ignored or overridden must be available.

Requirements or desirables for clinical trials should be included. Some examples are a patient clinical trial identifier as part of the patient's profile and clinical reports to assess clinical trial eligibility.

The CPOE system should have reporting functions that support continuous auditing and monitoring and that keep a log of all past activity.

Reports should be customizable by end-users. Type of data extracted should be limited by user role permissions.

## 27.4 Post-implementation phase

A post-implementation phase that includes upgrades, audits, and enhancements should be continued throughout the use of a CPOE system. Collaboration must occur with key stakeholders (such as informatics experts, clinical application specialists, and clinicians) to ensure continuous quality improvement. Institutions should formalize a governance structure to address the many decisions involved in implementing a CPOE system, and to continue to evaluate and improve workflow.

It is vital to regularly review and analyse data to assess system performance, identify trends, and identify problems to be addressed and resolved. Examples of quality assurance reporting might include the number and type of medication errors, patient waiting times, and compliance with evidence-based guidelines and protocols.

Other considerations include comparing actual outcomes with expected benefits (comparing post- and pre-implementation data). How has CPOE performed in the following areas?

- (a) number of medication errors;
- (b) number of pharmacy and nurse interventions;
- (c) patient waiting times;
- (d) order entry times for clinicians;
- (e) changes in workforce requirements;
- (f) qualitative feedback, such as clinician satisfaction.

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## Section 28 – Dose banding

### 28.1 Definition

Dose banding is a system in which chemotherapy doses calculated using patient body surface area (BSA) or other measures are fitted to pre-defined dose ranges, or “bands.” For each band, a dose usually corresponding to the mid-point of the range is assigned to be dispensed in standard pre-filled syringes or infusion bags. Rather than the patient-specific calculated dose, the patient receives the dose assigned to the band in which the calculated dose lies.

Dose banding was defined by Sewell, who implemented a wide-ranging dose banding scheme at Plymouth Hospitals NHS Trust, UK, in 1998.<sup>1</sup>

**Dose banding:** A system where through agreement between prescribers and pharmacists, doses of cancer chemotherapy (cytotoxic and targeted therapies) calculated on an individual basis, which are within defined ranges or bands, are approximated to standard doses (usually the mid-point of the band or range). Maximum variation between prescribed & standard dose is predefined (initially limited to +5% but more recently maximum variations of +10% are common). A limited range of pre-filled syringes or infusions, prepared in-house or obtained from commercial sources is used either singly or in combination to provide the standard dose.

Because syringes and infusions are prepared ahead and immediately available for labelling and dispensing, the delay associated with individualised dose compounding is avoided and the chemotherapy can be administered as soon as the patient and nursing staff are ready.

In the above scheme, a patient dose calculated by BSA as 880 mg would fit in the 875–925 mg band, and the standard dose of 900 mg (mid-point of the band) would be administered. This could be given either as a combination of three pre-filled syringes of 600 + 250 + 50 mg or in a single 900 mg syringe. Throughout the scheme, the maximum variation of the administered dose from the BSA-prescribed dose is at most 5%.

Dose banding is different from dose rounding, dose capping, and flat fixed dosing.

- (a) Dose rounding is the rounding up or down of a calculated dose, usually to a whole number of mg or drug vials, for convenience or to reduce drug wastage.

Rounded doses are prepared individually. No pre-defined, pre-made, standard doses are used.

- (b) Dose capping sets a maximum dose regardless of BSA. Dose capping is normally used to avoid dose-related toxicity and drug wastage from partly used vials.
- (c) Flat fixed dosing uses two or three pre-defined standard doses for all patients without taking BSA or other patient-specific measures into account. Flat-fixed dosing can result in wide variations between the individualised BSA-calculated dose and the dose administered.

### 28.2 Drawbacks of patient-specific dosing

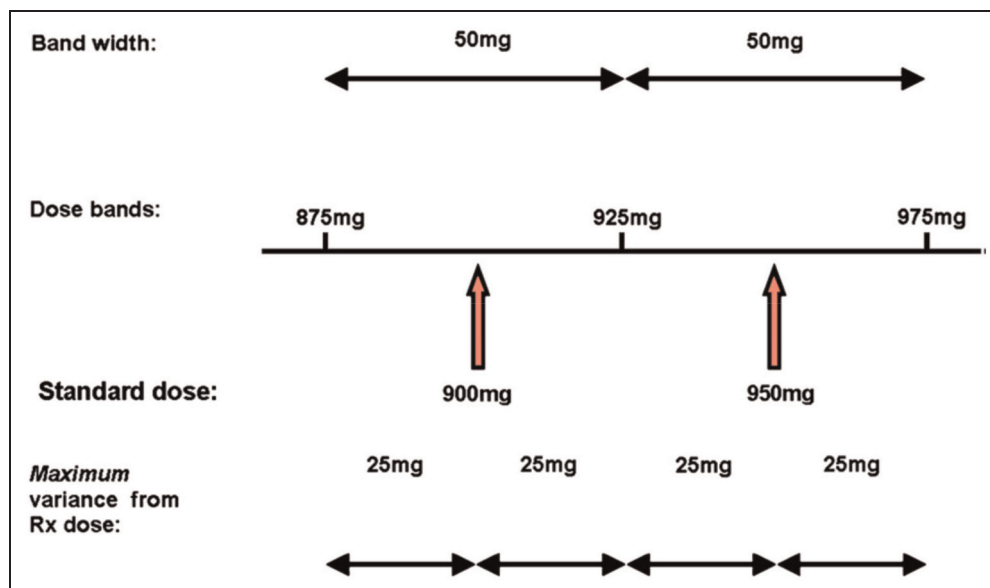
The conventional provision of patient-specific chemotherapy doses requires the preparation of bespoke infusions in the pharmacy, which can be costly and time-consuming. This has become particularly relevant with the increase in outpatient chemotherapy, where patients visit an oncology clinic and receive treatment the same day. The workload of oncology clinics can be variable and unpredictable, making the timely provision of chemotherapy a constant challenge for hospital pharmacies.<sup>2</sup> This situation also creates stress for other staff involved in providing and administering chemotherapy. Delays in providing chemotherapy also increase nurse overtime and non-availability of specialist staff if delays cause administration of chemotherapy to extend beyond normal working hours.

