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Safe Handling of Hazardous Drugs

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An assessment conducted in December 2023 deferred the review of Guideline 16-3 Version 3. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

Guideline 16-3 Version 3 is comprised of 5 sections. You can access the summary and full report here: <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2161>

Section 1: Guideline Recommendations
Section 2: Recommendations and Key Evidence
Section 3: Guideline Methods Overview
Section 4: Systematic Review
Section 5: Internal and External Review

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Table of Contents

Section 1: Recommendations.....	1
Section 2: Guideline - Recommendations and Key Evidence.....	17
Section 3: Guideline Methods Overview.....	37
Section 4: Systematic Review	41
Section 5: Internal and External Review	61
References	71
Appendix 1: Affiliations and Conflict of Interest Declarations.....	75
Appendix 2: Literature Search Strategy	77
Appendix 3: PRISMA Flow Diagram	80
Appendix 4: Technique for donning and doffing one pair of gloves (67)	81
Appendix 6: Guideline Document History.....	83

Safe Handling of Hazardous Drugs

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see [Section 2](#).

RECOMMENDATIONS

Recommendation 1: General Measures

Committee Responsible for Policy and Procedures for Hazardous Drugs

It is strongly recommended that all institutions administering hazardous drugs form such a committee. It is also strongly recommended that this committee include, but not be limited to, representatives from various departments and services such as: occupational health and safety, joint health and safety committee, pharmacy, nursing, medical oncology (physician), environmental services, risk management, and a patient representative.

This committee would be responsible for clear processes of developing, reviewing, and revising policies and procedures related to hazardous drugs. A risk assessment and gap analysis should be routinely conducted to identify gaps and to inform policies and procedures. In addition, this committee is responsible for ensuring that there is a process in place for orientation and ongoing education for the identified target population.

This committee is responsible for implementation and follow-up of the Risk Prevention Management Program related to the use of hazardous drugs.

Continuing Education and Orientation Program

It is legislated that initial and ongoing hospital-approved education be provided to all staff involved with hazardous drugs throughout the medication circuit including safe handling and spill or leak management (6). It is strongly recommended that all staff have initial and ongoing training related to best practice standards in place at the time.

It is legislated that there is documentation that annual training of safe handling of hazardous drugs has occurred (6). This should be documented by the institution's Committee Responsible for Policy and Procedures for Hazardous Drugs

Identification and Safety

It is strongly recommended that each institution maintain a list of hazardous drugs that are used in their facility, that is reviewed regularly, when policy is updated, and whenever a new agent or dosage is used (7).

It is legislated that hazardous drugs and their waste be properly identified with the symbol capital "C" and, under it, the words "CYTOTOXIC/CYTOTOXIQUE" in capital letters (8, 9). It is legislated that all hazardous waste under the Ministry of Environment, Conservation and Parks regulation (guideline C-4) include bilingual wording and both the words and the symbol appear on a dark grey rectangle (8, 9). Other countries may have their own systems for labeling and should be adhered to.



Purchasing of Drugs

When purchasing hazardous drugs, it is strongly recommended that institutions consider vendors that include safe handling measures such as pre-wiped or protective containers, or smaller receptacles to decrease volume of potential spills.

Spills Kit

It is strongly recommended that a spill-management kit be available in all areas where hazardous drugs are stored, transported, handled, and administered (10).

Precautionary Reassignment

It is strongly recommended that all staff be fully informed of the potential reproductive hazards of hazardous drugs (11).

It is strongly recommended that the facility consider alternative duties for staff who are pregnant, breast feeding or actively trying to conceive.

Recommendation 2: PPE

It is legislated that a worker work in compliance with the Occupational Health and Safety Act and regulations and use or wear the equipment, protective devices, or clothing that the employer requires to be used (1).

It is legislated that the appropriate PPE for the task (as described in Table 2-1) be worn throughout the medication circuit (1). It is the employer's responsibility to provide the necessary protective equipment and training on how to use the equipment.

Gloves

The gloves used to handle hazardous drugs are strongly recommended to comply with ASTM standard D-6978-(05)-13 and be powder free (12). Gloves are recommended to be nitrile, polyurethane, neoprene, or latex (12). Latex is a known allergen; therefore, it is strongly recommended that this be taken into consideration for glove selection. It is strongly recommended that vinyl gloves not be used (13). It is strongly recommended that the frequency of glove changes be adjusted according to the level of exposure at each step in the medication circuit. For example, when administering reconstituted medications, it is strongly recommended that workers change gloves immediately if torn, punctured, or visibly contaminated with a hazardous drug, and to ensure following Routine Practices (14). Gloves should be changed every 30 minutes unless otherwise recommended by the manufacturer's documentation (7, 10). It is strongly recommended that great care be taken in the removal of gloves to not contaminate the skin. When two pairs of gloves are required, put on the first pair before putting on the gown. See Appendix 4 for the donning and doffing of one pair of gloves and Appendix 5 for the donning and doffing of two pairs of gloves.

Gown

It is strongly recommended that the gowns used for handling hazardous drugs be disposable, made of lint-free, low-permeability fabric, have long sleeves with tight-fitting cuffs and fasten in the back. Gowns need to be changed in the event of contamination, spillage, rips, and at the end of the procedure. It is strongly recommended that the supplier be able to certify that the gown protects against hazardous drugs (10).

For medication preparation and administration, gowns need to be changed halfway through a shift or every 3 and a half hours (7, 10).

It is strongly recommended that care be taken to avoid contamination of the hands by avoiding touching the outside of the gown when removing the gown.

Facial Protection

Surgical/procedure masks are required while handling and preparing medications in a BSC and, in this instance, are worn to prevent microbial contamination of the sterile field.

Goggles and a face shield or full face-piece respirator should be worn when there is a risk of spills or splashes of hazardous drugs or hazardous waste materials when working outside of a BSC such as administration of hazardous drugs in the surgical suite, working at or above eye level, or cleaning a spill (7, 10).

Head and hair coverings (including beard and moustache, if applicable), and sleeve covers provide protection from contact with hazardous drug residue. Disposable sleeve covers may be used to protect areas of the arm that may come in contact with hazardous materials. Disposable sleeve covers made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials (7).

It is strongly recommended that full-facial protection be worn whenever there is a risk of splashing (e.g., during certain drug administration procedures). The use of a full-facial shield is preferred. If goggles are used, they need to be worn in conjunction with a fluid-resistant mask. For further information, see *Canadian Standard Association (CSA) standard Z94.3-07 - Eye and Face Protectors* (15). 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 (7).

Respiratory Protection Devices

It is strongly recommended that fit-tested respirators such as NIOSH-certified N95 or N100 be used when there is a risk that airborne powder or aerosol will be generated. It is legislated that respirators be used in accordance with a respiratory protection program such as that outlined in *CSA Standard Z94.4-18 "Selection, Use and Care of Respirators"* (16).

Caps

Caps are only required in the sterile preparation room and are worn to prevent microbial contamination of the sterile field.

Shoe Covers

Disposable shoe covers are worn to prevent contamination of the healthcare workers' shoes, and it is strongly recommended that they be worn when in the sterile preparation room or in the event of a spill. It is strongly recommended that shoe covers be removed immediately when leaving the sterile prep room to avoid contamination of other areas. When compounding hazardous drugs, a second pair of shoe covers must be donned before entering the Containment Secondary Engineering Control (C-SEC) and doffed when exiting the C-SEC (7, 10).

Table 2-1. Personal protective equipment to be worn throughout the medication circuit

Medication circuit steps	Gloves	Gown	RPD	Facial protection	Cap	Shoe covers
Unpacking and cleaning	✓ (2 pairs)	✓	✓ (Only if unpacking hazardous drugs that are not contained in plastic until assessment of the packaging integrity can be made)			
Sterile preparations	✓ (2 pairs)	✓		✓	✓	✓ (2 pairs)
Non-sterile preparations: - Counting of solid oral forms	✓ (1 pair)	✓				✓
Non-sterile preparations: -Preparing creams, ointments, oral solutions and crushing tablets	✓ (2 pairs)	✓			✓	✓ (2 pairs)
Routes of administration (intravenous, subcutaneous, intramuscular, intravesical, intraperitoneal, intrathecal, liquid oral)	✓ (2 pairs)	✓		✓ (If risk of splashing, e.g., bladder installation or NG, G, or J tube)		
Solid oral administration (tablets)*	✓ (1 pair)					
Topical administration	✓	✓		✓		

Medication circuit steps	Gloves	Gown	RPD	Facial protection	Cap	Shoe covers
(creams, ointments)	(2 pairs)			(If risk of splashing)		
Aerosolized administration (e.g., ribavirin, pentamidine) [†]	✓ (2 pairs)	✓	✓	✓ (If risk of splashing)		
Patient care	✓ (1 pair)	✓ (When at risk for exposure for bodily fluids)		✓ (If risk of splashing, e.g., disposal of bodily fluids)		
Management of extravasation	✓ (2 pairs)	✓		✓ (If risk of splashing)		
Handling of contaminated bedding on the wards	✓ (2 pairs)	✓				
Waste management (collection and transport)	✓ (2 pairs)					
Spill or damaged or broken container	✓ (2 pairs)	✓	✓ (If suspicion of powder or aerosolization is generated)	✓		✓ (If on the floor)
Cleaning of sterile preparation room and airlock	✓ (2 pairs)	✓			✓	✓ (2 pairs)
Cleaning of preparation cabinets (hoods)	✓ (2 pairs)	✓	✓	✓	✓	✓
Cleaning of other oncology pharmacy rooms and care units/clinics	✓ (1 pair)	✓				

Abbreviations: G = gastric tube, J = jejunostomy tube, NG = nasal gastric tube, RPD= respiratory protection device.

*Although the risk of contamination with oral medications is minimal, the Working Group members believe that consistency of practice for any handling of hazardous drugs is of primary importance, and the preference is to wear a standard chemotherapy glove.

† Although hazardous, they are not cytotoxic

Recommendation 3: Receiving and Transport

Handling Hazardous Drug Delivery Containers

It is strongly recommended that all receiving-dock workers receive training in the proper handling of hazardous drugs. It is strongly recommended that the receiving-dock workers check the integrity of the external packaging upon receipt; in the event of breakage or a damaged parcel likely to cause a spill, apply the Spill Protocol from your institution.

It is strongly recommended that delivery containers be taken immediately to the Pharmacy Department by the receiving-dock workers or the distributor.

It is strongly recommended that the receiving-dock or storeroom workers not open the delivery containers. It is strongly recommended that the delivery containers be handled with care to avoid breakage of the hazardous drug containers and not be left unattended in a corridor. Only trained workers (e.g., pharmacy technicians) are to proceed with the unpacking and subsequent steps.

Damaged Containers/Spill

It is strongly recommended that damaged containers be handled like spills. It is strongly recommended that the manufacturer or distributor be notified if the container is received in a damaged state. To limit exposure, it is strongly recommended that a damaged container not be returned to the manufacturer or distributor unless they require it returned. The damaged container will need to be returned in an impervious box. Notify the pharmacy if any damaged containers are suspected (7).

See *Recommendation 10: Management of Waste, Accidental Exposure, Spills and Returns.*

Recommendation 4: Unpacking and Storage

Packaging can have high levels of contamination. It is strongly recommended that there be an unpacking area in the pharmacy limiting exposure risks. It is strongly recommended that the unpacking area be a separate dedicated space, separate from eating areas, and preferably a separate room. It is regulated that there be adequate ventilation in the area, negative pressure, and preferably vented to the outside. It is strongly recommended that there be a receptacle for hazardous waste in the unpacking area, for the disposal of secondary packaging (6, 10, 17).

It is strongly recommended that workers at risk of exposure wear a protective gown and two (2) pairs of gloves when unpacking and cleaning hazardous drugs, from the opening of the external packaging to the placing of the secondary and/or primary packaging in their storage space. It is strongly recommended that workers check the integrity of all packaging at every step of the unpacking process. In the event of breakage or leaking, it is strongly recommended that the damaged contents be treated as a spill. It is strongly recommended that the primary and or secondary packaging be cleaned prior to being placed in storage.

It is strongly recommended that a regular cleaning protocol be in place either at this stage or prior to storage in the clean room. It is strongly recommended that all drug containers be cleaned to reduce external contamination. An example is the use of pre-moistened towelettes. It is important to ensure that the procedure does not damage the container or interfere with the reading of the label. It is also important to ensure than any product that is used will not further contaminate the product or work environment. However, it is strongly recommended that this procedure not increase the risk of incidents/accidents due to damage to the hazardous drug container or label.

It is strongly recommended that procedures be in place to minimize the risk of contamination of surfaces during the cleaning of vials (e.g., use of a disposable, plastic-backed, absorbent pad). It is strongly recommended that all surfaces be cleaned when the task is complete.

Establish a dedicated negative-pressure storage area for hazardous drugs that minimizes the risk of contamination (10).

When removing or transporting drugs out of the storage area, it is strongly recommended that one pair of gloves and a gown be worn and a spill kit be readily available.

Recommendation 5: Planning the Oncology Pharmacy

It is strongly recommended that the oncology pharmacy be in compliance with relevant guidelines from the Canadian Society of Hospital Pharmacists and Accreditation Canada standards. While the specific details of oncology pharmacy planning are beyond the scope of this document, details and some important considerations may be found in the National Association of Pharmacy Regulatory Authorities (NAPRA) guideline and *CSA document CSA Z8000-11* (5, 10, 18).

It is strongly recommended that special requirements for heating, ventilation, and air-conditioning systems in healthcare facilities be taken into consideration (10, 17).

A class II type B BSC is required with preference for the type B2 because it ensures that there is no recirculation of air within the cabinet (4, (5, 10).

There is emerging evidence suggesting some robotic devices that prepare hazardous drugs improve the accuracy of medication preparation and reduce potentially harmful staff safety events. Further studies are required to establish the cost effectiveness of these robotic implementations. Each healthcare facility will need to assess the need for such devices in their environment (5,19-21, 31).

It is strongly recommended that all mixing, and preparation of administration sets with a hazardous drug be performed in one centralized area in a specially designated class II type B BSC (17) that:

- a. is exhausted through a HEPA filter to the outside atmosphere in a manner that prevents recirculation into any inside area;
- b. has exhaust and ventilation systems that remain in operation for a sufficient period of time to ensure that no contaminants escape from the BSC into the workplace; and
- c. is equipped with a continuous monitoring device to permit confirmation of adequate airflow and cabinet performance.

It is recommended that airlocks be considered if there are particular concerns about the propagation of airborne hazardous drugs.

It is strongly recommended that priming of administration sets be prepared in the manner mentioned above.

It is strongly recommended that the layout allow and facilitate the unimpeded cleaning of all surfaces (walls, floors, ceilings, doors, diffusers, windows). It is strongly recommended that the furniture and equipment in the sterile preparation room be kept to a bare minimum.

It is strongly recommended that there be a visual link; for example, a sealed window and a way to communicate between the sterile preparation room and the pharmacy, to view the work in progress. It is strongly recommended that access to the sterile room be limited to trained and authorized workers (10). A pass-through window can be installed to minimize the risk of contamination when transferring products into and out of the clean room. The pass-through should be equipped with an interlocking system or procedure that prevents both doors from being open at the same time (10)

Limit worker traffic, particularly near unpacking and storage areas (to avoid accidental breakage) and near preparation cabinets (to avoid interfering with their proper operation).

It is legislated that the facilities include an emergency eyewash that may or may not be hooked up to the airlock sink (1). As a minimum, it is strongly recommended that emergency eyewash be able to provide 15 minutes of flushing to both eyes (22). It is strongly recommended that a full shower be accessible nearby (e.g., in the oncology units/clinics).

Closed system drug-transfer devices (e.g., PhaSeal®) are not a substitute for class II type B BSC. There is evidence from studies (23-30, 32-42, 57,58) that closed system drug-transfer devices can reduce contamination during preparation and increase or extend the beyond use date of a drug. Further emerging evidence suggests that when these devices are not used as specified, they could become open to the environment. Further research is needed to evaluate this possibility.

In the non-sterile drug preparation process (e.g., oral preparations), it is strongly recommended that the same level of worker protection be adhered to.

Pharmacy Policies and Procedures

Establish policies and procedures regarding preventive maintenance, monitoring, certification and the optimal use of facilities and equipment (45).

Recommendation 6: Hazardous Drug Preparation

The following recommendations apply but are not limited to the preparation of all hazardous medications including parenteral, oral, and topical, both sterile and non-sterile preparations. It is strongly recommended that policies and procedures include the use of appropriate PPE, the equipment for preparation including appropriate ventilation, and other automated equipment for packaging and a dedicated work area.

PPE

It is strongly recommended that workers (pharmacists or pharmacy technicians) wear a cap, surgical/procedure mask, shoe covers, a protective gown and two (2) pairs of gloves (see Table 2-1) to make sterile preparations of hazardous drugs in preparation cabinets.

Organization of the Work

Organize the work to limit microbial and environmental contamination.

For both sterile and non-sterile preparations, it is strongly recommended that workers cover the work surface with a disposable, absorbent, sterile, plastic-backed pad to absorb any liquid contamination that may occur during handling. It is strongly recommended that the

pad not cover the front and rear grilles of the preparation cabinet. It is strongly recommended that it be changed after 3.5 hours of continuous work or for a new batch of preparations (e.g., a set of vials of a given drug) or in the event of a spill or contamination (13). It is legislated that the pad be disposed of in a hazardous waste receptacle (7, 9).

Limit the quantity of supplies and hazardous drugs in the cabinet, to avoid adversely affecting the laminar flow and to facilitate regular cleaning of the work surface. Place the sterile products in the centre and the non-sterile products (e.g., waste receptacle) along the sides of the cabinet.

Removal of Packaging

Remove the packaging, when applicable, and clean all the drug containers before taking them into the preparation cabinet. For sterile preparations, adhere to aseptic technique for sterility.

Handling Techniques

Use handling techniques that limit the risk of injury or accidental exposure. Direct CSTD spikes can be used to connect the hazardous medication bag directly to the tubing if spiking must occur at the bedside. When this adaptor is not used, IV bags containing hazardous drugs should only be spiked in a BSC to prevent exposure.

Preparation, Priming and Removing Air from the Tubing

It is strongly recommended that hazardous drugs be reconstituted in the pharmacy environment as described above. It is strongly recommended that the drug containers not be overfilled to avoid compromising the integrity of the container. It is strongly recommended that the techniques used for priming and removal of air minimize the exposure risks. It is recommended to only remove air from an IV tubing that does not contain a solution with a hazardous drug(s). It is strongly recommended that IV tubing is primed and air removed in the pharmacy, prior to adding the hazardous drug(s) to the infusion solution. Glass containers are not recommended due to increased risk of breakage and exposure.

Labeling and Final Packaging

It is legislated that hazardous drugs be labeled to inform those handling these preparations of the nature of the drugs and the precautions to be taken. It is legislated that hazardous drugs display the “Cytotoxic” hazard symbol or the word “Cytotoxic” (8, 9).