The risk of compounding errors is also a concern with the preparation of individual infusions. Errors can result from increased demands placed on compounding units and from lack of end-product testing and quality control, since the compounded infusions are administered to the patient in total. One study reported that of 7382 compounded infusions evaluated, 8.8% varied 20% or more from the prescribed dose.<sup>3</sup>

The compounding of individual bespoke chemotherapy infusions is also inefficient and costly.<sup>4</sup> Dose banding permits planned batch-scale preparation of standard infusions and pre-filled syringes and allows them to be obtained from external suppliers.

### 28.3 Benefits of dose banding

Benefits of dose banding can be summarised as follows:



**Figure 1.** A partial dose banding scheme for 5-fluorouracil.

#### Improved patient experience

- Waiting times for chemotherapy are reduced.
- Most chemotherapy is administered during normal working hours when specialist oncology staff are available.

#### Reduced medication errors

- Prospective quality control and end-product testing of batches ensure compliance with specifications.
- Stability assessments guarantee efficacy and safety under storage and in-use conditions.

#### Benefits to hospital staff

- Workload planning for pharmacy and nursing staff is improved.
- All chemotherapy preparations are standardised.
- Stress in the workplace is reduced.

#### Economic benefits

- Advanced batch preparation is more efficient and economic than bespoke infusions.
- Drug wastage is reduced.
- Supply can be outsourced.

### 28.4 Scientific rationale for dose banding

There should be a clear understanding among all stakeholders of the scientific rationale for dose banding and the opportunities it may offer for service improvement.

Chemotherapy dosing based on BSA has been practiced for over 50 years. It was initially recommended to

extrapolate chemotherapy doses from animals into human phase-1 clinical studies.<sup>7</sup> It was subsequently employed in routine chemotherapy dosing to reduce inter-patient variability in therapeutic response and toxicity.

The intent of BSA dosing is to reduce variation between patients, not to define the optimal therapeutic dose of a drug. Although BSA is a valuable tool for scaling of doses between species, it has less utility in dose adjustment between individuals of the same species.<sup>6</sup>

In recent years, the scientific validity of traditional individualised dosing algorithms has been questioned.<sup>5,6</sup> There is a lack of correlation between BSA and the function of organs, such as the liver and kidneys, that are responsible for clearing chemotherapy from the body. It is also known that polymorphism in the expression and activity of key metabolizing enzymes and the emergence of drug resistance in tumour cells is independent of BSA.

Body composition, age, gender, concomitant disease, and co-administration of other drugs also limit the usefulness of BSA. Further, BSA itself is only an estimation, usually based on a height and weight formula dating from 1916.<sup>8</sup> There are many controversies concerning the introduction of bias into this calculation, but height and weight, which may change with disease progression, must be accurately determined.

Variability in chemical compounding and administration also affect the reliability of BSA-based individualised dosing. Drug potency may vary from vial to vial. Syringe accuracy typically varies about 5%. Spillage, dead volume, and priming of infusion lines during administration affect actual delivered doses.

Flexibility in BSA dosing has existed for many years in oral chemotherapy. Orally administered medicines such as

methotrexate and capecitabine are available in a limited range of tablet strengths. This means administered doses can only approximate the BSA-calculated dose.

Currently, carboplatin is the only cytotoxic drug for which dose is not calculated by BSA. Instead, a formula based on renal function and target area under the plasma drug concentration versus time curve (AUC) is used. Even here, it seems reasonable to fit the calculated carboplatin dose to a dose banding scheme because of the possibility of errors in the estimation of renal function and the influence of patient factors, compounding, and administration processes on the dose actually received.

Given the above considerations, the maximum variation from the prescribed BSA-calculated dose of +5% introduced by dose banding seems entirely justifiable. This limited maximum variation was employed in initial dose banding schemes to gain prescriber acceptance.<sup>1</sup> However, in recent years many centers have extended this to +10% variation or higher without observing any significant effect on therapeutic outcome.

## 28.5 Evidence in support of dose banding

It is unlikely that it will ever be possible to study the direct effect of dose banding on overall therapeutic outcomes. A very large number of patients would be required to detect what are likely to be very small differences in disease outcomes and toxicity, and the associated costs of such research would be prohibitive. However, it is important to establish that the potential of dose banding to add further to variation from the prescribed dose does not significantly affect therapeutic outcomes.

Two prospective studies have been conducted to evaluate the therapeutic effect of dose banding. In both studies, pharmacokinetic parameters were used as a surrogate measure. This is not unreasonable, since AUC, a measure of exposure of drug to tissues, can be expected to influence both anti-tumour activity and drug toxicity.

The first of these studies<sup>9</sup> evaluated the effect of dose banding 5-fluorouracil in an FEC regimen for breast cancer. An open-label prospective cross-over design was used. Patients received either conventional individualised or banded 5-fluorouracil doses on one treatment course and the other option on the next course. Blood samples were taken for both courses and plasma 5-fluorouracil levels and AUC calculated.

There was no statistical difference in AUC between the individualised and banded treatment courses ( $p = 0.29$ ,  $n = 19$ ). The CVs for AUC values in the individualised and in the dose-banded arms of the study were 31% and 22%, respectively, suggesting that inter-patient variability was reduced by dose banding. No correlation was found between 5-fluorouracil clearance and patient BSA ( $R^2 = 0.0503$ ).

A large study from France<sup>10</sup> evaluated the effect of dose banding vs individualised dosing on the clearance and AUC of six different drugs. Three wide bands were defined. For all six drugs, the distribution of AUC values was similar for both dosing methods. The precision was not significantly different for standard BSA dosing and dose banding except for paclitaxel. Even here, the difference between the actual CVs was small (32.0% and 30.7%, respectively). The authors concluded that dose banding resulted in no significant change in individual plasma exposure to the drugs tested.

A recent multinational study<sup>11</sup> obtained pharmacokinetic measurements from 385 drug administrations to 352 children (age 1 month to 18 years) for five different drugs administered in accordance with the NHS England (NHSE) dose banding tables.<sup>12</sup> Using AUC, the authors found no statistically significant difference in precision between the calculated and banded doses for any of the five drugs. They concluded that the results supported the implementation of the NHSE dose banding tables, and that inter-patient variability in drug clearance and drug exposure far outweighed the impact of the relatively small drug dose changes introduced by dose banding.

## 28.6 Implementation of dose banding

The successful implementation of dose banding requires buy-in from all stakeholders, including pharmacists, oncology nurses, and prescribing oncology physicians. Many would also argue for the inclusion of patient representation.

The patients, regimens, and disease states for which dose banding is to be used and the maximum permitted deviation between calculated and banded doses must be defined. In some countries, no variation to the exact prescribed dose is allowed.

When implementing dose banding for the first time, a dose banding project team should be established. This team might include the following, adapted for local needs:

- (a) director of pharmacy;
- (b) lead oncology or haematology pharmacist;
- (c) chief chemotherapy/compounding unit technician;
- (d) lead oncology and haematology nurse;
- (e) clinical director (physician) for oncology and haematology;
- (f) representative from oncology/haematology patient group.

If standard doses are to be compounded in-house, the lead pharmacists for aseptic preparation and compounding and the QA/QC pharmacist should be involved. If the acquisition of standard doses is to be outsourced to other hospitals, commercial compounding units, or the pharmaceutical industry, the pharmacist responsible for procurement should also be involved.

Meetings of the project team should be recorded and routinely sent to hospital managers and the hospital risk manager or medical director. If investment is required, or if financial savings are expected, it is sensible to have a representative from the finance department.

The project team should consider the suitability of dose banding for the chemotherapy case-mix at their hospital and identify limitations and boundaries for the use of dose banding. Will dose banding be used for pediatric patients? Will it be used in clinical trials, protocol permitting?

The project team will need to consider implications for staffing, explore and critically appraise options for providing standard doses, and evaluate the capacity of in-house compounding facilities. Safe systems of work should be considered, including the design, operation and approval of the overall dose banding scheme and the procedure for introducing new drugs.

Clear responsibilities and accountabilities need to be defined at an early stage, together with a communication process that will keep all pharmacy, nursing, and medical staff fully informed as the system develops and is implemented. A system for approval of all documentation and procedures associated with dose banding must be agreed upon. Many consider tri-partite approval (by pharmacist, nurse, and physician) to be optimal.

The project team should, where appropriate, be encouraged to engage with and visit other hospital sites where dose banding has already been successfully implemented. This approach can save significant time and money and should be encouraged even if foreign travel is necessary.

## 28.7 Opinions of non-pharmacy colleagues on dose banding

### 28.7.1 Chemotherapy nurses

Experience over the past 20 years suggests that nursing staff, once fully informed about dose banding, are supportive<sup>1</sup>. A system that facilitates timely chemotherapy is seen to be helpful to nurses in their patient-facing and chemotherapy administration roles. Initially there were concerns about the acceptance by nurses of using two or more infusions or syringes in combination to provide a standard dose for dose banding. These concerns were largely unfounded. The introduction of manifold systems allowing several infusions to be attached to a single infusion set has made this more manageable.

### 28.7.2 Prescribing physicians

The prescribing oncologist or hematologist has overall responsibility for the treatment of their patients and will have a keen interest in any proposed changes to the way chemotherapy doses are calculated or administered. Concerns that physicians would want to preserve their

clinical freedom or would not understand the practical issues faced by pharmacy and nursing staff when servicing outpatient clinics have only been a minor issue in the implementation of dose banding. Such issues are easily mitigated through regular communication with the oncology or haematology pharmacist and providing oncology physicians with the flexibility to opt-out of dose banding for certain patients and regimens.

Kaestner and Sewell<sup>13</sup> undertook a survey of prescribers' opinions on dose banding in the UK. A validated questionnaire was distributed to 1104 oncologists and hematologists, of which 387 responded. A summary of the responses is presented in Table 1.

Most prescribers were informed, supportive, and positive about dose banding. Some were already using it. Opinion was divided concerning the maximum permitted variation from the prescribed dose, with the majority supporting a limit of 5% or 10% variation. Opinion was also divided concerning whether non-BSA-dosed drugs (such as carboplatin) and non-cytotoxics (such as monoclonal antibodies) could be included in dose banding schemes. In recent years, greater than 10% variation from prescribed doses are not uncommon, and carboplatin and monoclonal antibodies have been incorporated into dose banding schemes.

## 28.8 Development of dose banding schemes

Wherever possible, it makes sense to adopt dose banding schemes from established dose banding practitioners to avoid unnecessary work. Additionally, if more hospitals use the same dose banding schemes for each drug, it is more likely that external suppliers of pre-made infusions will have an interest in entering the market. The NHS in England is encouraging hospitals to take up dose banding of chemotherapy and recently published its own dose banding for a wide range of cancer treatments.<sup>12</sup> This website is a good place to start in the search for existing dose banding schemes.