It is strongly recommended that the outside surface of the hazardous drug containers (e.g., syringes, infusion bags, tubing) in the preparation cabinet be cleaned in the cabinet.

Place each hazardous drug container (e.g., syringe, bag), as well as the administration supplies (e.g., tubing), in a clear, leak-proof plastic bag (e.g., Ziploc® type) to facilitate identification by the nurse without having to remove the container from the bag.

Following final verification in the pharmacy, it is strongly recommended that the plastic bags containing the hazardous drugs be placed in a rigid *transport container* (ideally opaque), properly identified with the “Cytotoxic” hazard symbol (7, 10).

Waste

It is strongly recommended that everything that comes out of the cabinet be wiped clean.

It is strongly recommended that all contaminated waste be disposed of in the chemotherapy waste stream.

Recommendation 7: Transport and Storage Following Preparation

On-site Transport of Hazardous Drugs

Transport hazardous drugs using a method that will prevent contamination of the environment in the event of breakage.

It is strongly recommended that hazardous drugs be placed in a closed, single-use leak-proof plastic bag (e.g., Ziploc® type).

It is strongly recommended that transport of the hazardous drug in a single-use closed, leak-proof plastic bag from the pharmacy to an area not adjacent to the preparation area (e.g., care unit, outpatient clinic), be done in a rigid, shock-resistant, leak-proof container made of a material that can be easily cleaned and decontaminated in the event of a drug leak (5). It is strongly recommended that the bottom be covered with an absorbent, plastic-backed cloth.

It is legislated that the transport container be identified with the “Cytotoxic” hazard symbol and be cleaned regularly (8, 9). This container should be cleaned according to the protocol outlined by a committee responsible for hazardous drug handling.

It is strongly recommended that mechanical transport systems, such as pneumatic tubes, not be used because of the stress they put on the contents, and the whole transport system would be compromised if a leak occurred (5, 7).

It is strongly recommended that prepared medications be stored in a designated area prior to administration. It is strongly recommended that this area be cleaned regularly.

Off-site Shipping and Transport of Hazardous Drugs

Establish policies and procedures regarding the shipping of hazardous drugs (46).

In the event that hazardous drugs are shipped off-site (e.g., from one institution to another), it is strongly recommended that they be packed separately from other drugs, according to the recommendations from the manufacturer and distributor. It is strongly recommended that pharmacy be consulted in the packaging of hazardous drugs.

It is strongly recommended that hazardous drugs be packed in a double plastic bag and placed in a box that is properly identified with the “Cytotoxic” hazard symbol. If necessary, immobilize the drug with packing (5) material. It is legislated that the “Cytotoxic” hazard symbol be visible on the outside of the delivery (8) container. It is strongly recommended that reusable delivery containers be cleaned regularly.

Ensure that the courier company will handle hazardous drugs.

Recommendation 8: Drug Administration

It is strongly recommended that safe handling and administration techniques be used to minimize possible exposure to individuals and the environment when administering hazardous drugs.

- It is legislated that appropriate PPE be made available to all healthcare workers and be worn as prescribed by the employer (Table 2-1) (1).
- It is strongly recommended that Luer lock connectors and needleless administration systems be used to administer any IV medications.
- Closed system drug-transfer devices may offer additional protection.
- It is strongly recommended that disposable plastic-backed absorbent pads be used over work surfaces and placed under tubing or bag connections and ports when attaching any tubing, bag or syringe that has been exposed to a hazardous drug.
- Unless a closed system is used, never disconnect tubing from hazardous drug bags. Discard bag with attached tubing into an appropriate waste container as a single unit.
- It is legislated that safety engineered needles be used as per Needle Safety Regulation 474/07 made under the Occupation Health and Safety Act Labour, 2010 (47). Do not purge air from the needle before administration.
- It is strongly recommended that oral hazardous drugs be handled in a manner that avoids skin contact, liberation of aerosols or powdered medicine into the air, and cross-contamination with other (48) medicines.
- It is strongly recommended that solid oral preparations (tablets) of hazardous drugs be crushed or cut within the BSC. If patients are unable to take in the solid format, it is strongly recommended that the pharmacy provide these drugs in an oral syringe or dissolve and dose container, in a ready-to-administer, liquid oral form.
- It is strongly recommended that application of topical hazardous drugs be done using appropriate PPE and in a way that prevents contamination of the environment. Between applications, it is strongly recommended that the hazardous medication (i.e., tube or jar) be kept in a safe container (i.e., Ziploc®) and in a secure place that prevents contamination of the surrounding environment.
- With any intravesical administration, e.g., bladder instillation, ensure there are detailed procedures in place to avoid risks of splashing.
- Use caution when administering intrathecal hazardous drugs, as there is risk of splashing due to increased intrathecal pressures. A closed system (i.e., Luer lock) should be used when possible.

Recommendation 9: Home Care

Home Care of Patients who Have Received Hazardous Drugs

It is strongly recommended that all hazardous drug preparations be compounded in pharmacies meeting the requirements for hazardous drug preparation (5).

It is strongly recommended that hazardous drugs be transported, administered and disposed of by individuals who have received appropriate training. It is strongly recommended that hazardous drug transport containers are not reused by patients for domestic purposes, which may expose the family to cytotoxic drugs (e.g., toy box, sewing basket, etc.).

It is legislated that the healthcare provider who administers hazardous drugs in the home wear PPE as outlined in Table 2-1 (1).

It is strongly recommended that healthcare providers follow the same recommendations outlined in *Recommendation 8 - Drug Administration*

It is strongly recommended that a spill kit be readily available in the home in case of accidental spills.

It is strongly recommended that patients be informed of and be provided with written instructions and PPE for the safe handling of hazardous drugs.

It is strongly recommended that contact information be provided for home care patients who require assistance with safe handling of hazardous.

Hazardous Drug Waste in the Home

It is strongly recommended that the institution have a clear process to address the issue of hazardous waste from patients in their homes, in compliance with municipal or local hazardous waste rules. It is strongly recommended that this process include patient and caregiver education.

It is strongly recommended that caregiving staff provide the patients/caregivers involved in administering cytotoxic drugs in the home with a process for appropriate disposal of hazardous waste, including leftover drugs.

Recommendation 10: Management of Waste

Bodily Fluid Waste

It is strongly recommended that workers who handle the biological fluids, excreta, contaminated bedding, and soiled equipment of patients who have received hazardous drugs wear two (2) pairs of gloves and a protective gown. It is strongly recommended that face protection be worn when there is a risk of splashing.

Cytotoxic Drug Waste

Establish policies and procedures as per provincial legislation regarding hazardous waste management.

The term “hazardous waste” includes any material that comes into contact with hazardous drugs during their storage, handling, preparation, administration and disposal (e.g., packaging material, protective equipment, preparation supplies, such as syringes, tubing, drug bags; soiled disposable incontinent briefs of patients who have received hazardous drugs during the previous 48 hours or longer depending on the drug [e.g., it is known that cyclophosphamide may persist for several days]; hood pre-filters and HEPA filters, etc.).

It is legislated that hazardous waste be placed in a waste container clearly identified with the “Cytotoxic” hazard symbol. It is legislated that hazardous waste be disposed of in the appropriate containers (9).

It is legislated that sharps be placed in rigid containers with a leak proof lid; CSA standard Z316.6--07 specifies the use of the colour red for the rigid containers (49). If the containers are another colour, follow the instructions of the company ensuring the final disposal (9).

It is strongly recommended that other waste (soft items, such as tubing, protective equipment, etc.) be placed in leak-proof and tear-resistant containers, identified with the “Cytotoxic” hazard symbol (7).

For final disposal outside the institution, it is legislated that all hazardous waste be in a rigid, leak proof, container identified with the “Cytotoxic” hazard symbol and scheduled for transport outside the institution (9).

It is legislated that any excess fluid from hazardous drugs (e.g., drug loss) be disposed of in a sealed container and placed in a rigid container, the bottom of which is to be covered with an absorbent pad. This rigid container will be handled like other hazardous waste (9).

It is recommended that disposable/incontinent briefs soiled by patients who have received hazardous drugs be placed in a hazardous waste container.

It is legislated that hazardous waste be incinerated according to ministry guidelines (9, 50).

It is legislated that hazardous waste not be disposed of in the receptacles used for infectious biomedical waste (which may be autoclaved and then sent to a landfill site) (9).

It is legislated that every area where hazardous drugs are handled will have an appropriate hazardous waste receptacle as close as possible to the work area (9).

The lids of hazardous drug receptacles must remain closed, except when depositing waste. Bins with foot pedals and lids, which lock automatically when full, are recommended to minimize exposure.

It is strongly recommended that workers be careful to avoid contaminating the outside of the receptacle when depositing waste.

It is legislated that the transport of hazardous waste receptacles be assigned to properly trained workers (6).

It is strongly recommended that workers who handle hazardous waste receptacles wear two pairs of disposable gloves and have a spill kit at their disposal. It is strongly recommended that the waste go through as few care units, public areas and areas containing food or linens as possible.

It is legislated that the final storage areas for hazardous waste receptacles be secure. Refer to Ontario storage (8, 9) requirements.

Recommendation 11: Accidental Exposure

Be aware of any mandatory reporting requirements under the Occupational Health and Safety Act and report requirements to Workplace Safety and Insurance Board (WSIB) (6).

Establish policies and procedures regarding accidental worker exposure.

If a hazardous drug accidentally comes into contact with a worker's skin or clothing, it is strongly recommended that the worker immediately remove the contaminated clothing and thoroughly wash the skin of the affected area with soap and water and continue to rinse for 15 minutes. If appropriate, it is strongly recommended that the contaminated worker take a shower. It is strongly recommended that a deluge shower be made available in the vicinity (e.g., in the oncology clinics/units). It is strongly recommended that all contaminated clothing be discarded in hazardous waste. Workers should seek medical attention after exposure.

If a hazardous drug comes into contact with a worker's eyes, it is strongly recommended that the worker flush their eyes at an eye wash station. Alternatively, it is recommended that the workers use an isotonic solution to flush their eyes (e.g., sterile NaCl 0.9%). It is strongly recommended that eyes be flushed for at least 15 minutes (22). It is strongly recommended that if contact lenses are worn, they be removed immediately prior to flushing. Workers should seek medical attention after eye exposure.

In the event of a needlestick or sharps injury, let the wound bleed freely. Under running water, gently and thoroughly wash the area with soap. Contact Occupational Health. Ensure that facility policies for needlestick or sharps injury are followed including completion of an incident report and reporting to WSIB if indicated.

Recommendation 12: Spills Management

It is strongly recommended that the facility develop policies and procedures for spills management that take into account the types of spills (i.e., amount, location, concentration, powder vs. liquid, etc.), incidence reporting, surveillance of spills and restocking of equipment.

All staff working in environments where hazardous drugs are handled should be trained in the use of a spill kit.

It is strongly recommended that a spill kit be readily available in all areas where hazardous drugs are stored, transported handled and administered.

It is strongly recommended that a spill kit be readily available in the home in case of accidental spills, but institutions must ensure patients, or their caregivers are trained on the use of the spill kit and PPE.

It is legislated that disposable items from the clean-up of spills be placed in the hazardous waste receptacle (9). Non-disposable items should be thoroughly cleaned and decontaminated.

The area of the spill should be decontaminated deactivated and disinfected (10).

Most spills can be contained and managed by trained staff (e.g., leaking IV tubing).

When a spill is not contained or easily managed (e.g., exposure to large volume of fluid that is a risk to the environment or a large crate of vials filled with powder broken in the receiving area), it is strongly recommended that a Code Brown or equivalent be called.

Recommendation 13: Environmental Cleaning

Establish environmental cleaning policies and procedures for all surfaces where contact with hazardous drugs may occur. Areas should be decontaminated deactivated and disinfected following legislative procedures. Examples may include unpacking and storage, preparation, administration, and disposal areas. Pharmacy counters are among the most contaminated surfaces (5, 7, 10).

It is strongly recommended that cleaning of the BSC be performed by trained personnel following manufacturer's and NAPRA's guidelines (7, 10).

Use of Pumps to Administer Hazardous Drugs

Make sure there is an appropriate policy to clean and inspect the equipment between uses.

Laundry

Ensure the facility complies with the Occupational Health and Safety Act - Ontario Regulation for Health Care and Residential Facilities (6). Contaminated items should be placed in sealable bags and washed separately from other items (5).

Recommendation 14: Medical Surveillance and Environmental Monitoring

Medical Surveillance

Methods used to investigate potential health effects of exposure to hazardous drugs are inconclusive and difficult to interpret. The ideal test should meet several requirements – it should be sensitive, specific, quantitative, rapid, and reproducible. Importantly, the procedures for taking a sample should be non-invasive and should not cause unnecessary duress or anxiety to the individual (7).

Unfortunately, there is currently no suitable test to meet these requirements. Therefore, there is conflicting information and opinion about the value of routine biological monitoring for employees handling hazardous drugs.

Employers do have a responsibility to ensure that they remain aware of and apply any future developments for monitoring the health of employees in the handling of hazardous drugs.

The panel supports further research to determine if there are adverse health effects that result from exposure to hazardous drugs.

Adherence to agreed standard operating procedures with sufficient initial and regular ongoing training in safe handling/administration is paramount to reducing potential for exposure and risk.

There is evidence in the literature of a higher rate of spontaneous abortion among women working in roles that expose them to hazardous drugs (51, 52). There are no other identified medical conditions known to result from chronic exposure of healthcare workers to hazardous drugs, no exposure limits set for hazardous drugs, and no standards for interpretation of test results of exposed healthcare workers to enable meaningful interpretation or action based on biological monitoring results.

Environmental Monitoring

It is recommended that the facility implement an environmental monitoring program. Surface testing would audit contamination of the environment (e.g., pharmacy counters, patient bedside tables) and provide a quality indicator of cleaning effectiveness and adherence to recommended work practices (5).

Safe Handling of Hazardous Drugs

Section 2: Guideline - Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To provide recommendations regarding the safe handling of hazardous drugs by healthcare workers.

TARGET POPULATION

Healthcare workers who may come into contact with hazardous drugs at any point in the medication circuit. The medication circuit includes all steps through which the drug travels, from the receiving dock to the storage facility, as well as its preparation, administration, and disposal. Exposure is possible throughout the medication circuit in the hospital or in the home setting.

INTENDED USERS

Intended users include, but are not limited to, hospital administrators, educators and managers, occupational health and safety services, pharmacy, nursing, porters, shipping and receiving, medical oncologists, and other healthcare workers.

APPLICABLE OCCUPATIONAL HEALTH AND SAFETY LEGISLATION

The overarching legislation that applies to all provincially governed workplaces is the Occupational Health and Safety Act (1). The goal is to achieve safe and healthy workplaces. The Act sets out the rights and duties of all parties in the workplace and establishes procedures for dealing with workplace hazards, including employers taking all reasonable measures necessary to protect workers from exposure to hazardous biological or chemical agents. A number of regulations under the Act also apply, including the Regulation for Health Care and Residential Facilities, the Needle Safety Regulation and the Control of Exposure to Biological or Chemical Agents Regulation.

Healthcare workplaces are required to comply with applicable provisions of the Occupational Health and Safety Act (OHSA), R.S.O. 1990, c.0.1 and its Regulations. Employers, supervisors, and workers have rights, duties and obligations under the OHSA. To see what the specific requirements are under the OHSA go to: http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_90o01_e.htm

A guide to the requirements of the Occupational Health and Safety Act may be found at: <https://www.ontario.ca/document/guide-occupational-health-and-safety-act>

Specific requirements for certain healthcare and residential facilities may be found in the Regulation for Health Care and Residential Facilities, which can be found at:

http://www.e-laws.gov.on.ca/html/regs/english/elaws_regs_930067_e.htm.

Requirements for antineoplastic drugs are found in Section 97.

Requirements for the use of safety-engineered needles may be found in the Needle Safety Regulation which can be found at: http://www.e-laws.gov.on.ca/html/regs/english/elaws_regs_070474_e.htm

Requirements for the Control of Exposure to Biological or Chemical Agents can be found at:

http://www.e-laws.gov.on.ca/html/regs/english/elaws_regs_900833_e.htm

HIERARCHY OF CONTROLS

“Controlling exposures to occupational hazards is the fundamental method of protecting workers,” as stated by The Centres for Disease Control and Prevention in the National Institute for Occupational Safety and Health (NIOSH) Engineering Controls Program Portfolio (2). It describes the Hierarchy of Controls used to implement feasible and effective controls. In descending order, they are Elimination, Substitution, Engineering Controls, Administrative Controls, and the use of Personal Protective Equipment. “Engineering controls are used to remove the hazard or place a barrier between the worker and the hazard (2).” In healthcare, examples of engineering controls include the use of biosafety cabinets and safety-engineered medical devices; particularly, safety engineered needles help protect the worker from blood-borne pathogen exposures. Administrative controls include policies and procedures and staff education and training. Although Personal Protective Equipment (PPE) is the last control between the hazard and the worker, it really is the primary control on which healthcare workers rely. It is very important that healthcare workers are educated in the appropriate selection and use of PPE for protection against exposure to hazardous drugs. This usually consists of the use of gloves, gowns, and eye protection as appropriate.

DEFINITION OF TERMS

Airlock: An enclosed space with two or more doors that is interposed between two or more rooms, usually of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when either people or goods need to enter or leave them (3).

Biological Monitoring: The systematic collection and analysis of a biological specimen for the presence of an indicator of exposure or response in the worker.

Biological Safety Cabinet (BSC): A ventilated containment cabinet with an inflow of air to protect the worker and a down-flow of high-efficiency particulate air (HEPA)-filtered air to protect the product. The exhaust is HEPA filtered to protect the environment.

- **Class II, Type B1 BSC (4)**
 - Hard-ducted through a dedicated duct exhausted to the atmosphere after passage through a HEPA filter; contain negative-pressure plena.
 - Maintain a minimum average face velocity of 0.5 m/s (100 ft/min).
 - Recirculate 30% of the air within the cabinet.
 - Suitable for work with low levels of volatile toxic chemicals and trace amounts of radionuclides.

- **Class II, Type B2 BSC (4)**
 - Does not recirculate air within the cabinet.
 - Maintains a minimum average face velocity of 0.5 m/s (100 ft/min).
 - Hard-ducted through a dedicated duct exhausted to the atmosphere, 100% of cabinet air, after passage through a HEPA filter; contain negative-pressure plena.
 - Suitable for work with volatile toxic chemicals and radionuclides. The exhaust canopy must allow for proper BSC certification. An alarm should be provided that is audible at the cabinet to indicate loss of exhaust flow from the building exhaust system.
 - The cabinet internal fan should also be interlocked to shut down when the building exhaust system fan fails to prevent pressurization of the cabinet.

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

hazardous drug outside the system, and the escape of hazardous drug or vapour concentrations outside the system (5).

Cytotoxics: See Hazardous drugs

Deactivation: “Deactivation is the treatment of a hazardous drug to create a less hazardous agent, for example, by chemical deactivation. The material safety data sheets for some hazardous drugs recommend sodium hypochlorite for this purpose, usually as a 2% solution. This compound will corrode stainless steel surfaces, so it must then be neutralized with sodium thiosulphate or removed with a germicidal detergent. Sodium hypochlorite also has an additional germicidal effect for disinfection” (10).

Decontamination: “Decontamination involves the transfer of a hazardous drug contaminant from a fixed surface (e.g., counter, bag of solution) to a disposable surface (e.g., wipe, cloth). The wipe is then contained and discarded as hazardous waste. Many solutions can be used for decontamination, for example, 70% isopropyl alcohol, sterile water, hydrogen peroxide and sodium hypochlorite” (10).

Disinfection: “Disinfection is the process of destroying microorganisms” (10).

Extravasation: Passage or escape into tissue of (hazardous) drugs. Signs and symptoms may be sudden onset of localized pain at an injection site, sudden redness or extreme pallor at an injection site, or loss of blood return in an intravenous (IV) needle. Tissue slough and necrosis may occur if the condition is severe. Treatment depends on the causative agent.

HEPA Filter: Filter that is composed of a mat of dense fibres arranged in folds, designed according to trap at least 99.97% of airborne particles measuring 0.3 microns in diameter.

Hazardous Drug: Drugs are classified as hazardous when they possess any one of the following six characteristics:

- Genotoxicity, or the ability to cause a change or mutation in genetic material
- Carcinogenicity, or the ability to cause cancer in humans, animal models, or both
- Teratogenicity, or the ability to cause defects in fetal development or fetal malformation
- Fertility impairment or reproductive toxicity
- Serious organ toxicity at low doses in humans or animal models
- Chemical structure and toxicity profile that mimic existing drugs determined to be hazardous by the five previous criteria (2)

Hazardous Waste: Any material that comes into contact with hazardous drugs during their storage, handling, preparation, administration and disposal (e.g., packaging material, protective equipment, preparation supplies [such as syringes, tubing, drug bags], soiled disposable incontinence briefs of patients who have received hazardous drugs during the previous 48 hours, hood prefilters, and HEPA filters, etc.).

Leak: Refers to fluid that escapes from a medication delivery system or container such as IV tubing, medication port, or connection.

Packaging:

- External packaging: outer cardboard box or shrink-wrap.
- Secondary packaging: manufacturer's cardboard box. It directly contains the vials.
- Primary packaging: the vials.

Spill: Refers to a significant amount of escaped liquid or powder that requires control and containment to avoid further exposure.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1: General Measures

Committee Responsible for Policy and Procedures for Hazardous Drugs

It is strongly recommended that all institutions administering hazardous drugs form such a committee. It is also strongly recommended that this committee include, but not be limited to, representatives from various departments and services such as: occupational health and safety, joint health and safety committee, pharmacy, nursing, medical oncology (physician), environmental services, risk management, and a patient representative.

This committee would be responsible for clear processes of developing, reviewing, and revising policies and procedures related to hazardous drugs. A risk assessment and gap analysis should be routinely conducted to identify gaps and to inform policies and procedures. In addition, this committee is responsible for ensuring that there is a process in place for orientation and ongoing education for the identified target population.

This committee is responsible for implementation and follow-up of the Risk Prevention Management Program related to the use of hazardous drugs.

Continuing Education and Orientation Program

It is legislated that initial and ongoing hospital-approved education be provided to all staff involved with hazardous drugs throughout the medication circuit including safe handling and spill or leak management (6). It is strongly recommended that all staff have initial and ongoing training related to best practice standards in place at the time.

It is legislated that there is documentation that annual training of safe handling of hazardous drugs has occurred (6). This should be documented by the institution's Committee Responsible for Policy and Procedures for Hazardous Drugs

Identification and Safety

It is strongly recommended that each institution maintain a list of hazardous drugs that are used in their facility, that is reviewed regularly, when policy is updated, and whenever a new agent or dosage is used (7).

It is legislated that hazardous drugs and their waste be properly identified with the symbol capital "C" and, under it, the words "CYTOTOXIC/CYTOTOXIQUE" in capital letters (8, 9). It is legislated that all hazardous waste under the Ministry of Environment, Conservation and Parks regulation (guideline C-4) include bilingual wording and both the words and the symbol appear on a dark grey rectangle (8, 9). Other countries may have their own systems for labeling and should be adhered to.



Purchasing of Drugs

When purchasing hazardous drugs, it is strongly recommended that institutions consider vendors that include safe handling measures such as pre-wiped or protective containers, or smaller receptacles to decrease volume of potential spills.

Spills Kit

It is strongly recommended that a spill-management kit be available in all areas where hazardous drugs are stored, transported, handled, and administered (10).

Precautionary Reassignment

It is strongly recommended that all staff be fully informed of the potential reproductive hazards of hazardous drugs (11).

It is strongly recommended that the facility consider alternative duties for staff who are pregnant, breast feeding or actively trying to conceive.

Recommendation 2: PPE

It is legislated that a worker work in compliance with the Occupational Health and Safety Act and regulations and use or wear the equipment, protective devices, or clothing that the employer requires to be used (1).

It is legislated that the appropriate PPE for the task (as described in Table 2-1) be worn throughout the medication circuit (1). It is the employer's responsibility to provide the necessary protective equipment and training on how to use the equipment.

Gloves

The gloves used to handle hazardous drugs are strongly recommended to comply with ASTM standard D-6978-(05)-13 and be powder free (12). Gloves are recommended to be nitrile, polyurethane, neoprene, or latex (12). Latex is a known allergen; therefore, it is strongly recommended that this be taken into consideration for glove selection. It is strongly recommended that vinyl gloves not be used (13). It is strongly recommended that the frequency of glove changes be adjusted according to the level of exposure at each step in the medication circuit. For example, when administering reconstituted medications, it is strongly recommended that workers change gloves immediately if torn, punctured, or visibly contaminated with a hazardous drug, and to ensure following Routine Practices (14). Gloves should be changed every 30 minutes unless otherwise recommended by the manufacturer's documentation (7, 10). It is strongly recommended that great care be taken in the removal of gloves to not contaminate the skin. When two pairs of gloves are required, put on the first pair before putting on the gown. See Appendix 4 for the donning and doffing of one pair of gloves and Appendix 5 for the donning and doffing of two pairs of gloves.

Gown

It is strongly recommended that the gowns used for handling hazardous drugs be disposable, made of lint-free, low-permeability fabric, have long sleeves with tight-fitting cuffs and fasten in the back. Gowns need to be changed in the event of contamination, spillage, rips, and at the end of the procedure. It is strongly recommended that the supplier be able to certify that the gown protects against hazardous drugs (10).

For medication preparation and administration, gowns need to be changed halfway through a shift or every 3 and a half hours (7, 10).

It is strongly recommended that care be taken to avoid contamination of the hands by avoiding touching the outside of the gown when removing the gown.

Facial Protection

Surgical/procedure masks are required while handling and preparing medications in a BSC and, in this instance, are worn to prevent microbial contamination of the sterile field.

Goggles and a face shield or full face-piece respirator should be worn when there is a risk of spills or splashes of hazardous drugs or hazardous waste materials when working outside of a BSC such as administration of hazardous drugs in the surgical suite, working at or above eye level, or cleaning a spill (7, 10).

Head and hair coverings (including beard and moustache, if applicable), and sleeve covers provide protection from contact with hazardous drug residue. Disposable sleeve covers may be used to protect areas of the arm that may come in contact with hazardous materials. Disposable sleeve covers made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials (7).

It is strongly recommended that full-facial protection be worn whenever there is a risk of splashing (e.g., during certain drug administration procedures). The use of a full-facial shield is preferred. If goggles are used, they need to be worn in conjunction with a fluid-resistant mask. For further information, see *Canadian Standard Association (CSA) standard Z94.3-07 - Eye and Face Protectors* (15). 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 (7).

Respiratory Protection Devices

It is strongly recommended that fit-tested respirators such as NIOSH-certified N95 or N100 be used when there is a risk that airborne powder or aerosol will be generated. It is legislated that respirators be used in accordance with a respiratory protection program such as that outlined in *CSA Standard Z94.4-18 "Selection, Use and Care of Respirators"* (16).

Caps

Caps are only required in the sterile preparation room and are worn to prevent microbial contamination of the sterile field.

Shoe Covers

Disposable shoe covers are worn to prevent contamination of the healthcare workers' shoes, and it is strongly recommended that they be worn when in the sterile preparation room or in the event of a spill. It is strongly recommended that shoe covers be removed immediately when leaving the sterile prep room to avoid contamination of other areas. When compounding hazardous drugs, a second pair of shoe covers must be donned before entering the Containment Secondary Engineering Control (C-SEC) and doffed when exiting the C-SEC (7, 10).

Table 2-1. Personal protective equipment to be worn throughout the medication circuit

Guideline 16-3 Version 3

Medication circuit steps	Gloves	Gown	RPD	Facial protection	Cap	Shoe covers
Unpacking and cleaning	✓ (2 pairs)	✓	✓ (Only if unpacking hazardous drugs that are not contained in plastic until assessment of the packaging integrity can be made)			
Sterile preparations	✓ (2 pairs)	✓		✓	✓	✓ (2 pairs)
Non-sterile preparations: - Counting of solid oral forms	✓ (1 pair)	✓				✓
Non-sterile preparations: -Preparing creams, ointments, oral solutions and crushing tablets	✓ (2 pairs)	✓			✓	✓ (2 pairs)
Routes of administration (intravenous, subcutaneous, intramuscular, intravesical, intraperitoneal, intrathecal, liquid oral)	✓ (2 pairs)	✓		✓ (If risk of splashing, e.g., bladder installation or NG, G, or J tube)		
Solid oral administration (tablets)*	✓ (1 pair)					
Topical administration (creams, ointments)	✓ (2 pairs)	✓		✓ (If risk of splashing)		
Aerosolized administration (e.g., ribavirin, pentamidine)†	✓ (2 pairs)	✓	✓	✓ (If risk of splashing)		
Patient care	✓ (1 pair)	✓ (When at risk for exposure for bodily fluids)		✓ (If risk of splashing, e.g., disposal of bodily		

Medication circuit steps	Gloves	Gown	RPD	Facial protection	Cap	Shoe covers
				fluids)		
Management of extravasation	✓ (2 pairs)	✓		✓ (If risk of splashing)		
Handling of contaminated bedding on the wards	✓ (2 pairs)	✓				
Waste management (collection and transport)	✓ (2 pairs)					
Spill or damaged or broken container	✓ (2 pairs)	✓	✓ (If suspicion of powder or aerosolization is generated)	✓		✓ (If on the floor)
Cleaning of sterile preparation room and airlock	✓ (2 pairs)	✓			✓	✓ (2 pairs)
Cleaning of preparation cabinets (hoods)	✓ (2 pairs)	✓	✓	✓	✓	✓
Cleaning of other oncology pharmacy rooms and care units/clinics	✓ (1 pair)	✓				

Abbreviations: G = gastric tube, J = jejunostomy tube, NG = nasal gastric tube, RPD= respiratory protection device.

*Although the risk of contamination with oral medications is minimal, the Working Group members believe that consistency of practice for any handling of hazardous drugs is of primary importance, and the preference is to wear a standard chemotherapy glove.

† Although hazardous, they are not cytotoxic

Recommendation 3: Receiving and Transport

Handling Hazardous Drug Delivery Containers

It is strongly recommended that all receiving-dock workers receive training in the proper handling of hazardous drugs. It is strongly recommended that the receiving-dock workers check the integrity of the external packaging upon receipt; in the event of breakage or a damaged parcel likely to cause a spill, apply the Spill Protocol from your institution.

It is strongly recommended that delivery containers be taken immediately to the Pharmacy Department by the receiving-dock workers or the distributor.

It is strongly recommended that the receiving-dock or storeroom workers not open the delivery containers. It is strongly recommended that the delivery containers be handled with care to avoid breakage of the hazardous drug containers and not be left unattended in a corridor. Only trained workers (e.g., pharmacy technicians) are to proceed with the unpacking and subsequent steps.

Damaged Containers/Spill

It is strongly recommended that damaged containers be handled like spills. It is strongly recommended that the manufacturer or distributor be notified if the container is received in

a damaged state. To limit exposure, it is strongly recommended that a damaged container not be returned to the manufacturer or distributor unless they require it returned. The damaged container will need to be returned in an impervious box. Notify the pharmacy if any damaged containers are suspected (7).

See *Recommendation 10: Management of Waste, Accidental Exposure, Spills and Returns*.

Recommendation 4: Unpacking and Storage

Packaging can have high levels of contamination. It is strongly recommended that there be an unpacking area in the pharmacy limiting exposure risks. It is strongly recommended that the unpacking area be a separate dedicated space, separate from eating areas, and preferably a separate room. It is regulated that there be adequate ventilation in the area, negative pressure, and preferably vented to the outside. It is strongly recommended that there be a receptacle for hazardous waste in the unpacking area, for the disposal of secondary packaging (6, 10, 17).

It is strongly recommended that workers at risk of exposure wear a protective gown and two (2) pairs of gloves when unpacking and cleaning hazardous drugs, from the opening of the external packaging to the placing of the secondary and/or primary packaging in their storage space. It is strongly recommended that workers check the integrity of all packaging at every step of the unpacking process. In the event of breakage or leaking, it is strongly recommended that the damaged contents be treated as a spill. It is strongly recommended that the primary and or secondary packaging be cleaned prior to being placed in storage.

It is strongly recommended that a regular cleaning protocol be in place either at this stage or prior to storage in the clean room. It is strongly recommended that all drug containers be cleaned to reduce external contamination. An example is the use of pre-moistened towelettes. It is important to ensure that the procedure does not damage the container or interfere with the reading of the label. It is also important to ensure that any product that is used will not further contaminate the product or work environment. However, it is strongly recommended that this procedure not increase the risk of incidents/accidents due to damage to the hazardous drug container or label.

It is strongly recommended that procedures be in place to minimize the risk of contamination of surfaces during the cleaning of vials (e.g., use of a disposable, plastic-backed, absorbent pad). It is strongly recommended that all surfaces be cleaned when the task is complete.

Establish a dedicated negative-pressure storage area for hazardous drugs that minimizes the risk of contamination (10).

When removing or transporting drugs out of the storage area, it is strongly recommended that one pair of gloves and a gown be worn and a spill kit be readily available.

Recommendation 5: Planning the Oncology Pharmacy

It is strongly recommended that the oncology pharmacy be in compliance with relevant guidelines from the Canadian Society of Hospital Pharmacists and Accreditation Canada

standards. While the specific details of oncology pharmacy planning are beyond the scope of this document, details and some important considerations may be found in the National Association of Pharmacy Regulatory Authorities (NAPRA) guideline and *CSA document CSA Z8000-11* (5, 10, 18).

It is strongly recommended that special requirements for heating, ventilation, and air-conditioning systems in healthcare facilities be taken into consideration (10, 17).

A class II type B BSC is required with preference for the type B2 because it ensures that there is no recirculation of air within the cabinet (4, (5, 10).

There is emerging evidence suggesting some robotic devices that prepare hazardous drugs improve the accuracy of medication preparation and reduce potentially harmful staff safety events. Further studies are required to establish the cost effectiveness of these robotic implementations. Each healthcare facility will need to assess the need for such devices in their environment (5,19-21, 31).

It is strongly recommended that all mixing, and preparation of administration sets with a hazardous drug be performed in one centralized area in a specially designated class II type B BSC (17) that:

- d. is exhausted through a HEPA filter to the outside atmosphere in a manner that prevents recirculation into any inside area;
- e. has exhaust and ventilation systems that remain in operation for a sufficient period of time to ensure that no contaminants escape from the BSC into the workplace; and
- f. is equipped with a continuous monitoring device to permit confirmation of adequate airflow and cabinet performance.

It is recommended that airlocks be considered if there are particular concerns about the propagation of airborne hazardous drugs.

It is strongly recommended that priming of administration sets be prepared in the manner mentioned above.

It is strongly recommended that the layout allow and facilitate the unimpeded cleaning of all surfaces (walls, floors, ceilings, doors, diffusers, windows). It is strongly recommended that the furniture and equipment in the sterile preparation room be kept to a bare minimum. It is strongly recommended that there be a visual link; for example, a sealed window and a way to communicate between the sterile preparation room and the pharmacy, to view the work in progress. It is strongly recommended that access to the sterile room be limited to trained and authorized workers (10). A pass-through window can be installed to minimize the risk of contamination when transferring products into and out of the clean room. The pass-through should be equipped with an interlocking system or procedure that prevents both doors from being open at the same time (10)

Limit worker traffic, particularly near unpacking and storage areas (to avoid accidental breakage) and near preparation cabinets (to avoid interfering with their proper operation).

It is legislated that the facilities include an emergency eyewash that may or may not be hooked up to the airlock sink (1). As a minimum, it is strongly recommended that emergency eyewash be able to provide 15 minutes of flushing to both eyes (22). It is strongly recommended that a full shower be accessible nearby (e.g., in the oncology units/clinics).

Closed system drug-transfer devices (e.g., PhaSeal®) are not a substitute for class II type B BSC. There is evidence from studies (23-30, 32-42, 57,58) that closed system drug-transfer devices can reduce contamination during preparation and increase or extend the beyond use date of a drug. Further emerging evidence suggests that when these devices are not used as specified, they could become open to the environment. Further research is needed to evaluate this possibility.

In the non-sterile drug preparation process (e.g., oral preparations), it is strongly recommended that the same level of worker protection be adhered to.

Pharmacy Policies and Procedures

Establish policies and procedures regarding preventive maintenance, monitoring, certification and the optimal use of facilities and equipment (45).

Recommendation 6: Hazardous Drug Preparation

The following recommendations apply but are not limited to the preparation of all hazardous medications including parenteral, oral, and topical, both sterile and non-sterile preparations. It is strongly recommended that policies and procedures include the use of appropriate PPE, the equipment for preparation including appropriate ventilation, and other automated equipment for packaging and a dedicated work area.

PPE

It is strongly recommended that workers (pharmacists or pharmacy technicians) wear a cap, surgical/procedure mask, shoe covers, a protective gown and two (2) pairs of gloves (see Table 2-1) to make sterile preparations of hazardous drugs in preparation cabinets.

Organization of the Work

Organize the work to limit microbial and environmental contamination.

For both sterile and non-sterile preparations, it is strongly recommended that workers cover the work surface with a disposable, absorbent, sterile, plastic-backed pad to absorb any liquid contamination that may occur during handling. It is strongly recommended that the pad not cover the front and rear grilles of the preparation cabinet. It is strongly recommended that it be changed after 3.5 hours of continuous work or for a new batch of preparations (e.g., a set of vials of a given drug) or in the event of a spill or contamination (13). It is legislated that the pad be disposed of in a hazardous waste receptacle (7, 9).