If a new scheme must be devised, the starting point is to decide the width of the dose bands and the dose range that will be covered. The latter is normally derived from the dose/m<sup>2</sup> and the expected range of patient BSA values. Most drugs will have different dose/m<sup>2</sup> for different regimens or schedules or when the drug is used as a single agent. Most dose banding schemes will be specific for a single regimen or a group of regimens if the dose is similar. With a constant dose band width, the maximum percent variation of the mid-point of the band from the prescribed dose will be greater at lower doses. Practitioners may decide that the extreme ends of the dose range should continue to be provided as bespoke individualised infusions. This may not be ideal, but usually applies to a small number of patients.



**Table 1.** Chemotherapy prescribers' opinions on dose banding: Summary of UK survey.<sup>13</sup>

Question	Yes	No	Don't know	No response	
1. Do you have concerns about the time out-patients have to wait?	281 (74%)	93 (25%)	5 (1%)	–	
2. Have you heard about dose banding previously?	308 (81%)	71 (19%)	–	–	
3. Does your hospital use dose banding?	238 (63%)	83 (22%)	20 (5%)	37 (10%)	
4. Do you think dose banding is sensible?	308 (81%)	10 (3%)	55 (15%)	6 (2%)	
5. Do you think there are benefits with dose banding?	349 (92%)	4 (1%)	7 (2%)	19 (5%)	
6. Which do you think the maximum deviation from the individualised dose should be?	< 5%	197 (52%)		7 (2%)	
	< 10%	150 (40%)			
	< 15%	8 (2%)			
	Other/do not know	17 (4%)			
7. Would it be acceptable to dose-band drugs with non BSA-based dose?	a. Carboplatin	203 (54%)	79 (21%)	70 (18%)	27 (7%)
	b. Targeted antibodies	232 (61%)	37 (10%)	72 (19%)	37 (10%)

An alternative approach has been proposed<sup>14,15</sup> where doses are banded according to a logarithmic dose scale. This has the effect of maintaining a fixed percent maximum variation between the banded dose and the calculated dose. Logarithmic dose banding remains controversial, with advocates claiming that it can reduce the dose variation introduced by dose banding schemes and detractors expressing concerns about increased complexity and risk of errors through confusion. New evidence<sup>11</sup> strongly supports the NHSE Banding Tables and shows that the variation introduced by conventional (linear) dose banding is of little pharmacological significance. This makes the additional complexities of logarithmic dose banding more difficult to justify. The challenge for proponents of logarithmic dose banding is to provide evidence of need and safety, and to produce evidence of pharmacological and therapeutic outcomes to the level of that published for linear dose banding.<sup>9–11</sup>

It will be necessary to devise a range of pre-filled infusions or pre-filled syringes to provide the standard dose for each band. Ideally, standard doses should be provided with the minimum number of pre-filled infusions or injections possible when used singly or in combination. In general, a dose banding scheme with narrow bands and a wide range will require a larger range of pre-filled infusions than a scheme with wide bands and a narrow range.

In the scheme excerpted in Figure 1 example, seven different strengths of pre-filled 5-fluorouracil syringes are required, and between one and four of these are necessary to provide the standard doses. Most dose banding schemes would be simpler however, and a smaller dose range with a 10% maximum variation from the prescribed dose would normally require only four different pre-filled syringes or infusions and no more than three of these used in combination.

## 28.9 Documentation

Control is a key part of the safe and effective operation of a dose banding system. It is crucial for prescribers and nursing staff to have access to and understand the core documents defining the dose banding system. All members of the clinical team need to know what standard dose will be given for any prescribed dose and how that standard dose will be provided.

The main documentation required for dose banding is shown in Table 2. This table does not include the additional documentation required for compounding of pre-made syringes and infusions and for QA/QC of infusions.

## 28.10 Pharmaceutical issues in dose banding

### 28.10.1 Preparation of pre-filled syringes and infusions

The aseptic compounding requirements for the preparation of batches of standard doses of chemotherapy with extended shelf-lives are different from those used for dispensing named-patient aseptic preparations for immediate use. It is known that microbiological viability is supported in many cytotoxic drug infusions.<sup>16</sup> In view of the highly compromised immune status of many oncology patients, it is essential that sterility of batch-prepared infusions is assured. Compounding units intending to prepare batches of chemotherapy for dose banding must meet the highest level of regulatory standards applied to that country or region (such as EUGMP in Europe), and must be authorised by the regulator for this type of activity. All aspects of the aseptic process will be considered before such approval is granted, including the following:



**Table 2.** Documentation required for the safe management of dose banding.

Type of document	Purpose of document
Principles and scope of dose banding	Sets out principles, limits and restrictions on dose banding Identifies approvals given from clinical and managerial staff and responsibilities of staff leading dose banding Provides dose banding service specifications and service agreements Provides policy documents on sourcing and dispensing pre-made infusions
Staff training in dose banding	Sets out training process for different staff groups for staff who are new to dose banding Identifies who is responsible for training Maintains training and re-training records for staff involved
Dose banding scheme	Provides schemes for each drug/regimen/schedule combination
Selection of pre-made infusions	Provides an infusion selection table for each drug, giving infusion or syringe combinations for each dose band
Records of errors, unusual occurrence	Records errors or unusual occurrences that may be associated with dose banding Documents any investigations undertaken, with responsible individuals and timelines

- management and leadership structures;
- knowledge, expertise, and training of personnel;
- standard of facilities and equipment;
- written and electronic control documentation, such as standard operating procedures, preparation records, intervention records, and QA/QC and quarantine procedures to ensure the safe release of products;
- function and security of IT systems and overall regulatory compliance.