Limit the quantity of supplies and hazardous drugs in the cabinet, to avoid adversely affecting the laminar flow and to facilitate regular cleaning of the work surface. Place the sterile products in the centre and the non-sterile products (e.g., waste receptacle) along the sides of the cabinet.

Removal of Packaging

Remove the packaging, when applicable, and clean all the drug containers before taking them into the preparation cabinet. For sterile preparations, adhere to aseptic technique for sterility.

Handling Techniques

Use handling techniques that limit the risk of injury or accidental exposure. Direct CSTD spikes can be used to connect the hazardous medication bag directly to the tubing if spiking must occur at the bedside. When this adaptor is not used, IV bags containing hazardous drugs should only be spiked in a BSC to prevent exposure.

Preparation, Priming and Removing Air from the Tubing

It is strongly recommended that hazardous drugs be reconstituted in the pharmacy environment as described above. It is strongly recommended that the drug containers not be overfilled to avoid compromising the integrity of the container. It is strongly recommended that the techniques used for priming and removal of air minimize the exposure risks. It is recommended to only remove air from an IV tubing that does not contain a solution with a hazardous drug(s). It is strongly recommended that IV tubing is primed and air removed in the pharmacy, prior to adding the hazardous drug(s) to the infusion solution. Glass containers are not recommended due to increased risk of breakage and exposure.

Labeling and Final Packaging

It is legislated that hazardous drugs be labeled to inform those handling these preparations of the nature of the drugs and the precautions to be taken. It is legislated that hazardous drugs display the “Cytotoxic” hazard symbol or the word “Cytotoxic” (8, 9).

It is strongly recommended that the outside surface of the hazardous drug containers (e.g., syringes, infusion bags, tubing) in the preparation cabinet be cleaned in the cabinet.

Place each hazardous drug container (e.g., syringe, bag), as well as the administration supplies (e.g., tubing), in a clear, leak-proof plastic bag (e.g., Ziploc® type) to facilitate identification by the nurse without having to remove the container from the bag.

Following final verification in the pharmacy, it is strongly recommended that the plastic bags containing the hazardous drugs be placed in a rigid *transport container* (ideally opaque), properly identified with the “Cytotoxic” hazard symbol (7, 10).

Waste

It is strongly recommended that everything that comes out of the cabinet be wiped clean.

It is strongly recommended that all contaminated waste be disposed of in the chemotherapy waste stream.

Recommendation 7: Transport and Storage Following Preparation

On-site Transport of Hazardous Drugs

Transport hazardous drugs using a method that will prevent contamination of the environment in the event of breakage.

It is strongly recommended that hazardous drugs be placed in a closed, single-use leak-proof plastic bag (e.g., Ziploc® type).

It is strongly recommended that transport of the hazardous drug in a single-use closed, leak-proof plastic bag from the pharmacy to an area not adjacent to the preparation area (e.g., care unit, outpatient clinic), be done in a rigid, shock-resistant, leak-proof container made of a material that can be easily cleaned and decontaminated in the event of a drug leak (5). It is strongly recommended that the bottom be covered with an absorbent, plastic-backed cloth.

It is legislated that the transport container be identified with the “Cytotoxic” hazard symbol and be cleaned regularly (8, 9). This container should be cleaned according to the protocol outlined by a committee responsible for hazardous drug handling.

It is strongly recommended that mechanical transport systems, such as pneumatic tubes, not be used because of the stress they put on the contents, and the whole transport system would be compromised if a leak occurred (5, 7).

It is strongly recommended that prepared medications be stored in a designated area prior to administration. It is strongly recommended that this area be cleaned regularly.

Off-site Shipping and Transport of Hazardous Drugs

Establish policies and procedures regarding the shipping of hazardous drugs (46).

In the event that hazardous drugs are shipped off-site (e.g., from one institution to another), it is strongly recommended that they be packed separately from other drugs, according to the recommendations from the manufacturer and distributor. It is strongly recommended that pharmacy be consulted in the packaging of hazardous drugs.

It is strongly recommended that hazardous drugs be packed in a double plastic bag and placed in a box that is properly identified with the “Cytotoxic” hazard symbol. If necessary, immobilize the drug with packing (5) material. It is legislated that the “Cytotoxic” hazard symbol be visible on the outside of the delivery (8) container. It is strongly recommended that reusable delivery containers be cleaned regularly.

Ensure that the courier company will handle hazardous drugs.

Recommendation 8: Drug Administration

It is strongly recommended that safe handling and administration techniques be used to minimize possible exposure to individuals and the environment when administering hazardous drugs.

- It is legislated that appropriate PPE be made available to all healthcare workers and be worn as prescribed by the employer (Table 2-1) (1).
- It is strongly recommended that Luer lock connectors and needleless administration systems be used to administer any IV medications.
- Closed system drug-transfer devices may offer additional protection.

- It is strongly recommended that disposable plastic-backed absorbent pads be used over work surfaces and placed under tubing or bag connections and ports when attaching any tubing, bag or syringe that has been exposed to a hazardous drug.
- Unless a closed system is used, never disconnect tubing from hazardous drug bags. Discard bag with attached tubing into an appropriate waste container as a single unit.
- It is legislated that safety engineered needles be used as per Needle Safety Regulation 474/07 made under the Occupation Health and Safety Act Labour, 2010 (47). Do not purge air from the needle before administration.
- It is strongly recommended that oral hazardous drugs be handled in a manner that avoids skin contact, liberation of aerosols or powdered medicine into the air, and cross-contamination with other (48) medicines.
- It is strongly recommended that solid oral preparations (tablets) of hazardous drugs be crushed or cut within the BSC. If patients are unable to take in the solid format, it is strongly recommended that the pharmacy provide these drugs in an oral syringe or dissolve and dose container, in a ready-to-administer, liquid oral form.
- It is strongly recommended that application of topical hazardous drugs be done using appropriate PPE and in a way that prevents contamination of the environment. Between applications, it is strongly recommended that the hazardous medication (i.e., tube or jar) be kept in a safe container (i.e., Ziploc®) and in a secure place that prevents contamination of the surrounding environment.
- With any intravesical administration, e.g., bladder instillation, ensure there are detailed procedures in place to avoid risks of splashing.
- Use caution when administering intrathecal hazardous drugs, as there is risk of splashing due to increased intrathecal pressures. A closed system (i.e., Luer lock) should be used when possible.

Recommendation 9: Home Care

Home Care of Patients who Have Received Hazardous Drugs

It is strongly recommended that all hazardous drug preparations be compounded in pharmacies meeting the requirements for hazardous drug preparation (5).

It is strongly recommended that hazardous drugs be transported, administered and disposed of by individuals who have received appropriate training. It is strongly recommended that hazardous drug transport containers are not reused by patients for domestic purposes, which may expose the family to cytotoxic drugs (e.g., toy box, sewing basket, etc.).

It is legislated that the healthcare provider who administers hazardous drugs in the home wear PPE as outlined in Table 2-1 (1).

It is strongly recommended that healthcare providers follow the same recommendations outlined in *Recommendation 8 - Drug Administration*

It is strongly recommended that a spill kit be readily available in the home in case of accidental spills.

It is strongly recommended that patients be informed of and be provided with written instructions and PPE for the safe handling of hazardous drugs.

It is strongly recommended that contact information be provided for home care patients who require assistance with safe handling of hazardous.

Hazardous Drug Waste in the Home

It is strongly recommended that the institution have a clear process to address the issue of hazardous waste from patients in their homes, in compliance with municipal or local hazardous waste rules. It is strongly recommended that this process include patient and caregiver education.

It is strongly recommended that caregiving staff provide the patients/caregivers involved in administering cytotoxic drugs in the home with a process for appropriate disposal of hazardous waste, including leftover drugs.

Recommendation 10: Management of Waste

Bodily Fluid Waste

It is strongly recommended that workers who handle the biological fluids, excreta, contaminated bedding, and soiled equipment of patients who have received hazardous drugs wear two (2) pairs of gloves and a protective gown. It is strongly recommended that face protection be worn when there is a risk of splashing.

Cytotoxic Drug Waste

Establish policies and procedures as per provincial legislation regarding hazardous waste management.

The term “hazardous waste” includes any material that comes into contact with hazardous drugs during their storage, handling, preparation, administration and disposal (e.g., packaging material, protective equipment, preparation supplies, such as syringes, tubing, drug bags; soiled disposable incontinent briefs of patients who have received hazardous drugs during the previous 48 hours or longer depending on the drug [e.g., it is known that cyclophosphamide may persist for several days]; hood pre-filters and HEPA filters, etc.).

It is legislated that hazardous waste be placed in a waste container clearly identified with the “Cytotoxic” hazard symbol. It is legislated that hazardous waste be disposed of in the appropriate containers (9).

It is legislated that sharps be placed in rigid containers with a leak proof lid; CSA standard Z316.6--07 specifies the use of the colour red for the rigid containers (49). If the containers are another colour, follow the instructions of the company ensuring the final disposal (9).

It is strongly recommended that other waste (soft items, such as tubing, protective equipment, etc.) be placed in leak-proof and tear-resistant containers, identified with the “Cytotoxic” hazard symbol (7).

For final disposal outside the institution, it is legislated that all hazardous waste be in a rigid, leak proof, container identified with the “Cytotoxic” hazard symbol and scheduled for transport outside the institution (9).

It is legislated that any excess fluid from hazardous drugs (e.g., drug loss) be disposed of in a sealed container and placed in a rigid container, the bottom of which is to be covered with an absorbent pad. This rigid container will be handled like other hazardous waste (9).

It is recommended that disposable/incontinent briefs soiled by patients who have received hazardous drugs be placed in a hazardous waste container.

It is legislated that hazardous waste be incinerated according to ministry guidelines (9, 50).

It is legislated that hazardous waste not be disposed of in the receptacles used for infectious biomedical waste (which may be autoclaved and then sent to a landfill site) (9).

It is legislated that every area where hazardous drugs are handled will have an appropriate hazardous waste receptacle as close as possible to the work area (9).

The lids of hazardous drug receptacles must remain closed, except when depositing waste. Bins with foot pedals and lids, which lock automatically when full, are recommended to minimize exposure.

It is strongly recommended that workers be careful to avoid contaminating the outside of the receptacle when depositing waste.

It is legislated that the transport of hazardous waste receptacles be assigned to properly trained workers (6).

It is strongly recommended that workers who handle hazardous waste receptacles wear two pairs of disposable gloves and have a spill kit at their disposal. It is strongly recommended that the waste go through as few care units, public areas and areas containing food or linens as possible.

It is legislated that the final storage areas for hazardous waste receptacles be secure. Refer to Ontario storage (8, 9) requirements.

Recommendation 11: Accidental Exposure

Be aware of any mandatory reporting requirements under the Occupational Health and Safety Act and report requirements to Workplace Safety and Insurance Board (WSIB) (6).

Establish policies and procedures regarding accidental worker exposure.

If a hazardous drug accidentally comes into contact with a worker's skin or clothing, it is strongly recommended that the worker immediately remove the contaminated clothing and thoroughly wash the skin of the affected area with soap and water and continue to rinse for 15 minutes. If appropriate, it is strongly recommended that the contaminated worker take a shower. It is strongly recommended that a deluge shower be made available in the vicinity (e.g., in the oncology clinics/units). It is strongly recommended that all contaminated clothing be discarded in hazardous waste. Workers should seek medical attention after exposure.

If a hazardous drug comes into contact with a worker's eyes, it is strongly recommended that the worker flush their eyes at an eye wash station. Alternatively, it is recommended that the workers use an isotonic solution to flush their eyes (e.g., sterile NaCl 0.9%). It is strongly recommended that eyes be flushed for at least 15 minutes (22). It is strongly recommended that if contact lenses are worn, they be removed immediately prior to flushing. Workers should seek medical attention after eye exposure.

In the event of a needlestick or sharps injury, let the wound bleed freely. Under running water, gently and thoroughly wash the area with soap. Contact Occupational Health. Ensure that facility policies for needlestick or sharps injury are followed including completion of an incident report and reporting to WSIB if indicated.

Recommendation 12: Spills Management

It is strongly recommended that the facility develop policies and procedures for spills management that take into account the types of spills (i.e., amount, location, concentration, powder vs. liquid, etc.), incidence reporting, surveillance of spills and restocking of equipment.

All staff working in environments where hazardous drugs are handled should be trained in the use of a spill kit.

It is strongly recommended that a spill kit be readily available in all areas where hazardous drugs are stored, transported handled and administered.

It is strongly recommended that a spill kit be readily available in the home in case of accidental spills, but institutions must ensure patients, or their caregivers are trained on the use of the spill kit and PPE.

It is legislated that disposable items from the clean-up of spills be placed in the hazardous waste receptacle (9). Non-disposable items should be thoroughly cleaned and decontaminated.

The area of the spill should be decontaminated deactivated and disinfected (10).

Most spills can be contained and managed by trained staff (e.g., leaking IV tubing).

When a spill is not contained or easily managed (e.g., exposure to large volume of fluid that is a risk to the environment or a large crate of vials filled with powder broken in the receiving area), it is strongly recommended that a Code Brown or equivalent be called.

Recommendation 13: Environmental Cleaning

Establish environmental cleaning policies and procedures for all surfaces where contact with hazardous drugs may occur. Areas should be decontaminated deactivated and disinfected following legislative procedures. Examples may include unpacking and storage, preparation, administration, and disposal areas. Pharmacy counters are among the most contaminated surfaces (5, 7, 10).

It is strongly recommended that cleaning of the BSC be performed by trained personnel following manufacturer's and NAPRA's guidelines (7, 10).

Use of Pumps to Administer Hazardous Drugs

Make sure there is an appropriate policy to clean and inspect the equipment between uses.

Laundry

Ensure the facility complies with the Occupational Health and Safety Act - Ontario Regulation for Health Care and Residential Facilities (6). Contaminated items should be placed in sealable bags and washed separately from other items (5).

Recommendation 14: Medical Surveillance and Environmental Monitoring

Medical Surveillance

Methods used to investigate potential health effects of exposure to hazardous drugs are inconclusive and difficult to interpret. The ideal test should meet several requirements – it should be sensitive, specific, quantitative, rapid, and reproducible. Importantly, the procedures for taking a sample should be non-invasive and should not cause unnecessary duress or anxiety to the individual (7).

Unfortunately, there is currently no suitable test to meet these requirements. Therefore, there is conflicting information and opinion about the value of routine biological monitoring for employees handling hazardous drugs.

Employers do have a responsibility to ensure that they remain aware of and apply any future developments for monitoring the health of employees in the handling of hazardous drugs.

The panel supports further research to determine if there are adverse health effects that result from exposure to hazardous drugs.

Adherence to agreed standard operating procedures with sufficient initial and regular ongoing training in safe handling/administration is paramount to reducing potential for exposure and risk.

There is evidence in the literature of a higher rate of spontaneous abortion among women working in roles that expose them to hazardous drugs (51, 52). There are no other identified medical conditions known to result from chronic exposure of healthcare workers to hazardous drugs, no exposure limits set for hazardous drugs, and no standards for interpretation of test results of exposed healthcare workers to enable meaningful interpretation or action based on biological monitoring results.

Environmental Monitoring

It is recommended that the facility implement an environmental monitoring program. Surface testing would audit contamination of the environment (e.g., pharmacy counters, patient bedside tables) and provide a quality indicator of cleaning effectiveness and adherence to recommended work practices (5).

RELATED GUIDELINES

- Leung M, Bland B, Baldassarre F, Green E, Kaizer L, Hertz S, et al. Safe administration of systemic cancer therapy: introduction and general methods. Toronto (ON): Cancer Care Ontario; 2012 Jul 9. Program in Evidence-based Care Practice Guideline Report No.: 12-12 Methods.
- Leung M, Bland B, Baldassarre F, Green E, Kaizer L, Hertz S, et al. Part 1: Safety during chemotherapy ordering, transcribing, dispensing, and patient identification. Toronto (ON): Cancer Care Ontario; 2012 Jul 9. Program in Evidence-based Care Practice Guideline Report No.: 12-12-1.
- Leung M, Bland R, Bladassarre F, Green E, Kaizer L, Hertz S, et al. Part 2: Administration of chemotherapy and management of preventable adverse events. Toronto (ON): Cancer Care Ontario; 2014 Mar 10. Program in Evidence-based Care Practice Guideline Report No.: 12-12-2.
- Trudeau M, Green E, Cosby R, Charbonneau F, Easty T, Ko Y, et al. Patient safety issues: key components of chemotherapy labelling. Toronto (ON): Cancer Care Ontario; 2009 Aug 6. Program in Evidence-Based Care Practice Guideline Report No.: 12-11

Safe Handling of Hazardous Drugs

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see [Section 4](#).

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND AND GUIDELINE OBJECTIVE

The original guideline objective was to provide recommendations regarding the safe handling of parenteral hazardous drugs by healthcare workers.

The objective of this update is: to update and address new issues in hazardous drug handling that have developed since the previous guideline, including the use of oral hazardous drugs, selection and use of personal PPE, and treatment in diverse settings including in the home setting.

GUIDELINE DEVELOPERS

This guideline was developed by the Nursing GDG. The project was led by a small Working Group of the Safe Handling of Hazardous Drugs GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group members had expertise in nursing, pharmacy, medical oncology, and health research methodology. Other members of the Safe Handling of Hazardous Drugs GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the [PEBC Conflict of Interest Policy](#).

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (53, 54). This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework (55) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological

rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the [PEBC Document Assessment and Review Protocol](#). PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the [PEBC Handbook](#) and the [PEBC Methods Handbook](#).

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed at least one research question were included; guidelines older than five years (published before 2015) were excluded.

The following sources were searched for guidelines on August 27, 2020 with the search term(s): Safe handling, Hazardous, Cytotoxic, Chemotherapy Antineoplastic agents: National Institute for Health and Care Excellence Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council - Australia Clinical Practice Guidelines Portal, and Cancer Council Australia - Cancer Guidelines Wiki, NAPRA, NIOSH, Oncology Nursing society (ONS), The United States Pharmacopeial Convention (USP) The International Society of Oncology Pharmacy Practitioners (ISOPP) and The Canadian Association of Provincial Cancer Agencies

Assessment of Guideline(s)

Eight guidelines were found and three were retained. The Guideline from NAPRA was included since NAPRA “is an alliance of the provincial and territorial pharmacy regulatory authorities as well as the Canadian Forces Pharmacy Services. The members regulate the practice of pharmacy in their respective jurisdictions in Canada and their primary mandate is protecting and serving the public interest” (10). The recommendations in the NAPRA guideline had to be added to the safe handling guideline to adhere to national standards. This is one of the reasons that the safe handling of hazardous drugs guideline needed to be updated. The other guideline that was retained was the USP 800 guideline (7). The USP is a non-profit scientific organization founded in 1820 in Washington, D.C., that develops and disseminates public compendial quality standards for medicines and other articles. While [NIOSH](#) defines criteria and identifies [hazardous drugs](#), the USP develops standards for handling these hazardous drugs to minimize the risk to public health. The ISOPP standard was also retained as this was used in the previous version of the guideline and a new version was found. This society is an international society of oncology pharmacy practitioners (5). The AGREE II scores for the guidelines are listed below in Table 3-1. All guidelines scored poorly on the rigor of development portion of the AGREE tool. The recommendations were well presented, but the overall quality was low, owing to the absent methodology used to arrive at them. Guidelines are not often endorsed with such low Rigour of Development scores, but since these are guidelines from important government agencies that are setting national standards, they were included. The lack of methodology does not imply that there was no methodology used in writing the guideline, but rather that it was not included in the published version. The USP does have a

Standard-setting process (<https://www.usp.org/sites/default/files/usp/document/health-quality-safety/healthcare-safety-standard-setting-process-2018.pdf>), that includes feedback and reviews, but there was no mention of this process in the guideline.

Table 3-1. Agree scores

Domain	NAPRA	USP-800	ISOPP
Scope and purpose	80%	72%	75%
Stakeholder involvement	39%	27%	41%
Rigor of development	0	0	14%
Clarity of presentation	70%	55%	82%
Applicability	33%	9%	9%
Editorial independence	0	0	0

Abbreviations: NAPRA = National Association of Pharmacy Regulatory Authorities; USP = United States Pharmacopoeial Convention, ISPOPP: The International Society of Oncology Pharmacy Practitioners

In areas where there were no updates to recommendations the original guideline recommendations were left unchanged. All references were checked and updated. The previous Safe Handling of Hazardous Drugs Working Group chose the “Prevention Guide: Safe Handling of Hazardous Drugs” (13) document since it was still current, broad, and sufficiently detailed. In the previous version of this guideline a significant amount of work was required to tailor the content of that guide for the purpose of this document. For example, there were some recommendations in the “Prevention Guide: Safe Handling of Hazardous Drugs” document that were too detailed and prescriptive for the purpose of this document. In these instances, the recommendations were re-worded to convey the underlying principles to give centres some flexibility when developing their own policy and procedures. The current Working Group went through each recommendation of the previous guideline that was retained to check it for currency and applicability.

The other four guidelines did not meet criteria for endorsement. The American Society of Clinical Oncology, the Canadian Association of Provincial Cancer agencies (CAPCA) and ONS guidelines were based on the previous version of this guideline as well as the NAPRA and USP 800 guidelines. The NIOSH guideline that was found lists hazardous drugs but does not provide guidance as to their handling (2).

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external

review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

Patient and Caregiver-Specific Consultation Group

Four patients/survivors/caregivers participated as Consultation Group members for the Safe Handling of Hazardous Drugs Working Group. They reviewed copies of the project plan/draft recommendations and provided feedback on its/their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

Implementation of guidelines developed by the PEBC may be undertaken by the Nursing Program.

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- Sara Miller for copy editing.

Safe Handling of Hazardous Drugs

Section 4: Systematic Review

INTRODUCTION

It is well established that antineoplastic agents help treat people with cancer. However, the improvement in patient outcomes must be weighed against the risk of adverse health outcomes in the healthcare workers who handle them. There is no known safe amount of exposure; therefore, healthcare workers must take proper precautions to minimize contact with hazardous drugs (56).

The Working Group of the Safe Handling of Hazardous Drugs GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. This guideline is a revision of the previous 2013 OH (CCO) guideline. The guideline needed to be updated to conform with the NAPRA standards.

As described in Section 3 of this document, the Safe Handling of Hazardous Drugs GDG chose the NAPRA, USP 800 and ISOPP guidelines to update this guideline. In places where no updates were needed the “Prevention Guide: Safe Handling of Hazardous Drugs,” developed by the *Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales* (ASSTSAS), and the *Institut de recherche Robert-Sauvé en santé et en sécurité du travail* (IRSST) (13), were left as the basis for the guideline. As part of the adaptation/endorsement process, the Working Group determined that there were three areas where the evidence base found in the NAPRA, ISOOP, USP 800 and “Prevention Guide: Safe Handling of Hazardous Drugs” was insufficient to fully inform the necessary recommendations. These areas were:

- closed-system transfer devices,
- pregnancy outcomes in healthcare workers who handle hazardous drugs, and
- general health outcomes in healthcare workers who handle hazardous drugs.

All these areas had been reviewed in the previous Ontario guideline, and the Working Group believed that it was necessary to update the evidence in these three areas to fully support the adaptation/endorsement process. Therefore, the Working Group conducted a systematic review of the medical literature in these three areas.

RESEARCH QUESTIONS

1. What are the proper procedures for safe handling of hazardous drugs through the medication circuit?
2. Are there any adverse health outcomes for healthcare workers who handle hazardous drugs?
3. Do closed-system transfer devices reduce contamination when used to prepare chemotherapy?

METHODS

This evidence review was conducted in three planned stages, including a search for guidelines, then systematic reviews, followed by a search for primary literature. These stages are described in the subsequent sections.

Search for Systematic Reviews

Systematic reviews were included if they met the following criteria: addressed at least one research question with similar inclusion/exclusion criteria, and the review had a low risk of bias as assessed with the ROBIS tool or a moderate/high overall rating as assessed with the AMSTAR 2 tool.

If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per research question was selected by one reviewer (NC) based on its age, quality, and the best match with our study selection criteria stated below.

Search for Primary Literature

For each outcome per research question, if no systematic review was included, then a search for primary literature was conducted. For any included systematic review, an updated search for primary literature was performed. If any included systematic review was limited in scope, then a search for primary literature to address the limitation in scope was conducted.

Literature Search Strategy

MEDLINE and EMBASE were searched for primary studies if there were no systematic review included, or from the point that the search timeframe from an included systematic review ended. Please see Appendix 3 for the full search strategy.

Study Selection Criteria and Process

Inclusion Criteria

- Technology assessments, systematic reviews, clinical trials, and studies investigating the safe handling of hazardous drugs
- Comparative studies

Exclusion Criteria

- 1) Review articles
- 2) Letters and editorials that reported clinical trial outcomes.

A review of the titles and abstracts was done by one reviewer (NC) independently. For studies that warranted full-text review, one reviewer (NC) reviewed each study independently with a second reviewer (KK, KV), if uncertainty existed.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by NC independently, with all extracted data and information audited subsequently by an independent auditor. Ratios, including hazard ratios (HRs), were expressed with a ratio of <1.0 indicating that the outcome was better in the intervention group compared to the control group.

Randomized controlled trials (RCTs) were assessed for quality and potential bias using the second version of the Cochrane Risk of Bias tool (RoB2) and all non-RCTs, if any were included, were assessed using the Cochrane Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool (<https://sites.google.com/site/riskofbiastool/>).

Synthesizing the Evidence

Meta-analysis was not planned due to the use of an existing systematic review with meta-analysis and existing guidelines.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each research question, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed.

RESULTS

Search for Systematic Reviews

A search for systematic reviews was conducted from January 2017 to August 27, 2022 and it uncovered 43 documents. Of these, four underwent full-text review and one met the pre-planned inclusion criteria. This systematic review was used for Question 3.

Search for Primary Literature

A search for primary literature was conducted for Question 2 and in Question 3 from the point when the searches for the included systematic reviews ended. A search for primary literature for Question 1 was not conducted as recommendations from existing guidelines were adopted.

Literature Search Results

A search for primary literature was conducted from January 2017 to August 27, 2022. There were 2421 hits. Of these, 115 underwent full-text review and 29 were retained. For a summary of the full literature search results (including guidelines and systematic reviews) and a flow diagram depicting the inclusion and exclusion of all studies identified for this guidance document, please refer to Appendices 2 and 3. A summary of all included studies can be found in Table 4-1.

Table 4-1. Studies selected for inclusion

QUESTION	Number of papers retained	References
1. What are the proper procedures for safe handling of hazardous drugs through the medication circuit?	3 guidelines	(5, 7, 10)
2. Are there any adverse health outcomes for healthcare workers who handle hazardous drugs?	3 studies	(51 52, 57)
3. Do closed-system transfer devices reduce contamination when used to prepare chemotherapy?	1 systematic review 26 studies	(19-21, 23-44, 58)

Certainty of the Evidence

Various study designs are included in this guidance document, guidelines, systematic reviews observational and comparative studies. The included guidelines were evaluated using the AGREE II tool (55) (see Section 3). and were deemed to be sufficient to include in the current guidance. One systematic review was retained and was evaluated using the AMSTAR 2 tool (60) (Table 4-2). The other studies were accessed using the Cochrane Risk of Bias tool (RoB2) (<https://sites.google.com/site/riskofbiastool/>) (Table 4-3).

Table 4-2. Evaluation of the included systematic review using AMSTAR2

Guideline 16-3 Version 3

ITEM	Gurusamy 2018 (25)
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Y
4. Did the review authors use a comprehensive literature search strategy?	Y
5. Did the review authors perform study selection in duplicate?	Y
6. Did the review authors perform data extraction in duplicate?	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Y
8. Did the review authors describe the included studies in adequate detail?	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	PY
10. Did the review authors report on the sources of funding for the studies included in the review?	Y
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y

Abbreviations: N = no; PICO = Population, Intervention, Comparison, Outcome; PY = partial yes; Y = yes

Table 4-3. Evaluation of included studies using Cochrane’s Risk of Bias tool

Study	Confounding Bias	Selection Bias	Bias in classification of the interventions	Bias due to deviation from the intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of reported result
Soefje 2022 (43)	Some concerns	Low	Low	Some concerns	Some Concerns	Serious	Low
Szkiladz 2022(44)	Some concerns	Low	Low	Some concerns	Some Concerns	Serious	Low
Forges 2021 (24)	Some concerns	Low	Low	Serious	Low	Serious	low
Piccardo 2021 (42)	Some concerns	Low	Low	Some concerns	Some Concerns	Serious	Low
Kulju 2020 (27)	Some concerns	Low	Low	Some Concerns	Low	Serious	Low
Forshay 2019 (25)	Some concerns	Low	Low	Low	Some Concerns	Serious	Low
Wilkinson 2019 ABSTRACT (34)	Some Concerns	Low	Low	Some Concerns	Some Concerns	Serious	Some Concerns
Masson 2018 ABSTRACT (29)	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns	Serious	Low

Study	Confounding Bias	Selection Bias	Bias in classification of the interventions	Bias due to deviation from the intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of reported result
González-Haba Peña 2016 (38)	Some concerns	Low	Low	Some Concerns	Some Concerns	Serious	Low
González-Haba Peña 2018 (39)	Some concerns	Low	Low	Some Concerns	Some Concerns	Serious	Low
Smith 2018 (32)	Some concerns	Low	Low	Low	Some Concerns	Serious	Low
Valero 2018 (33)	Some Concerns	Low	Low	Some Concerns	Some Concerns	Serious	Low
Vasseur 2018 (41)	Some concerns	Low	Low	Low	Some Concerns	Serious	Low
Wilkinson 2018 (35)	Some concerns	Low	Low	Low	Some Concerns	Serious	Low
Garcia 2018 (58)	Some concerns	Low	Low	Low	Some Concerns	Serious	Low
Call 2017 (23)	Some concerns	Low	Low	Low	Some Concerns	Serious	Some Concerns
Gómez-Álvarez 2016 (37) Abstract in English only	Some Concerns	Low	Low	Some concerns	Some concerns	Serious	Some concerns
Garrigue 2016 (36)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Serious	Low
Schierl 2016 (31)	Some concerns	Low	Low	Some concerns	Some concerns	Serious	Low
Lalande (2015) (28)	Some concerns	Low	Low	Low	Some concerns	Serious	Low
Savry 2014 (30)	Some concerns	Low	Low	Low	Some concerns	Serious	Low
Wakui 2013 (40)	Some concerns	Low	Low	Some concerns	Some concerns	Serious	Low
Nassan 2021 (51)	Some concerns	Low	Low	Low	Some concerns	Serious	Low
Nassan 2019 (52)	Some concerns	Some concerns	Low	Low	Some concerns	Serious	Low
Dugheri 2018 (57)	Some concerns	Low	Low	Low	Some concerns	Serious	Low
Riestra 2021 (21)	Some concerns	Low	Low	Some concerns	Some Concerns	Serious	Low
Jobard 2020 (20)	Some concerns	Low	Low	Low	Some concern	Serious	Low
Deljehier 2019 (19)	Some concerns	Low	Low	Low	Some concerns	Serious	Low

Confounding bias

There was insufficient information to assess the risk of confounding bias in all studies (19-21, 23-25, 27-45, 51, 52, 57, 58).

Selection bias

Twenty-five studies (19-21, 23-25, 27, 28, 30-35, 37-44, 51 57 58) had a low risk of bias and three (29, 36, 52) had some concerns due to how participants were selected upon return of questionnaires.

Bias in classification of intervention

All the studies are at low risk of bias since the classification of CSTD versus control was clearly stated (19-21, 23-25, 27-45, 51, 52, 57, 58).

Bias due to deviations from intended interventions

Thirteen studies had low risk of bias (19, 20, 23, 25, 28, 30, 32, 35, 41,51, 52, 57, 58). There is insufficient information to assess the risk of bias due to deviations from intended interventions in 14 studies (21,27, 29, 31, 33,35 37-40, 42-44, 59) as they did not report whether the training periods and other co-interventions were similar in both groups. One study (24) is at serious risk of bias, since it is clear that only CSTD groups received additional training while the control group did not receive an equivalent period of training in safe handling.

Bias due to missing data

Two studies (24, 27) are at low risk of bias due to missing data. There is insufficient information to assess the risk of bias in the remaining 26 studies (19-21, 23, 25,28-44, 51, 52, 57,58).

Bias in measurement of outcomes

All studies are at serious risk of bias in measurement of outcomes since none of the studies used blinded assessment of outcomes 19-21, 23-25, 27-45, 51, 52, 57, 58).

Bias in selection of the reported result

Twenty-five (19-21, 24, 27-36, 38-44, 51,52, 57, 58) studies are at low risk of bias in selection of the reported result. The remaining three (23, 25, 37) studies have some concerns as they reported partial results.

Outcomes

Question 1: What are the proper procedures for safe handling of hazardous drugs through the medication circuit?

Three guidelines produced by NAPRA (10), ISOPP (5) and USP (7) were retained from the guideline search as they sufficiently addressed the issues of proper procedures for the safe handling of hazardous drugs and were therefore endorsed by the Working Group. The NAPRA guideline was produced by a national association of the regulatory bodies for pharmacy. NAPRA's main purpose is to serve its membership and to act as a resource for the public by providing information and guidance on pharmacy regulation in Canada (10). It was mandated that the hazardous drugs handling guideline conform to NAPRA standards. USP is the same type of national agency, but American. American pharmacies and pharmacists must adhere to USP mandates. ISOPP is the International Society of Oncology Pharmacy Practitioners. It was used in the first version of the guideline and an updated version has been found. In places where no changes were necessary, the Working Group maintained the recommendations from the previous version of the hazardous drug handling guideline (61).

Question 2: Are there any adverse health outcomes for healthcare workers who handle hazardous drugs?

The primary literature search revealed three comparative studies (51, 52, 57). The study by Dugheri et al. (57) was an environmental monitoring study that compared wipe samples before and after the use of CSTDs. The centralized pharmacy department went from 15,793 administrations in 2009 to 48,086 in 2017. To handle this higher volume, in 2012 the preparation and administration unit introduced ChemoClave (ICU Medical Inc., USA) and the CareFusion set for Multivia infusion (Becton Dickinson, USA). Additional equipment, such as the Diana Hazardous Drug Compounding System (ICU Medical Inc., USA), a needle-free, user-controlled system for the safe reconstitution and preparation of hazardous drugs, has been used since 2014. Data collected from 2009-2017, for a total of 3749 wipe tests and 57,720 determinations, were evaluated. The results showed that the proportion of positive samples gradually decreased from 11.7% in 2010 to 1% in 2017; the highest concentration of positives was on the floors (24%),

the door handles (21%), the work surface of the laminar flow hoods (11%), and the syringe pumps (10%) (57).

The two studies by Nassan et al. focused on the fecundity of nurses administering antineoplastic agents (51, 52). The 2019 study focused on the use of PPE in nurses administering antineoplastic agents. Data from the Nurse's Health Study 3 were used for this study. During the baseline questionnaire, nurses self reported on the use of PPE and needleless systems. There were 2649 participants who were actively attempting pregnancy. Every six months, the nurses reported the current duration of their pregnancy attempt. Multivariable accelerated failure time models were used to estimate time ratios and 95% confidence intervals (CIs) were adjusted for age, race, body mass index, smoking, marital status, hours of work, and other occupational risk factors. Among the nurses that were currently administering antineoplastic agents, those who had administered antineoplastic agents for six years and over had a 27% (95% CI, 6% to 53%) longer duration of pregnancy attempt than nurses who never handled antineoplastic agents in unadjusted analyses. However, this difference disappeared in multivariable analyses (time ratio [TR], 1.01; 95% CI, 0.85 to 1.21). At baseline, 93% (n=270) of the nurses currently administering antineoplastic agents stated that they consistently used PPE. These nurses had a similar median duration of pregnancy attempt to those who never handled antineoplastic agents (TR, 1.00; 95% CI, 0.87 to 1.15) (52).

The second study by Nassan et al. (51) also used data from the Nurses Health Study 3. The purpose of this study was to examine the association between antineoplastic drug handling and risk of miscarriage. There were 2440 nurses who reported 3327 pregnancies and 550 (17%) ended in miscarriages. When nurses who handled antineoplastic agents were compared with nurses who did not, the nurses who handled the drugs had an adjusted HR of miscarriage of 1.26 (95% CI, 0.97 to 1.64). After 12 weeks' gestation this association was even larger (HR, 2.39; 95% CI, 1.13 to 5.07). The HR for nurses who did not always use gloves was 1.51 (95% CI, 0.91 to 2.51) compared with 1.19 (95% CI, 0.89 to 1.60) for those who always use gloves. Nurses who did not always wear gowns had an HR of 1.32 (95% CI, 0.95 to 1.83) compared with 1.19 (95% CI, 0.81 to 1.75) for nurses who always wore gowns.

This study was not statistically significant but showed a suggestive association between handling antineoplastic drugs and miscarriage, particularly among nurses who did not consistently use PPE, with stronger associations for second trimester losses (51).

Question 3: Do closed-system transfer devices reduce contamination when used to prepare chemotherapy?

One systematic review was retained. The systematic review by Gurusamy et al. (26) examined the use of CSTD plus safe handling techniques versus safe handling techniques alone. This systematic review included 24 observational cluster studies. All the studies were at a serious risk of bias and the certainty of evidence was considered low. No randomized trials were found. This systematic review showed that the very low certainty evidence from small studies is inadequate to show if there is any important difference between CSTD and control groups in the proportion of people with positive urine tests for exposure between the CSTD and control groups for any of the drugs: cyclophosphamide alone (risk ratio [RR] 0.83; 95% CI 0.46 to 1.52; $I^2=12%$; 2 studies; 2 hospitals; 20 participants; CSTD: 76.1% versus control: 91.7%); cyclophosphamide or ifosfamide (RR, 0.09, 95% CI 0.00 to 2.79; 1 study; 1 hospital; 14 participants; CSTD: 6.4% versus control: 71.4%); and cyclophosphamide, ifosfamide, or gemcitabine (RR not estimable; 1 study; 1 hospital; 36 participants; 0% in both groups) (26).