This list is not exhaustive. Practitioners will need to work with regulatory authorities in their own locality to obtain approval.

In-house preparation of chemotherapy for dose banding requires considerable investment to ensure compliance with regulatory requirements and obtain equipment. Even for moderate batch sizes (30–100 units), semi-automatic equipment such as filling pumps are essential. Similar consideration must be given to labeling and product inspection systems. Batches of standard chemotherapy infusions for various drugs at different strengths will require considerable storage space that, in most cases, must be refrigerated.

This will be required for storage of quarantined and released batches ready for use, which in practice means the provision of a controlled and monitored cold-room facility. For large-scale preparation, more substantial investment in automatic syringe or infusion filling systems, or even robotic systems, will be required.

It is beyond the scope of these guidelines specific to dose banding to detail the exact requirements for in-house preparation of batches on a global basis. However, this activity requires expert planning and consultation before it can be considered.

Purchase of pre-made syringes and infusions from external sources does not absolve the purchasing institution from responsibility for the quality and safety of the preparations. Purchasing institutions are responsible for ensuring that all regulatory and quality standards have been met and that each batch of outsourced infusions or syringes fully complies with an approved specification.

### 28.10.2 Quality assurance and quality control

The QA/QC systems applied must meet the approval of the appropriate regulator. QA requirements are likely to include monitoring of staff, facilities, equipment, the preparation environment, and all processes used in the preparation of chemotherapy batches. An excellent document summarising these requirements for UK hospitals has been produced by the National QC Network.<sup>17</sup>

Unlike single-unit named-patient individualised infusions, the batch-scale preparation of standard infusions with extended expiration dates permits the use of quality control through end-product testing. This prospective intervention enables much greater assurance of efficacy and safety than with individual chemotherapy preparation. At a minimum, end-product testing of standard infusion batches should include identification of the active components and their assay. This can be conveniently and safely done using computer-aided spectroscopic methods. The use of the correct diluent is important with many infusions, and this can be confirmed with simple physical techniques such as measurement of refractive index and pH. It may also be possible to include prospective sterility testing before the batch is released for patient use. However, sterility testing of aseptically prepared cytotoxic infusions remains controversial, both in terms of scientific validity and health and safety considerations.

Sampling strategies for end-product testing of standard infusions require careful consideration. In many centers, batches of standard chemotherapy infusions are prepared by pooling the contents of all drug vials into a large sterile infusion bag, adding the required volume of diluent, mixing thoroughly, and dispensing the required infusion volume into infusion bags or syringes for patient use. Semi-automatic infusion pumps

**SELECTION OF FLUOROURACIL PREFILLED SYRINGES  
FOR THE FOLLOWING PROTOCOL  
CMF (using IV cyclophosphamide)  
Fluorouracil 600mg /m<sup>2</sup> IV Bolus Day 1**

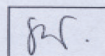
Syringe Sizes Available: 50mg, 100mg, 125mg, 250mg, 500mg, 600mg, 900mg

**TABLE 2**

Dose Calculated According to Body Surface Area (mg)	Dose to be Supplied using Prefilled Syringes (mg)	Syringe Combination
588 - 612	600	1 x 600mg
613 - 637	625	1 x 125mg, 1 x 500mg
638 - 662	650	1 x 50mg, 1 x 600mg
663 - 687	675	1 x 50mg, 1 x 125mg, 1 x 500mg
688 - 712	700	1 x 100mg, 1 x 600mg
713 - 737	725	1 x 125mg, 1 x 600mg
738 - 762	750	1 x 50mg, 1 x 100mg, 1 x 600mg
763 - 787	775	1 x 50mg, 1 x 125mg, 1 x 600mg
788 - 812	800	2 x 100mg, 1 x 600mg
813 - 837	825	1 x 100mg, 1 x 125mg, 1 x 600mg
838 - 862	850	1 x 250mg, 1 x 600mg
863 - 887	875	1 x 125mg, 1 x 250mg, 1 x 500mg
888 - 912	900	1 x 900mg
913 - 937	925	2 x 100mg, 1 x 125mg, 1 x 600mg
938 - 962	950	1 x 50mg, 1 x 900mg
963 - 987	975	1 x 125mg, 1 x 250mg, 1 x 600mg
988 - 1012	1000	1 x 100mg, 1 x 900mg
1013 - 1037	1025	1 x 125mg, 1 x 900mg
1038 - 1062	1050	1 x 50mg, 1 x 100mg, 1 x 900mg
1063 - 1087	1075	1 x 50mg, 1 x 125mg, 1 x 900mg
1088 - 1112	1100	2 x 100mg, 1 x 900mg
1113 - 1137	1125	1 x 100mg, 1 x 125mg, 1 x 900mg
1138 - 1162	1150	1 x 250mg, 1 x 900mg
1163 - 1187	1175	1 x 50mg, 1 x 125mg, 2 x 500mg
1188 - 1212	1200	2 x 600mg

**MASTER DOCUMENT**

Written by:  
Chemotherapy Pharmacist



Checked by:  
Research and Technical Services Manager



**PLYMOUTH HOSPITALS NHS TRUST  
PHARMACY TECHNICAL SERVICES DEPARTMENT  
CHEMOTHERAPY SOP 3**

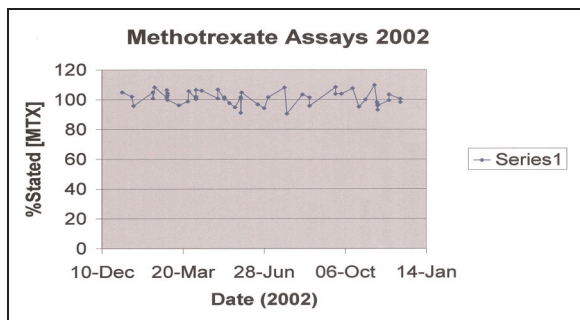
SW/tp/Document/Proced/Chemo/SOP3.doc

**Figure 2.** Example of pre-filled 5-FU syringes for dose banding scheme in Figure 1 and the combinations used to provide standard doses for a CMF regimen.

are often used for this purpose, particularly with larger batch sizes (>50 units). The infusions will be homogeneous, and the end-product testing can be conducted by aseptic sampling of the bulk solution prior to filling. This approach also confirms that mixing of the

bulk solution has been completed correctly. Where no pooling of drug vials takes place and the infusions are made as individual sub-batches, sampling for chemical and physical testing must include each sub-batch. In both cases, if sterility testing is to be carried out, an





**Figure 3.** Summary of methotrexate assay values over a 12-month period for methotrexate 10 mg in 10 mL pre-filled syringes used in a dose banding scheme.

appropriate number of infusions or syringes must be sampled in the final container.

A specification for each standard infusion must be drawn up and the compliance of each batch must be assessed from end-product testing before the batch can be released. These prospective QC processes significantly reduce the risk of compounding errors reaching the patient. With individualised infusion preparation, no end-product testing is possible. Test data from batches of the same standard infusion or pre-filled syringe can be collected over time to monitor the aseptic manufacturing process. An example showing assay data for the active drug in methotrexate standard syringes over a 12-month period is presented in Figure 3.

### 28.10.3 Stability assessment

To avoid drug wastage, dose banding requires that standard infusions or pre-filled syringes ready and available for immediate use have a shelf-life of at least 28 days. Ideally this will be 3 to 6 months, or even longer. With individualised chemotherapy infusions it is not possible to test every concentration variant that could arise, so stability is assessed at high and low drug concentrations. A key advantage of dose banding is that the use of defined standard infusions in each dose banding scheme allows a robust stability assessment to be made on each standard infusion and avoids interpolation or extrapolation to different drug concentrations.

The most comprehensive guidelines on anticancer drug stability studies, “Guidelines for the practical stability studies of anticancer drugs,” were published by a European Consensus Conference<sup>18</sup> with the extended shelf-lives of infusions for dose banding in mind. This document recommends that the normal permitted drug degradation of 10% be lowered to 5% for cytotoxic drugs. For most of these drugs, there is little information about chemical structure, pharmacology, or toxicology of drug degradation products. The guidelines also advocate the application

of sequential temperature study designs instead of the conventional parallel temperature design where studies are conducted at the storage temperature (normally 2 °C–8 °C) and in-use temperature (25°C). The sequential temperature method builds a complete picture of infusion stability as the infusion is transferred from storage to in-use temperatures. It can include additional steps such as being returned into storage for a further period if for any reason the infusion is unused (e.g. if treatment is delayed at the last minute). This approach ensures that any effect of temperature cycling on physical stability of the infusion is fully considered and helps further reduce drug wastage. Some stability studies on drug infusions have been published specifically for dose banding, for example a sequential-temperature study on the extended stability of carboplatin infusions for dose banding.<sup>18</sup> Databases such as Stabilis<sup>20</sup> are a further source of valuable information on stability of anticancer infusions, but the primary reference source in all databases should be consulted to establish the validity and applicability of the data provided.

The pharmaceutical industry is another potential source of infusion stability data. Some companies are happy to supply extended stability data, or to point pharmacists to studies published in the literature. Others restrict information to their product data sheet, regulated by license restrictions. Some companies are unwilling to extend shelf-life recommendations beyond 24 h, which is nominally applied for microbiological rather than physicochemical reasons.

Stability studies must include an assessment of both chemical and physical stability. Guidance on the specific tests to include and the validation of tests to ensure that any changes in stability are recorded are detailed in the literature.<sup>18</sup> Biological agents such as MABs have different considerations because of the secondary and tertiary molecular structures that are critical to pharmacological activity. Assessment of the stability of these drugs is limited to relatively few specialist laboratories with the appropriate equipment and expertise. Some well-researched studies from these specialist laboratories are beginning to appear in the scientific literature, such as those on the physicochemical stability of trastuzumab<sup>21</sup> and rituximab.<sup>22</sup>

Patients receiving chemotherapy are likely to have compromised immune systems and are particularly susceptible to infections. Aseptic processes are potentially vulnerable to microbiological contamination. Batches of standard infusions for dose banding are given extended shelf-lives and storage periods, presenting an opportunity for proliferation of contaminating microorganisms which can remain viable even in cytotoxic infusions.<sup>16</sup> Pre-filled syringes are designed for parenteral drug administration and not long-term infusion storage. For all these reasons, a rigorous assessment of sterility and container integrity over the proposed storage and in-use periods must be undertaken for all

standard infusions and pre-filled syringes used for dose banding. Such assessments should be capable of recovering a wide range of microorganisms (aerobic and anaerobic bacteria, fungi, and yeasts), and should be conducted in addition to the QA and QC testing carried out on each batch.

Assignment of extended expiry dates to chemotherapy infusions for dose banding must be made by an experienced pharmacist with a clear understanding of both clinical and pharmaceutical issues. In the case of infusions purchased from an outside supplier, the designated pharmacist at the purchasing hospital has a legal and professional responsibility to ensure that the supplier has assessed stability to an appropriate standard and that the results of stability studies are fully compliant with the infusion specification and the shelf-life and storage condition assigned.