Once again, small studies with a very low certainty of evidence were inadequate to show whether there is any important difference between CSTDs and control groups in the proportion of surfaces contaminated or the quantity of contamination. In 24 comparisons in pharmacy areas or patient-care areas, there was a reduction in the proportion of surfaces contaminated

in only one comparison and out of 15 comparisons in pharmacy areas or patient-care areas, there was a reduction in the quantity of contamination in only two comparisons (26).

Short-term health outcomes such as reduction in skin rashes, medium-term reproductive health outcomes such as fertility and parity, or long-term health outcomes related to the development of any type of cancer or adverse events were not reported in this systematic review (26).

The Gurusamy et al. systematic review demonstrated that “no firm conclusions can be drawn on the effect of CSTD combined with safe handling versus safe handling alone due to very low certainty evidence available for the main outcomes” (26).

A search for primary studies from the point that the Gurusamy et al. (26) systematic review ended was conducted. Studies included in the Gurusamy et al. systematic review were not duplicated. The search for primary literature yielded 25 studies. No randomized trials were found. All studies compared a CSTD to usual practice or another CSTD. The results of these studies are reported in Table 4-4. Four studies were found that investigated a compounding robot (19-21, 31). These results are reported in Table 4-5. Five studies compared a CSTD to the standard compounding procedures (24, 27, 33, 40, 41). The studies by Forges et al. (24), Valero et al. (33) and Wakui et al. (40) favoured the CSTD compared to usual practice and the study by Vasseur et al. (41) found variable results depending on the drug used. The study by Kulju et al. assessed volume loss and found variable results depending on the device used compared to CSTD (27). Fourteen studies compared CSTDs to other CSTDs. Eight studies investigated various devices against each other and performed different tests such as vapour escape, particulate contamination, and microbiological growth (25, 28, 30, 32, 34-36, 44). They are reported in Table 4-4. Eight studies compared CSTDs against other CSTDs to see which ones were optimal at containing contamination (23, 29, 37-39, 42, 43, 58). The study by Piccardo compared the Texium/Smart Shield to Equashield. The Equashield device showed no contamination after use (42). The abstract by Masson et al. showed that out of seven devices the Equashield showed no contamination out of all the tests (29). In the Garcia study no statistically significant differences were found between the Mini-Spike 2, Chemo + Puresite (MSCP) and Phaseal devices (59). The two similar studies by González-Haba Peña et al. showed that PhaSeal outperformed ChemoClave and SmartSite (38, 39). In the Call et al. study, five CSTDs were compared: ICU medical, PhaSeal, Onguard, CareFusion and SEVA. SEVA was the only device that showed no visible contamination (23). The Gómez-Álvarez et al. 2016 Abstract compared two devices, CareFusion and ICU Medical, and found the CareFusion System performed better (37).

Four studies evaluated compounding robots (19-21, 31). The study by Riestra compared the productivity of the KIRO Oncology compounding robot in three hospital pharmacy departments and tried to identify the optimal compounding time. A total of 16367 preparations were analysed. The automatic compounding time showed a relevant positive correlation ($|r_s| > 0.40$) with the number of preparations, number of vials and total volume per cycle. Therefore, these cycle specific parameters were chosen as independent variables for the mathematical model. Considering cycles lasting 40 minutes or less, predictability of the model was high for all three hospitals (R^2 : 0.81; 0.79; 0.72) (21). The study by Jobard et al. evaluated the accuracy and precision of robots dispensing various volumes into pumps, bags, and syringes. The robot filled all items to within the limit of 10%. Twenty-four operator gloves were tested, and two pairs showed microbiological growth, which was a point of concern (20). The study by Deljehier et al. also evaluated fill levels, which were found to be within acceptable limits. Contamination was found on working surfaces such as vial adaptors and waste containers. However, the final products were not contaminated on the surfaces except once on a syringe used on a positive pressure vial (19). The Schierl et al. study compared environmental contamination of cyclophosphamide during one week of drug compounding by conventional manual procedure in a BSC with laminar airflow and a new compounding robot. The detection

rate with wipe samples was 70% in the BSC versus 15% in the compounding robot. During the preparation using the BSC, contamination with cyclophosphamide was below 0.001 ng/cm² at most locations, but significant on gloves (0.0004-0.0967 ng/cm²) and the majority (70%) of infusion bags (<0.0004-2.89 ng/cm²). During robotic preparation, the contamination on gloves was (1 of 8: 0.0007 ng/cm²) and infusion bags (3 of 20: 0.0005, 0.0019, and 0.0094 ng/cm²). These were considerably less contaminated than using the BSC. However, residual contamination was found on the surfaces under the dosing device in the compounding area (0.0293-0.1603 ng/cm²) inside the robotic system (31).

Table 4-4. Data table for CSTD

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
Soefje 2022 (43)	To evaluate the effectiveness of a needle-free and a needle-based CSTD to minimizing surface contamination during simulated compounding, preparation, and administration.	PhaSeal ChemoLock	Post-trial wipe sample analyses following each of the 3 needle-free trials did not detect cyclophosphamide. For the needle-based CSTD, the wipe sample analyses after the first trial showed no contamination; however, cyclophosphamide was detected on the right biological safety cabinet workbench at concentrations of 0.223 ng/cm ² and 0.021 ng/cm ² , respectively, following the second and third trials. No cyclophosphamide was found on the technician's gloves after any of the 3 needle based CSTD trials.	Not stated	Laboratory
Szkiladz 2022 (44)	The objective of this study was to evaluate the performance of 3 CSTDs in preventing the escape of drug vapor in accordance with the 2015 NIOSH draft protocol during simulated compounding and administration tasks.	Chemolock PhaSeal Equashield	The three CSTDs had statistically equivalent performance and maintained IPA vapor levels below the limit of detection (LOD) of 1.0 ppm. Positive controls had mean vapor release of 17.40 ppm and 23.45 ppm for tasks 1 and 2, respectively. Positive controls also required statistically longer mean time to complete both tasks, followed in decreasing order by PhaSeal, Equashield, and Chemolock.	No conflicts of interest 2 authors were compensated by ICU Medical, to the time devoted to the review of data and development of manuscript.	Laboratory
Forges 2021 (24)	To evaluate the efficacy of Safe Infusion Devices in reducing drug exposure compared	Not stated	The usual practice led to a rate of 58.3% of contaminated samples while Safe Infusion Devices to a rate of 15%: Safe Infusion Devices reduced the risk of gloves contamination by 85% in multivariate	None	Oncology day hospital

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
	to usual infusion practices.		analysis (odds ratio=0.15; 95%CI = 0.05-0.46; p<0.001). Topotecan was identified in 100% of the samples. Only one case of cross-contamination occurred.		
Piccardo 2021 (42)	To evaluate the effectiveness of 2 CSTDs in reducing leakage during antineoplastic drug compounding.	Texium /SmartSite™ Equashield®	Wipe sampling showed gemcitabine contamination after compounding using Texium™/SmartSite™, with positive samples ranging from 9 to 23%. Gemcitabine was not present at detectable levels in the Equashield® II system in all of the evaluated samples.	None	Centralized cytotoxic drug preparation unit
Kulju 2020 (27)	Six CSTDs were assessed to determine if they contribute to volume loss and delivery of less than the intended dose during simulated drug administration.	PhaSeal™ Texium /SmartSite™ OnGuard™/Tevadaptor® Equashield® ChemoClave® ChemoLock™	The volume losses for ChemoLock (p=0.00001), Equashield (p=0.00005), OnGuard (p=0.0000), and Texium (p=0.0009) were significantly different than the control. The volume losses for ChemoClave (p=0.9780) and PhaSeal (p=0.8031) were not significantly different than the control.	None	Not stated
Forshay 2019 (25)	To evaluate the vapor containment abilities of CSTD technologies to provide meaningful comparisons between products.	SmartSite™ VialShield™ PhaSeal™ ChemoLock™ OnGuard™ with Tevadaptor® ChemoClave® Equashield®	For Task 1, two CSTD products (PhaSeal™ and Equashield®) adequately contained the isopropyl alcohol vapour and passed the predefined testing criteria. The same two products, plus one additional product (ChemoLock™), contained the vapour for Task 2 manipulations. Based on the results of this study, only two of the six CSTD brands passed testing criteria for both tasks, functioning as truly closed systems.	This work was supported by a grant from Equashield.	Not stated
Wilkinson 2019 ABSTRACT (34)	The syringe integrity of a closed system (Tevadaptor SAL) was tested in	Tevadaptor® (Simplivia Healthcare Ltd) SAL were tested in	All Tevadaptor SAL/syringe combinations showed no evidence of microbiological growth, demonstrating that sterility was maintained. Positive control tests (n=2)	Not stated	Not stated

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
	combination with a range of Luer lock syringe sizes reflecting clinical practice according to the 2013 NHS yellow cover document (YCD) guidelines	combination with Luer lock syringes at: 1 mL, 20 mL and 60 mL.	produced growth following inoculation with <100 cfu of <i>B. diminuta</i> and incubation for three days at 30-35°C. Physical integrity: Limit of detection (LOD) for the methylene blue dye was determined at 1:10,000 dilution of 0.4% w/v stock for both visual and instrumental readout. Combinations of Tevadaptor SAL+ Luer lock syringe (n=20) at the three syringe sizes tested were found to be below the LOD, indicating no ingress of methylene blue dye at the end of test. Positive control tests (n=3) at each size showed ingress of dye with absorbances 0.010 (0.005) mAU confirmed spectrophotometrically and by visual appearance.		
Masson 2018 ABSTRACT (29)	Usability and leak test	Phaseal™, Tevadaptor®, Chemo-Clave®, Equashield®, ChemoLock™, Viashield and Qimono	After the usability test 3 devices were selected: Chemolock, Tevadaptor and Equashield The same 3 devices showed zero spots of fluorescein on the CSTD: When test was repeated 10 times only Equashield showed no contamination.	Not stated	Hospital
Valero Garcia 2018 (58)	To evaluate the devices, use on contamination surface levels, professionals' satisfaction, and compounding time at pharmacy.	Mini-Spike 2 Chemo + Puresite (MSCP) Phaseal™	No statistically significant differences in the median contamination surface levels between basal and final sampling time, CYP (0.140; 95% CI -1.135, 1.601), 5FU (-0.506; 95% CI -1.756, 0.287). A difference of 10 s on compounding times between the two devices tested (p<0.001) favouring MSCP	None declared	Hospital pharmacy
González-Haba Peña 2018 (38)	The objective of this study was to compare the environmental	A - ChemoCLAVE® B - SmartSite® C - PhaSeal™	Qualitative contamination at the critical points during preparation was seen in groups A and B for every mixture that was processed.	None declared	Not stated

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
	contamination generated during the preparation of HDs		No contamination at all in critical points was seen in any of the mixtures prepared using PhaSeal™. Statistically significant differences were found between arms A and C (p<0.001) and arms B and C (p<0.001); no differences were found between arms A and B.		
González-Haba-Peña 2018 (39)	To compare the environmental contamination generated during the preparation of HDs using three different methods through simulations using fluorescein	A - ChemoCLAVE® B - SmartSite® C - PhaSeal™	Qualitative contamination at the critical points during preparation, was seen in groups A and B for every mixture that was processed. No contamination at all in critical points was seen in any of the mixtures prepared using PhaSeal™. Statistically significant differences were found between arms A and C (p<0.001) and arms B and C (p<0.001); no differences were found between arms A and B.	None declared	Not stated
Smith 2018 (32)	The aim of this study was to determine whether substituting the BD PhaSeal™ Protector P50 with the BD PhaSeal™ Protector P55 reduced the level of particulate contamination in hazardous compounded products	PhaSeal™ Protector P50 PhaSeal™ Protector P55	Phase 1 baseline - 134 products were contaminated out of 2501 (5.3%). Phase 2 - substitute the Protector P50 with the P55 into the compounding process to compound a single medicine product, vincristine in sodium chloride 0.9% 50 mL. One out of 75 vincristine products had particulate contamination (1.3%) using P55. Phase 3 - 28 contaminated products out of 3877 (0.72%) using P55.	No conflicts declared	Hospital pharmacy
Valero 2018 (33)	To demonstrate that the use of a CSTD (BDPhaseal™) reduces antineoplastic drug surface contamination levels in the	Phaseal™ Spinning Spiros Closed male Luer, Purple Cap, Spike with Bonded CLAVE connector and Locking Universal	4 sampling times: baseline; just after a decontamination procedure; four months after introduction of PhaSeal™; and after eight months using PhaSeal™ There was a decrease at the number of positive samples at the beginning/end of the study for all the drugs tested: 28/15 for	Research grant from Becton Dickinson, S.A.	Hospital pharmacy

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
	compounding are of our pharmacy department in comparison to the drug transfer device currently used	Vented vial spike Clave	cyclophosphide, 29/23 for iphosphamide and 7/1 for 5FU. Compared to the baseline, median cyclophosphamide levels significantly decreased ($p < 0.001$) at 4 and 8 months sampling time (baseline: 1.01 ng/cm ² to 0.06 ng/cm ² and 0.01 ng/cm ²), and median iphosphamide levels significantly decreased ($p < 0.001$) at 8 months sampling time (baseline: 3.02 ng/cm ² to 0.06 ng/cm ²). 5FU did not show significant differences between the sampling times (baseline: 0.09 ng/cm ² to 0.09 ng/cm ²).		
Vasseur 2018 (41)	To compare the decontamination level obtained using a CSTD+ standard cleaning procedure with a CSTD + standard cleaning procedure + specific decontamination procedure.	Phaseal™	Results are presented as the odds ratio (OR) of contamination and as overall decontamination efficiency (Eff _Q %). The proportion of Eff _Q ≥ 90% was assessed by a Fisher's exact test ($p < 0.05$). Overall contamination rates (CR,%) were significantly different from one isolator to the other (CR Control = 25.3% vs. CR Isolator = 10.4%; OR = 0.341; $p < 0.0001$). Overall Eff _Q values (median; 1 st and 3 rd quartiles) were higher in the intervention isolator (I: 78.3% [34.6%; 92.6%] vs. C: 59.5% [-5.5%; 72.6%]; $p = 0.0015$) as well as the proportion of days with an Eff _Q ≥ 90% (I: 42.9% vs. C: 7.1%; $p = 0.077$) but very variable depending on drugs.	Becton-Dickinson laboratories financed the study	Hospital pharmacy
Wilkinson 2018 (35)	(A) Select the most appropriate surrogate (B) Validate the NIOSH protocol using this surrogate (C) Determine the containment performance of	Tevadaptor® PhaSeal™ Chemo Clave® vial shield and Spiros Equashield®	The Equashield®, Tevadaptor®, and PhaSeal™ devices all showed average releases based on 10 measurements from five tests, that were less than the LOQ (i.e., <0.88 ppb), while the Chemo Clave Vial Shield with Spinning Spiros showed average releases of 2.9±2.3 ppb and 7.5±17.9 ppb for NIOSH tasks 1 and 2, respectively, at the 95% CI. The open system	Research grant from Teva Pharmaceuticals	Laboratory

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
	four commercial CSTDs as compared with an open system of needle and syringe using the validated NIOSH protocol.	Needle and syringe	of needle and syringe showed releases, based on two measurements from a single test, of 4.2 ± 2.2 ppb and 5.1 ± 1.7 ppb for NIOSH tasks 1 and 2, respectively, at the 95% CI.		
Call 2017 (23)	This study's aim was to determine how HD might spread through touch after handling contaminated vials in simulated pharmacy and nursing environments	ICU medical, PhaSeal™, Onguard™ CareFusion SEVA	Transfer of the HD testing medium (Glo Germ) to IV sets, pharmacy PPE, and nursing PPE was observed in 4 of 5 CSTDs tested. The only CSTDs that showed no observable contamination was the Allison Medical Safety Enclosed Vial Adapter (SEVA) system (Littleton, CO).	No conflicts	Laboratory
Gómez-Álvarez 2016 (37) Abstract in English only	To assess the impact of two closed-system drug transfer devices on the local and environmental contamination and preparation times in the process of preparation of parenteral chemotherapy compared to the standard system	CareFusion and ICU Medical	75 preparations were prepared. Local contamination was reduced 21% and 75% in closed-system ICU Medical® and CareFusion®, respectively. In the CareFusion® closed system, local contamination was significantly lower than the standard system to the vial, syringe, and final package, while ICU Medical® closed system only was significantly lower in the connection to the vial.	Unknown, study in Spanish	Unknown, study in Spanish
Garrigue 2016 (36)	Evaluation of ease to use by nine operators in practical conditions,	PhaSeal™ VialShield classic spike device (Spike Swan, Codan)	No microbiological growth was observed with any the devices. A leakage of smoke was observed only with Spike Swan. Fluorescein leakage assessment confirmed that PhaSeal™ is a performing closed system	PhaSeal devices and VialShield /Texium devices were	Hospital pharmacy

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
	microbiological safety performance and leakage assessment		with a dry connection. Spike Swan showed fluorescein leaks. Fluorescein drops were visible on the connection sites of the VialShield/Texium. No fluorescein was found on compress after connection swapping.	provided by Becton Dickinson and CareFusion, respectively Other conflicts not stated	
Lalande (28) (2015)	To determine the ability of these systems to reduce HD exposure of nurses. The study also examined the ability of these systems to reduce the amount of HD not administered to the patient and evaluated the feasibility of these systems' integration into clinical practices	HD safe infusion systems (CSISs) Cair, Codan, and ICU Medical	The average HD residual volume in the chemotherapy tubing and chemotherapy bags was to 4 mL (3-6 mL) for Codan, 1.5 mL (0-3 mL) for Cair, and 2.5 mL (1-5mL) for ICU Medical. For all manufacturers, the residual volume was significantly decreased compared with traditional administration ($p < 0.0001$). The average cytotoxic residual volume measured traditional administration was 13 mL (5-20 mL). The ultraviolet-visible spectroscopy analysis of the fluid volume collected at the end of the tubing did not find any HD residue.	The authors have no conflicts to disclose	University teaching hospital in France
Savry 2014 (30)	The results of a MFT study to validate processes for HD preparation inside and outside aseptic compounding isolators are presented. The team also tested	A classical spike and two protective devices PhaSeal™ system and Spiros/Genie system	Three operators did three MFTs (10 MFT units per test for a total of 30 units per operator) under simulated blackout conditions, each time with a different protective device. <i>Bacillus</i> species proliferated in only 1 unit of the 90 units produced; that incident involved the use of the Spiros/Genie system. When the test was repeated by the same operator using the same device, with increased attention to the decontamination procedure, no microbiological contamination was observed.	The authors have no conflicts to disclose	University teaching hospital in France