### 28.11 Future developments in dose banding

The emergence of collective approaches to dose banding, where multiple institutions agree to use identical dose banding schemes, will lead to the realisation of the full potential of dose banding. This approach enables regional collaboration among groups of hospitals to rationalise their cytotoxic compounding activities, enable each institution to focus on a limited range of batch-produced infusions or syringes, and contribute to a regional pool providing a comprehensive cytotoxic compounding service. Efficiency can be improved and prospective QC, subject to adequate extended stability data, will enhance efficacy and patient safety.

A more widely implemented scheme across one or more countries would require the provision of large number of identical standard infusions and syringes. This scale of requirement would encourage commercial compounding units to enter the market and, in those cases where sufficient extension of shelf-life is possible, encourage the pharmaceutical industry to provide a range of licensed, ready to use standard infusions or pre-filled syringes. Such development should not be seen as a threat to hospital pharmacy compounding units, but rather viewed as complementary. This has certainly been the case in the UK. Outsourcing to commercial compounding units has been practiced for many years, yet hospital pharmacy units remain as busy as ever. Pharmacy units have been able to devote a greater proportion of their resource to more complex aseptically compounding work, such as clinical trials and targeted therapies, while outsourcing some of their routine cytotoxic compounding needs.

An example of a national scheme is the national dose banding tables produced by NHS England (NHSE).<sup>12</sup> These were introduced 18 years after the first UK dose

banding scheme was implemented and embrace virtually all cytotoxic drugs used in cancer chemotherapy. This scheme is predicated on a maximum of 6% deviation of the banded dose from the calculated dose and has recently been validated in the peer-reviewed scientific literature.<sup>11</sup> The NHSE scheme also includes a large number of monoclonal antibodies. Hospitals in England are strongly encouraged to use these common tables. In addition to the benefits already discussed, the scheme will ensure that oncology staff moving from one hospital to another will already be familiar with the chemotherapy dosing scheme. The NHSE initiative has support at the highest level in NHS Cancer leadership.<sup>11</sup> It is seen as facilitating the strategic ambition of enabling some cancer treatments to be administered in the primary care setting.

The application of dose banding to targeted therapies such as MABs is another important ongoing development. This has been facilitated by the extension of shelf-lives of diluted MABs.<sup>21,22</sup> The NHSE dose banding tables<sup>12</sup> cover a wide range of MABs, including cetuximab, trastuzumab, rituximab, bevacizumab, and panitumumab. For MABs, the NHSE tables permit a wider maximum variation (+10%) from the calculated dose. Coupled with extended shelf-life, there are opportunities for significant reductions in drug wastage with these expensive medicines.

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## Section 29 – Safe handling of hazardous drugs in research facilities

### 29.1 Definitions and scope

An academic research facility (ARF) is defined as any university where cytotoxic agents, classified as hazardous, are manipulated, temporarily or permanently, to investigate and enhance drug properties. A cytotoxic academic research center (CAR) is an ARF dedicated to hazardous agents.

This section addresses ARFs that are not CARs. The handling of anticancer agents at industry research facilities is not within the scope of this section.

### 29.2 Background

Anticancer agents are used extensively to treat cancer and nonmalignant diseases by inhibiting proliferation of rapidly dividing cells. Because these agents are non-selective, healthy cells are also usually affected. The possibility of cure or remission typically outweighs the risk of adverse effects on healthy cells.

Occupational exposure to anticancer agents poses a serious health risk to workers. Exposure continues to be documented in the literature despite the use of guidelines for safe handling practices.

Studies using wipe samples to detect and quantify contamination of workplaces with anticancer agents have been performed across Europe and the US. One such study is the Monitoring-Effect Study of Wipe Sampling in Pharmacies (MEWIP), aimed at identifying contamination levels at 130 randomly selected hospitals in Germany. These hospitals frequently handled cyclophosphamide, etoposide, 5-fluorouracil, ifosfamide, gemcitabine, methotrexate, paclitaxel, and docetaxel. The analysis identified drug contamination in 774 of 1269 samples (61%). The study concluded that it is difficult to eliminate contamination despite monitoring and improvement of safety practices.

Efforts to control and educate on occupational exposure are increasing with the rise in the use of these agents. However, there are no guidelines for how anticancer agents should be handled in ARFs specifically. Guidelines authored by ISOPP and others pertaining to clinical settings are not considered sufficient for ARFs. In the absence of a

safe threshold of exposure to cytotoxics, there is an urgent need to assess current practices at research facilities.

In a recent study conducted in the United Kingdom, a survey of 39 university health and safety officers revealed a major gap between current acceptable safety measures and ARF practice. Cleaning staff were generally not informed of required cleaning practices. Staff at the reception point were not trained on the risk of handling parcels containing anticancer agents and were not always aware they were handling such parcels. Personal protective equipment (PPE) was underutilised: gloves 94.9%, goggles 87.2%, impermeable gowns 59%, shoe covers 41%, and masks 25.6%.

In light of these disappointing results, a working group of experts from academic, clinical, and research settings was assembled. The working group scrutinised the trajectory of anticancer agents within ARFs.

This section summarises the recommendations generated by this working group. These should be used in conjunction with ISOPP standards of practice, which cover additional guidance related to ventilation, standard hygiene, PPE, closed-system drug transfer devices (CSTDs), and other topics relevant for ARFs.

Recommendations are summarised under the following headings:

- (a) receipt and stocking of agents;
- (b) access;
- (c) cleaning.

### 29.3 Receipt and stocking

Request that the supplier of the agents label the packaging as hazardous to alert staff at the reception point. The parcel will then be handled with caution and stored in the proper allocated space.