Reference	Purpose / Scope	Type of device	Results	Conflict of Interest / Disclosure	Test environment
	alternative compounding systems, two closed-system transfer systems for use during power outages or other emergencies precluding drug preparation within isolators				
Wakui 2013 (40)	To reduce the exposure to drug preparations, and develop drug preparation equipment without external drug leaks in a closed state for oral anticancer drugs	The CSTD was developed by connecting the 10mL disposable syringe that was attached to the projections for crushing the tablet and the no-processing 30mL disposable syringe to the three-way stopcock. In addition, the gasket of the plunger of the syringe was flattened using a hot plate to create a stable foundation for placing the tablet.	The experiment was performed 5 times. Cyclophosphamide was detected in trace amounts in two of the samples. It was confirmed that cyclophosphamide exposure of the preparer was reduced using the developed closed oral preparation device method.	Not stated	Not stated (Japan)

Abbreviations: cfu = colony-forming unit; CI = Confidence interval; CSTD = closed system transfer device; CYP = cyclophosphamide; 5FU = 5-fluorouracil; HD = hazardous drugs; ICU = intensive care unit; IV = intravenous; MFT = Media fill test; NHS = National Health Service; NIOSH = National Institute for Occupational Safety and health; LOQ = Limit of Quantification; mAU = milli-absorbance unit; ppb = part per billion; PPE = personal protective equipment

Table 4-5. Data tables for compounding robots

Reference	Study type	Results	Conflict of interest / Source of funding
Riestra 2021 (21)	To compare productivity of the KIRO Oncology compounding robot in three hospital pharmacy departments and identify the key factors to predict and optimize automatic compounding time	6367 preparations were analysed. Automatic compounding time showed a relevant positive correlation ($ r_s > 0.40$) with the number of preparations, number of vials and total volume per cycle. Therefore, these cycle specific parameters were chosen as independent variables for the mathematical model. Considering cycles lasting 40 minutes or less, predictability of the model was high for all three hospitals (R^2 : 0.81; 0.79; 0.72).	One of the authors works for the company of the robotic compounding
Jobard 2020 (20)	Describes the qualification procedure applied prior to production phases. Peristaltic pumps that ensure the reconstitution of drugs were tested with water and NaCl 0.9%. The performance of the robot (accuracy and precision) to prepare bags, syringes and elastomeric pumps was evaluated with three placebo solutions (aqueous, foaming, and viscous) using gravimetric controls. Microbiological controls were also performed.	The pumps met the requirements set for volumes ranging from 5 to 100 mL. A total of 274 preparations was compounded. For the bags, the filling accuracy was within the limit of $\pm 10\%$ from 1 to 48 mL with aqueous solution, from 0.6 to 48 mL with foaming solution and from 5 to 48 mL with viscous solution. For all syringes and elastomeric pumps, it was within the limit of $\pm 10\%$. The precision was validated for all preparations, except for bags and syringes prepared with 0.6 and 0.25 mL, respectively. The samples of surfaces and air complied with ISO 5 class environment. Among the 24 gloves tests performed, two presented microbiological growth. All Media fill tests were validated. The qualification procedure led to excluding injections of any active principle volume strictly lower than 1 mL.	Declaration of Conflicting Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Funding: the authors received no financial support for the research, authorship, and/or publication of this article.
Deljehier 2019 (19)	The aim of this study was to develop a specific simulation program for the validation of a hazardous compounding robot, KIRO Oncology robot. The risk of chemical contamination was simulated by using fluorescent	Over 187 preparations performed and among the six different excipients formulations, when using factory settings of the robot, only viscous solutions (dextrose 50% and paclitaxel-like formulation) and foaming solution exhibited internal accuracies over the limit of $\pm 10\%$.	The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors received no financial support for the

	dye of the process with high-risk excipient formulation and overpressure vials.	For vial reconstitution step, 5003 reconstitutions were analyzed, and 4906 (98.1%) were in the range [-2%;+5%], 77 (1.5%) were lower than -2% and 20 (0.4%) were higher than +5%, which led the robot to reject a total of 97 vials. The mean overall reconstitution accuracy was 101.48% with a standard deviation of 2.33%. Contamination with fluorescent dye was found on working surfaces depending on the excipient formulation and the internal vial pressure. Fluorescent spots were mainly found on vial adaptors and waste containers with foaming solution and positive pressure vials. End-products were not contaminated on surfaces regardless of the formulation except one time on a syringe used on a positive pressure vial	research, authorship, and/or publication of this article.
Schierl 2016(31)	To compare environmental contamination of cyclophosphamide (CP) during 1 week of drug compounding by conventional manual procedure in a biological safety cabinet (BSC) with laminar airflow and a new robotic drug preparation system (APOTECACHemo).	The detection rate was 70% in the BSC versus 15% in APOTECACHemo. During manual preparation of admixtures using BSC contamination with CP was below 0.001 ng/cm ² at most locations, but significant on gloves (0.0004-0.0967 ng/cm ²) and the majority (70%) of infusion bags (<0.0004-2.89 ng/cm ²). During robotic preparation by APOTECACHemo, gloves (1 of 8: 0.0007 ng/cm ²) and infusion bags (3 of 20: 0.0005, 0.0019, and 0.0094 ng/cm ²) were considerably less contaminated. Residual contamination was found on the surfaces under the dosing device in the compounding area (0.0293-0.1603 ng/cm ²) inside the robotic system.	None declared

Abbreviations: BSC = Biological Safety Cabinet; NaCl = sodium chloride

Ongoing, Unpublished, or Incomplete Studies

No studies were found.

DISCUSSION

Three systematic reviews were found: closed-transfer systems, pregnancy-related outcomes, and general health outcomes. The searches spanned 2013 to 2021, in order to update the previous version of this guideline. The corporate sponsors influenced the literature on closed systems, as they subsidized numerous tests and comparisons. Therefore, the group interpreted the results of these studies cautiously. The other systematic reviews on pregnancy and general health outcomes did not identify many studies. Most of the research on this topic was conducted before 2006 and is, therefore, captured in the previous versions of this guideline.

Previous data on CSTDs were similar to what we found in this update. Most studies were observational, and few were comparative. Studies on pregnancy from the first version of this guideline showed that there is a slightly elevated risk for spontaneous abortion among healthcare workers who handle hazardous drugs, but not for congenital malformations. The first version of this guideline also found a slight risk for cancer in healthcare workers exposed to hazardous drugs.

In addition, the articles that were retrieved, while published recently, used older study data. While there are numerous studies about wipe sampling where hazardous drugs are handled, those data neither translate into general health outcomes nor show whether the preventive measures currently used will prevent adverse health effects in the future to those who handle them. Due to insufficient evidence, the group cannot state whether workers handling hazardous drugs are at an increased risk of cancer and other acute toxic effects.

CONCLUSIONS

While hazardous drugs cause adverse effects in health workers who handle them without proper protection, the evidence does not show any tests, guidelines or amounts that are safe. There is no one CSTD or compounding robot that is flawless and operator error should also be considered. The best protection against hazardous drugs is constant vigilance and a combination of measures that are defined in the recommendations.

Safe Handling of Hazardous Drugs

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group’s responses are described below.

Expert Panel Review and Approval

Of the six members of the GDG Expert Panel, six members voted and zero abstained, for a total of 100% response in December 2021. Of those who voted, five approved the document (83%). The main comments from the Expert Panel and the Working Group’s responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group’s responses to comments from the Expert Panel.

Comments	Responses
I think there is a typo under Intended users, as it says “intended used include” should it be “intended users include”?	We have modified the document.
Is the change back to wearing two pairs of gloves in some steps in the medication circuit a result of more recent research related to CSTDs?	This is a due to a change in the NAPRA standards.
I would probably not have chosen the term “cytotoxic” for the title. It is limiting and implies a narrower category of implicated drugs because many anti-cancer drugs are not cytotoxic. I believe the correct term should be Hazardous Drugs. For example, tamoxifen, a Group I International Agency for Research on Cancer carcinogen, and carfilzomib (a Table 2 Drug in NIOSH) are not considered true cytotoxics. Tamoxifen is cytostatic.	We have modified the document to also include hazardous drugs.
I think I need more justification for why two pairs of shoe covers are required for counting of solid oral dosage forms. This is a huge economic and process impact on our outpatient pharmacy as well as for our clinical trial processes.	We have modified the document; two pairs of shoe covers are not required for counting dosages.
I would also suggest there be more instructions about crushing. While you strongly recommend crushing be managed in a BSC, this is only a readily accessible solution for hospital facilities (even then, it	That is beyond the scope of this document. A new CAPCA and CCO document provide guidance for community pharmacies. Sick Kids Hospital in Toronto provides information for

<p>is not always logistically easy). Given the target population of your guideline includes “nursing and other healthcare workers”, this guideline is also targeting clinicians who do NOT have access to a BSC.</p>	<p>administration of drugs at home and also the use of dissolve-a-dose.</p>
<p>Spill management:</p> <ul style="list-style-type: none"> - all staff working in environments where hazardous drugs are handled should be trained in the use of a spill kit - spills should only be cleaned by trained staff. I'm not sure why you specify “healthcare worker”, it should be all staff including those responsible for transporting and housekeeping. - it is legislated that DISPOSABLE items from the clean up of spills be placed in the cytotoxic waste receptacle. Non-disposable items should be thoroughly cleaned and decontaminated. - policies and procedures should include the reporting and surveillance of spills. - follow-up after a spill includes incident reporting and restocking of equipment. - I prefer your wording in Section 1 rather than “It is strongly recommended that a spill management kit be readily available within the work area.” It should also be in all areas where storage, receiving and transport occurs. - It is strongly recommended that a spill kit be readily available in the home in case of accidental spills. But, hospitals must ensure patients or their caregivers are trained on the use of the spill kit and the donning of PPE. 	<p>We have modified the document.</p>
<p>Environmental Cleaning</p> <ul style="list-style-type: none"> - The following statement is confusing.....”It is strongly recommended that cleaning of the biological safety cabinets be performed by trained personnel following manufacturer’s guidelines”. We never follow manufacturer guidelines for the cleaning of the inside of the BSC. Manufacturer guidelines are too vague! Do you mean the maintenance of the BSC? Or the OUTSIDE surface of the BSC? 	<p>We have modified the document for environmental cleaning to align with NAPRA.</p> <p>Specific recommendations on monitoring are outside the scope of this document.</p>

<p>- isn't environmental monitoring mandatory as per NAPRA? It should not be a consideration</p>	
<p>I would like to see the document provide more direction about the cleaning of administration areas; for example, how often and with what agents should administration areas be cleaned? In the spill management area it references decontaminating, deactivating and disinfecting the area but with what products?</p>	<p>Out of scope of the document.</p>
<p>Patient Care - is a level 3 chemo gown determined as necessary when providing patient care, or does the language just need to be changed to patient care when at risk of exposure to bodily fluids? I am thinking of transfers, helping them to get dressed, measuring vital signs when there is no risk of contact with bodily fluids. Shouldn't gloves and face protection be sufficient? Just thinking of waste. Currently, chemo gowns are only worn if a patient is incontinent, bleeds, etc., at our facility. For routine care is a chemo gown necessary when there is no risk of exposure?</p>	<p>We have modified the document.</p>
<p>Management of extravasation - if a physician is performing the instillation of normal saline to flush the medication out of a large site should a mask be recommended as well for the removal of saline (via physical compression of the arm - potential splash hazard) for anyone assisting?</p>	<p>We have modified the document.</p>
<p>Recommendation 8: Drug administration Would recommend additional inclusion that only those with the ongoing competency and training to manage the administration of cytotoxic medications are able to do so. This includes CCO treatment ordering guidelines and administration competencies, rather than just safe handling training. Many centres allow staff to administer cytotoxic medications with no training.</p>	<p>There is another CCO guideline that addresses this issue.</p>
<p>I would also recommend that Luer lock connectors and CSTDs are always used to mitigate the risk of exposure during</p>	<p>Already addressed in document.</p>

<p>administration and that needless devices are never used in administration sets. I realize this may put smaller centres at a disadvantage, but it would significantly lower any risk of exposure and improve safe handling.</p>	
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RAP Review and Approval

Three RAP members reviewed this document in December 2021. The RAP approved the document. The main comments from the RAP and the Working Group’s responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group’s responses to comments from RAP.

Comments	Responses
<p>There are multiple acronyms in the document. Make sure to explain the meaning in full at the start of each section.</p>	<p>We have modified the document</p>
<p>While the general methods used to formulate the recommendations are described, these are broad. There are so many recommendations; most seem to make common sense, but some are not that obvious and there is no justification to the recommendations section where one can read more about the rationale for each recommendation.</p>	<p>This document is different from other PEBC guidelines in that it must adhere to the Health and Safety Act, and NAPRA standards. We did not include the customary justification for each recommendation and chose a broad statement.</p>
<p>There did not appear to be different options to manage exposures, but rather a series of recommendations to follow. Are there options for PPE or for storage or handling of cytotoxic agents? If there are not, perhaps an explicit sentence to state that the authors do not feel that there are alternative options for any of these recommendations.</p>	<p>Before the recommendations, there is a definition of the hierarchy of workplace controls which explain how reduction of exposure takes place.</p>

Patient and Caregiver-Specific Consultation Group

Patients/survivors/caregivers participated as Consultation Group members for the Working Group. They reviewed the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the Working Group’s Health Research Methodologist. The main comments from the Consultation Group are summarized in Table 5-3.

Table 5-3. Summary of the Working Group’s responses to comments from the Consultation Group.

Comments	Responses
<p>I think you should have a patient and/or caregiver that handled cytotoxic drugs at</p>	<p>We have modified the document.</p>

home on the committee in the recommendation.	
There should be an assessment of the patient's home and living situation to see whether they should receive the cytotoxic drugs at home.	There is another document that addresses this point from CCO.
Would the oral hazardous medication be labelled as such?	All hazardous drugs including oral medications will be labelled.
What should the patients do about bathrooms? Should they use the same one at home?	Using the same one is fine. If there are any spills they should be cleaned up.
Can a caregiver be present if the patient is receiving medication in the home?	Yes.
What if the patient vomits after receiving the medication? There should be instructions.	As part of general home care, there should be instructions about spill management and vomiting of medications. Also, you can call your cancer centre for further information.
What if someone in the family is pregnant and the patient receives this medication in the home? What would be the precautions?	Family can be present, but they should not be handling or cleaning up any medications or body fluids.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Four targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two agreed to be the reviewers (Appendix 1). One response was received. Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewer and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (N=1)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.		X			
2. Rate the guideline presentation.		X			
3. Rate the guideline recommendations.			X		
4. Rate the completeness of reporting.				X	
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			X		

6. Rate the overall quality of the guideline report.					
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.		X			
8. I would recommend this guideline for use in practice.	(NA)				
9. What are the barriers or enablers to the implementation of this guideline report?	<p>In order for a facility to implement the guidelines, they will need to have a strong safety culture. This means that senior management shows commitment to ensuring the health and well-being of the workforce by taking health and safety seriously, being proactive and responding to incidents and concerns in a timely manner.</p> <p>Barriers would include financial resources as CSTDs and negative pressure areas are expensive. Another barrier would be ensuring that the BSC is installed and functioning properly as there are cost considerations and appropriate expertise is required.</p>				

Table 5-4. Summary of the Working Group’s responses to comments from targeted peer reviewers.

Comments	Responses
<p>1. I have reservations about the fact that the evidence was reviewed systematically because there was only one primary reviewer, only two databases were searched (without a thorough justification), search terms were not included, and the limited number of studies included in this review. Also, the systematic review for the CSTDs that was included in the review has been questioned by some of the leading researchers in the area of healthcare workers’ exposure to hazardous drugs. In my opinion, if the committee were to have their systematic review process published as a peer-reviewed article, it would strengthen the entire process. See other comments on this matter embedded in draft guideline.</p>	<p>Searching two databases with one reviewer is standard procedure for systematic reviews. Any issues or discrepancies are looked at the lead authors.</p> <p>The full literature search is in Appendix 2. It states this in the document.</p> <p>It is beyond our control as to how many studies were found. All studies in the systematic review portion of the guideline were comparative. The quality and limitation of the systematic review are outlined in the document. We use AMSTAR2 to access the quality of systematic reviews.</p> <p>The full systematic review methods and PEBC processes are available if you follow the link in Section 3.</p>

2. There also appears to be lack of consultation with departments outside of pharmacy and nursing, which is important if you are considering all the risks associated with hazardous drug exposure throughout the medication circuit. Other departments affected and, therefore, ought to be consulted, would be shipping/receiving, transport (e.g., porters), and housekeeping	This is an update of an existing guideline to make sure it is incorporating NAPRA and USP 800. Consultation with other departments took place when the original guideline was written.
3. I personally believe that the guideline could be better organized	All of our guidelines including recommendations follow the same format.
Recommendations are consistent with most other best practices on the safe handling of hazardous drugs. However, there were instances of inconsistency with respect to terminology and lack of evidence for some of the recommendations, e.g., vinyl gloves not be worn and changing absorbent pad every 3.5 hours (see attached with comments embedded). In my opinion, if this is an evidence-based guideline, then the listed recommendations ought to be supported/justified.	We have modified the document.
An element that is currently missing and should be included as a general recommendation is the need for an organization to conduct a risk assessment and/or gap analysis. The risk assessment would be important because the layout of every facility will differ as well as the amount and type of hazardous drugs handled. The gap analysis should be conducted to identify where there are gaps with the facility’s current practice relative to the occupational health and safety legislation and the best practice guidelines.	We have modified the document.
Please be consistent in use of terminology, e.g., CSTD is not used throughout, face protection vs. facial protection.	We have modified the document for consistency.
Some PPE usage requirements in body of the guideline is not consistent with requirements in Table 2-1.	We have modified the document.
Also, more guidance regarding environmental monitoring should be provided.	We did not want to make this guideline over prescriptive.
Minor corrections and typos.	We have modified the document.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Medical oncologists, nurses, and pharmacists in the PEBC database were contacted by email to inform them of the survey. One hundred ninety-five individuals were contacted. Seventeen (8.7%) responses were received, and 178 stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 17 people are summarized in Table 5-5. The main comments from the consultation and the Working Group’s responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number 17 (8.7%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				8	9
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1	4	12
3. I would recommend this guideline for use in practice.				3	14
4. What are the barriers or enablers to the implementation of this guideline report?	<ul style="list-style-type: none"> • Cost may be a barrier factor to facilities depending on what parts of the guidelines would have gaps to be addressed • Enablers: added clarity Barrier: requires re-education to support enhanced understanding of risks and updated practices/evidence. • It is good guideline and there should be no major barriers • The challenge is having those individuals who would be affected by the guideline reading and implementing the recommendations as it is rather lengthy with a total of 14 recommendations. • Barriers - target audience can be difficult to reach (chemo nursing staff, pharmacy, etc., and it will be important to also facilitate appropriate learning/teaching opportunities at the various centres. • Barrier: Time constraints. lack of a desire to engage in safety guideline. Lack of education/knowledge Enablers: Strong desire and commitment to adhere to best practices and safety guidelines. Education and having safe handling champions in this area. 				