Coach the staff on anticancer agent hazards and the use of PPE and spill kits. The staff must be aware of the hazards associated with anticancer agents and prepared to handle incidents appropriately.

Advise the staff of expected deliveries to ensure that the staff on call at the time of delivery is equipped and able to handle hazardous parcels.

Implement a stock management system. Researchers can note amounts of each agent used and remnants to discard. Ordering can coordinate the needs of multiple researchers using the same agent, minimising ordered vials and waste. Health and safety officials can track exposure of researchers to the agents.

Provide a dedicated refrigerator and storage space for anticancer agents in a low-traffic area to minimise contamination from spills. Label the space “Cytotoxic” or “Hazardous.”

## 29.4 Access

Ensure access is restricted. Clearly visible, simple signage on doors should warn of the hazard and alert domestic and maintenance staff that they should not enter without supervision.

Use temporary signage to alert researches and maintenance crew to areas of exceptional handling of anticancer agents.

Engineers, carpenters, and maintenance staff accessing the lab for safety checks and services should be accompanied by a trained lab member and should take place when the lab is not engaged in an ongoing experiment. The visit should be documented, appropriate PPE used, and contaminated waste such as spent filters properly disposed of.

Define a standard operating procedure and reporting system for exposure incidents.

## 29.5 Cleaning

Define standard procedures for cleaning, including approved cleaning agents, to ensure that surfaces are decontaminated properly and thoroughly at specified times.

Delineate dedicated workbenches where anticancer agents are handled. Clean surfaces daily with water and detergent soap.

Implement an instrument-specific cleaning regimen to guarantee that parts of an instrument (such as an injector or high-performance liquid chromatography (HPLC) column) that come into direct contact with anticancer agents will be decontaminated and safe for the next user.

Cover buttons and keyboards of instruments and computers used near anticancer agents. Alternatively, wipe them thoroughly after use.

Label eluent waste bottles as cytotoxic and discard them accordingly.

Make a spill kit available.

## 29.6 Animal testing

Animal testing in laboratories is governed by guidance published by several national and international bodies.<sup>3</sup> Experiments with anticancer agents are often conducted in these labs. Excrement and carcasses of animals treated with anticancer agents should be discarded as cytotoxic waste. The ISOPP standards of practice regarding laboratory access, use of PPE, cytotoxic waste disposal, and other applicable issues must also be implemented. The stricter of the ISOPP Guidelines or the applicable national or international guidance should be applied.

## 29.7 Conclusion

The handling of anticancer agents in ARFs is a frequent practice. Guidelines have been put forward to help ensure the safety of researchers and the work environment in ARFs and to prevent and manage hazardous exposure. It may also be prudent to conduct periodic audits of the handling of anticancer agents and provide feedback that can be used to improve this guidance.

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## Section 30 – Glossary

Term	Definition
Anteroom	Clean area for donning personal protective equipment that precedes the buffer zone
Anticancer drug	A drug used to treat cancer
Antineoplastic drug	A drug that prevents, halts or inhibits the development of a neoplasm (tumour)
Beyond-use date (BUD)	Either the date, or hour and date, after which a compounded product must not be used. The BUD is determined from the date/time that preparation is initiated
BSC	Biological Safety Cabinet. An enclosed, ventilated workspace used to protect personnel against biohazardous or infectious agents and maintain quality control of the material being worked with. BSCs are classified into classes I, II, and III depending on the level of protection provided
Buffer zone	area in which the cleanest work surface (ventilation tool) is located
C-SEC	Containment-Secondary Engineering Control. A C-SEC incorporates specific design and operational parameters required to contain the potential hazard within the compounding room
CACI	Compounding Aseptic Containment Isolator. A CACI is a specific type of compounding aseptic isolator that is designed for the compounding of sterile hazardous drugs
CDSC	Cytotoxic Drug Safety Cabinet. An enclosed, ventilated workspace to provide an aseptic environment and containment of cytotoxic materials. CDSCs are a type of BSC
Chemotherapy	A drug(s) used to stop the growth of cancer cells
Clean room	Area designated for preparing sterile products; a room in which the concentration of airborne particles is controlled by minimising the introduction, generation, and retention of particles
Cleaning	A process that results in the removal of contaminants (e.g. soil, microbial contamination, HD residue) from objects and surfaces using water, detergents, surfactants, solvents, and/or other chemicals. Cleaning agents used on compounding equipment should not introduce microbial contamination.
Closed-system drug-transfer device (CSTD)	A drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapour concentrations outside the system <sup>43</sup>
Cytostatic	A substance that stops or slows the growth of cancer cells without killing them
Cytotoxic	A substance that kills cells
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, neutralisation, or removal of toxic agents, usually by chemical means
Detergent	Cleaning agent with wetting and emulsifying (tensioactive) properties
Disinfect	Destroy pathogenic microorganisms or inhibit their growth and vital activity
Formulary	A list of brand-name and generic prescription and non-prescription drugs that are approved to be prescribed by a health insurance policy or in a specific health system or hospital
Medication access program	A program offered by a pharmaceutical company to facilitate access to a drug, including compassionate access and cost-share arrangements
Non-shedding, non-linting, low-lint, or lint-free	Materials that generate a low number of particles
Personal protective equipment (PPE)	Equipment worn to ensure the sterility of the end product and protect the operator
Prescription	Written directions provided by a prescribing practitioner for a specific medication(s) to be administered to an individual. This may be in electronic or handwritten format
Sanitise	Free from dirt and germs by cleaning
Standard operating procedure (SOP)	A set of step-by-step instructions compiled by an organisation to help workers carry out complex routine operations
Sump	Chamber at the bottom of a machine into which wastes gather before disposal
Wiper	Towel, sponge, gauze, cloth, or other item used to wipe