	<ul style="list-style-type: none"> • need dissemination plan to the large audience that needs to be aware of this guideline - likely needs a toolkit to simplify • Barriers to this report include: <ol style="list-style-type: none"> 1) access and review of the contents by the multiple individuals involved in therapy administration 2) The document uses, for the most part the phrasing strongly recommended, which is an impediment to adoption of recommendations. • Barriers: <p>Many items are “strongly recommended” and not mandated (especially if taking to hospital administration).</p> <p>Very expensive to implement some of the infrastructure recommendations/requirements. Very expensive to provide all patients on Take Home hazardous drugs with spill kits. Back order of supplies has (in the past) temporarily impacted our ability to maintain some of the requirements we already practice. Some of the steps for donning and doffing of PPE we have modified (i.e., the way gloves are pulled up, to prevent tearing), but maintain the goal of the process.</p> <p>Enablers:</p> <p>Very thorough literature search and review. Good citation of references. Outlines a thorough list of points for consideration. Diverse panel from various disciplines. Comprehensively covers all areas of potential exposure to hazardous drugs.</p> • Barriers are ensuring a committee is always maintained and providing up-to-date information. Readily available PPE can be a barrier. Enablers are having the committee and ensuring an online recertification course for those staff who handle cytotoxic materials. • Oral chemotherapy is administered in many care settings where staff may not have Oncology-specific knowledge of safe handling. Equipment and supplies for safe handling and associated costs may be a factor in settings such as long-term care, retirement/assisted living, and rehabilitation. <p>Province-wide dissemination of guidelines will need to be inclusive of all care settings.</p>
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	<ul style="list-style-type: none"> Barriers include proper training of personnel or personnel compliance and variations between different physical settings of institutions.
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Table 5-6. Summary of the Working Group’s responses to comments from professional consultants.

Comments	Responses
1. Several comments were made about visual improvements to the recommendation tables.	We have a guideline structure that we follow for all recommendations.
2. Several comments were made about the use of strongly recommended.	We feel that strongly recommend is the highest level we can use. These are only recommendations based on the evidence, anything that is law is stated as “it is legislated”.
3. Why are medical oncologists not target audience? They manage extravasations and need to understand what happens when they order a hazardous drug.	The target audience has been modified.
4. There is not a specific section on management in hospital or management in private infusion clinics as these are areas where there are always a lot of questions.	This document is intended for hospitals or out-patient clinics. Private infusion clinics are not in the scope of this document, but many recommendations could be applied to them.
5. There is a comment that staff who are trying to conceive or pregnant etc should be accommodated to not have exposure - this is typically not the case with physicians and maybe we need to consider this wording as this may impact care if a guideline indicates that staff should be accommodated.	We feel that our wording of “staff” is broad enough to include anyone working with hazardous drugs.
6. Minor corrections and typos	We have modified the document

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Members of the Safe Handling of Hazardous Drugs Working Group

Name	Affiliation	Declarations of interest
Working group		
Kardi Kennedy	Program Operational Director Kingston Health Sciences Centre Kingston, Ontario	None declared
Kathy Vu	Clinical Lead, Safety Initiatives - Cancer Care Ontario Toronto, Ontario	Received a research grant on behalf of the University of Toronto from Pfizer.
Nadia Coakley	Health Research Methodologist Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared
Jennifer Daley-Morris	Clinical Coordinator Southlake Regional Health Centre Newmarket, Ontario	\$500 or more to act in a consultancy capacity: Jansen Amgen, Roche, AbbVie, Eli Lilly, Pfizer
Leta Forbes	Medical Oncologist, Provincial Head, Systemic Treatment Program Ontario Health, Cancer Care Ontario Toronto, Ontario	None declared
Renee Hartzell	Program Manager Kingston Health Sciences Centre Kingston, Ontario	None declared
Darrilyn Lessels	Patient Care Manager Lakeridge Health Oshawa, Ontario	None declared
Expert Panel		
Heather Bussey	Clinical Educator, Outpatient Oncology MHCW Regional Oncology Nursing Lead Mississauga Halton Central West Regional Cancer Program Trillium Health Partners Mississauga, Ontario	None declared
Anna Granic	Coordinator, Grand River Regional Cancer Centre Pharmacy Kitchener, Ontario	\$500 or more to act in a consultancy capacity: Adult acute myeloid leukemia education
Mova Leung	Oncology Pharmacist Practitioner North York General Hospital Toronto, Ontario	None declared

Guideline 16-3 Version 3

Devon Pilkington	Clinical Educator Cancer Care London Regional Cancer Program London, Ontario	\$500 or more in a single year to act in a consulting capacity as a speaker.
Karen Roberts	Manager Clinic Operations, Nursing, Systemic Therapy, Palliative and Supportive Care - Thunder Bay Regional Health Sciences Centre Thunder Bay, Ontario	None declared
Amanda Trigiani	Interim Pharmacy Operations Coordinator Southlake Regional Health Centre Newmarket, Ontario	None declared
Targeted Peer Reviewers		
Chun-Yip Hon	School of Occupational and Public Health Ryerson University Toronto, Ontario	None declared
Report Approval Panel		
Jonathan Sussman	Chair, Department of Oncology McMaster University Juravinski Cancer Centre Hamilton Ontario	None declared
William (Bill) Evans	Medical Oncologist Professor Emeritus McMaster University Hamilton, Ontario	\$500 or more in a single year to act in a consulting capacity? Advisory Boards: Novartis (ruxolitinib) Feb 2021; GSK (dolstarimab) June 2021 Consulting services; Lilly (Selpercatinib in NSCLC) July 2021; Abbvie (AML economic burden) Oct 2021; Novartis (Jakavi in cGVHD) Sept 2021; Roche (various hematologic products/disease) March 2021
Muriel Brackstone	Surgical Oncologist London, Ontario	None declared
Members of the Patient Consultation Group		
Bob Tuck		None declared
Lise Craig		None declared
Laurie Petz		None declared
Lynne Sevean		None declared

Appendix 2: Literature Search Strategy

Medline and Embase combined general search on cytotoxics and health care workers

1. exp occupational exposure/
2. exp health personnel/
3. oncologic nursing.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
4. oncology service, hospital.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
5. pharmacy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
6. pharmacy service, hospital.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
7. nurs:.mp.
8. pharmac:.mp.
9. or/2-8
10. 1 and 9
11. exp antineoplastic agents/ad, ae, po, st, to
12. 10 and 11
13. exp epidemiologic study characteristics/
14. cohort.mp.
15. control.mp.
16. 13 or 14 or 15
17. 12 and 16
18. exp occupational diseases/
19. abnormalities, drug-induced.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
20. exp environmental exposure/
21. carcinogens.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
22. teratogens.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
23. exo drug toxicity.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
24. hazardous substances.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
25. or/18-24
26. 1 or 25
27. 26 and 9 and 11 and 16

Medline and Embase search on closed systems

1. phaseal.mp.
2. closed-system.ti.
3. antineoplastic agents.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
4. drug compounding.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
5. occupational exposure.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
6. 2 or 4 or 5
7. 3 and 6
8. chemoclave.mp.
9. Spiros.mp.
10. onguard.ti.
11. baxa.mp.
12. phaseal.mp.
13. Tevadaptor.mp.
14. or/8-13
15. 7 or 14

Medline and Embase search on pregnancy

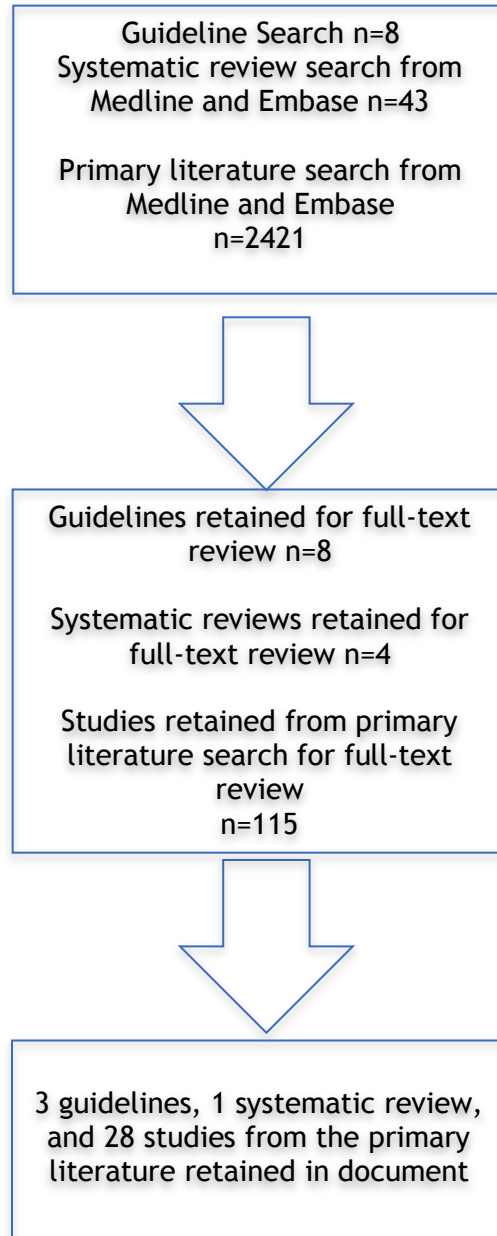
1. environmental monitoring/mt
2. occupational exposure/an
3. antineoplastic agents.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
4. pregnancy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
5. exp pregnancy/
6. occupational exposure/ae
7. neoplasms/dt
8. neoplasms/nu
9. nurses.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
10. antineoplastic agents/ae
11. antineoplastic agents/pc
12. 1 or 2 or 6
13. 3 or 7 or 10 or 11
14. 8 or 9
15. 12 and 13
16. health care worker.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
17. pharmacist.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
18. pharmacy technician.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
19. pharmacy technician.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, ui]
20. 14 or 16 or 17 or 18
21. 12 and 20
22. 12 and 20
23. 13 and 22
24. 4 and 5
25. 23 and 24

Medline and Embase search on general effects of cytotoxics

1. environmental monitoring/mt
2. occupational exposure/an
3. antineoplastic agents.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
4. occupational exposure/ae
5. neoplasms/dt
6. neoplasms/nu
7. nurses.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
8. antineoplastic agents/ae
9. antineoplastic agents/pc
10. adverse outcome.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
11. cancer chemotherapy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
12. nurses.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
13. healthcare worker.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
14. health care worker.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
15. pharmacist.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
16. chemotherapy.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
17. exp occupational exposure/
18. environmental monitoring/mt
19. occupational exposure/an
20. antineoplastic agents.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]

21. occupational exposure/ae
22. neoplasms/dt
23. neoplasms/nu
24. nurses.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
25. antineoplastic agents/ae
26. antineoplastic agents/pc
27. health care worker.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
28. pharmacist.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
29. pharmacy technician.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
30. pharmacy technician.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]
31. biological monitoring.mp.
32. 1 or 2 or 4 or 10 or 17 or 18 or 19 or 21 or 31
33. 7 or 12 or 13 or 14 or 15 or 24 or 27 or 28 or 29 or 30
34. 32 and 33
35. 3 or 5 or 6 or 8 or 9 or 11 or 16 or 20 or 22 or 23 or 25 or 26
36. 34 and 35

Appendix 3: PRISMA Flow Diagram

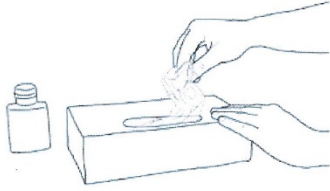


Appendix 4: Technique for donning and doffing one pair of gloves (62)

Source: http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

When the hand hygiene indication occurs before a contact requiring glove use, perform hand hygiene by rubbing with an alcohol-based handrub or by washing with soap and water.

I. HOW TO DON GLOVES:



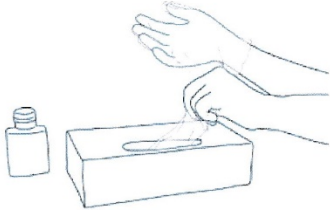
1. Take out a glove from its original box



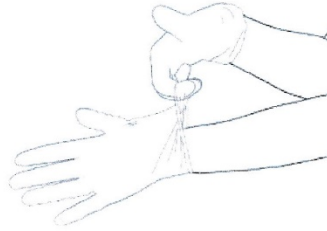
2. Touch only a restricted surface of the glove corresponding to the wrist (at the top edge of the cuff)



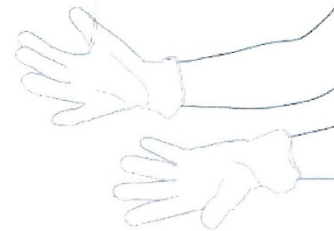
3. Don the first glove



4. Take the second glove with the bare hand and touch only a restricted surface of glove corresponding to the wrist

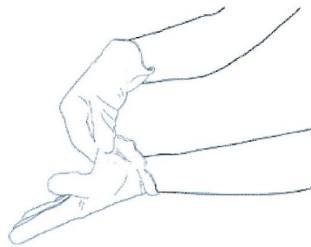


5. To avoid touching the skin of the forearm with the gloved hand, turn the external surface of the glove to be donned on the folded fingers of the gloved hand, thus permitting to glove the second hand

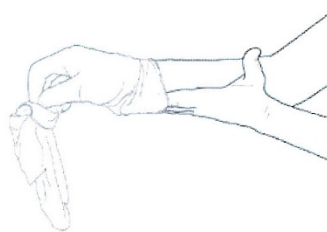


6. Once gloved, hands should not touch anything else that is not defined by indications and conditions for glove use

II. HOW TO REMOVE GLOVES:



1. Pinch one glove at the wrist level to remove it, without touching the skin of the forearm, and peel away from the hand, thus allowing the glove to turn inside out



2. Hold the removed glove in the gloved hand and slide the fingers of the ungloved hand inside between the glove and the wrist. Remove the second glove by rolling it down the hand and fold into the first glove



3. Discard the removed gloves

4. Then, perform hand hygiene by rubbing with an alcohol-based handrub or by washing with soap and water

Appendix 5: Technique for donning and doffing two pairs of gloves (13).

Source: <http://www.irsst.qc.ca/-publication-irsst-guide-de-prevention-manipulation-ecuritairedes-medicaments-dangereux-cg02.html>.

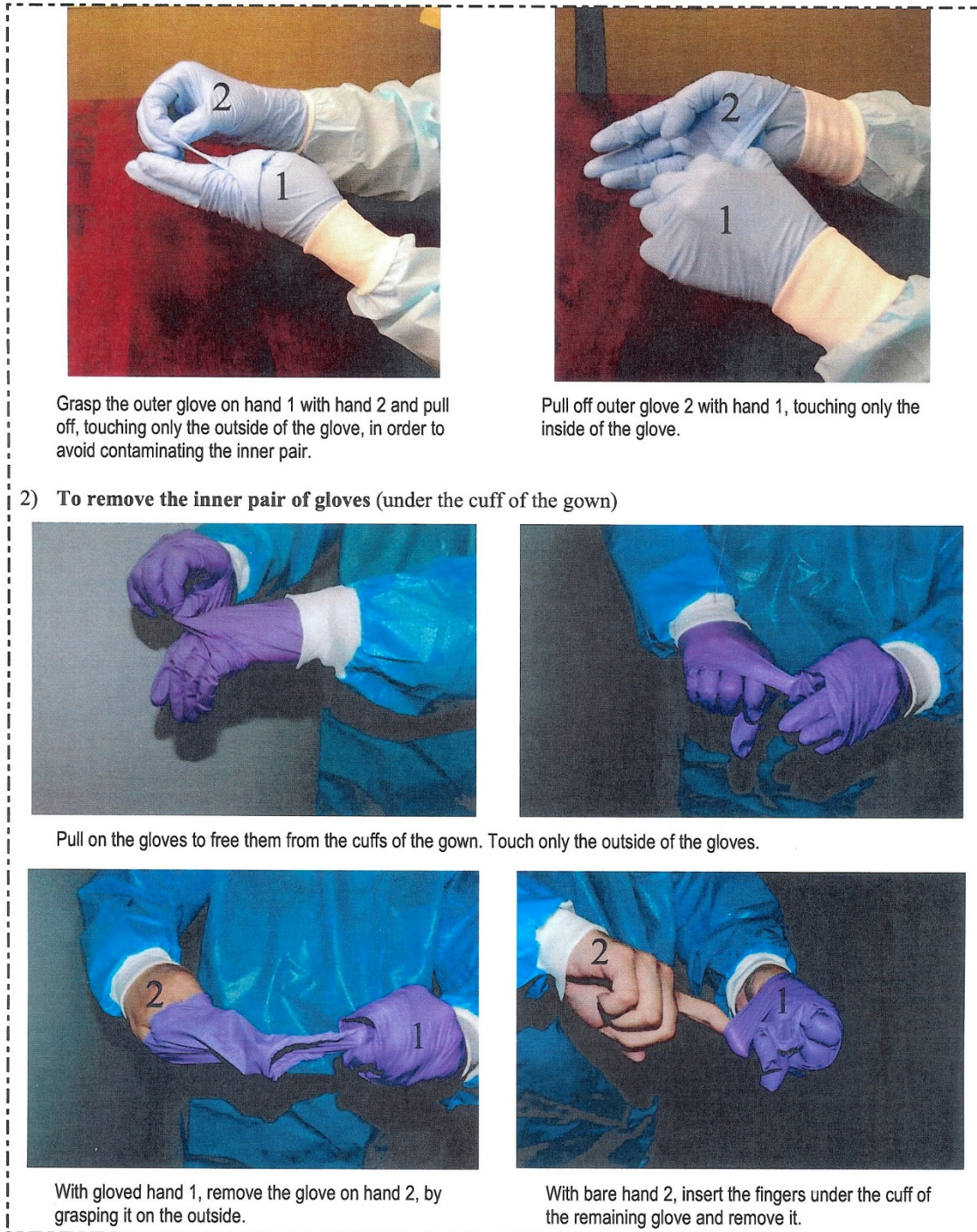


FIGURE 6

Procedure for removing gloves if the gown is kept on and two pairs of gloves are worn.

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Appendix 6: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2007	1966 to July 2006	Full Report	Peer review publication. Web publication.	Not applicable
Version 2 2013	July 2006 to January 2013	New data added to original Full Report	Updated web publication. Peer review publication.	Incorporated changes to include how cytotoxic drugs should be handled throughout each step of the medication circuit. New recommendations have been added and previous recommendations have been expanded.
Version 2 Reviewed June 2018	January 2013 - November 2017	New data found in Section 4	Updated web publication	2013 recommendations REQUIRE UPDATING
Version 3 2022	November 2017 to August 2022	New data added to original Full Report	Updated web publication	Incorporated changes to include how hazardous drugs should be handled throughout each step of the medication circuit. New recommendations have been added and previous recommendations have been expanded.