Abbreviations

ACOEM—American College of Occupational and Environmental Medicine
ACPH—air changes per hour
AHFS—American Hospital Formulary Service
APIs—active pharmaceutical ingredients
ASCO—American Society of Clinical Oncology
ASHP—American Society of Health-System Pharmacists
ASTM—American Society for Testing and Materials
BCG—bacillus Calmette-Guérin
BSC—biosafety cabinet
BUD—beyond-use dating
CA—chromosomal aberration
CACI—compounding aseptic containment isolator
CDC—Centers for Disease Control and Prevention
CETA—Controlled Environment Testing Association
CI—confidence interval
CN/CS—riot control gases
CNS—central nervous system
CP—cyclophosphamide
C-PEC—containment primary engineering control
C-SCA—containment segregated compounding area
C-SEC—containment secondary engineering control
CSF—cerebrospinal fluid
CSP—compounded sterile preparation
CSTD—closed-system drug-transfer device
CYT—cytarabine
DAD—diode array detection
DNA—deoxyribonucleic acid
DOX—doxorubicin
EPA—U.S. Environmental Protection Agency
EPI—epirubicin
FBAL—α-fluoro-β-alanine
FDA—U.S. Food and Drug Administration
FISH—fluorescence in situ hybridization
5-FU—5-fluorouracil
GC—gas chromatography
HCW—healthcare worker
HD—hazardous drug
HEPA—high-efficiency particulate air
HILIC—hydrophilic interaction chromatography
HIPEC—hyperthermic intraperitoneal chemotherapy
HPLC—high-performance liquid chromatography
IARC—International Agency for Research on Cancer
IF—ifosfamide
IM—intramuscular
IP—intraperitoneal
IPA—isopropyl alcohol
ISMP—Institute for Safe Medication Practices
ISO—International Organization for Standardization
IV—intravenous
IVP—intravenous push
LC—liquid chromatography
LOD—limit of detection
LOQ—limit of quantification
MN—micronuclei
MS—mass spectrometry
MS/MS—tandem mass spectrometry
MTX—methotrexate
NCCN—National Comprehensive Cancer Network
NG—nasogastric
NIOSH—National Institute for Occupational Safety and Health
NTP—National Toxicology Program
OEL—occupational exposure limit
ONS—Oncology Nursing Society
OR—operating room
OSHA—Occupational Safety and Health Administration
OV—organic vapors
PAPR—powered air-purifying respirator
PEC—primary engineering control
PIPAC—pressurized intraperitoneal aerosol chemotherapy
PPE—personal protective equipment
Pt—platinum
RCRA—Resource Conservation and Recovery Act
REL—recommended exposure limit
RN—registered nurse
SC—subcutaneous
SCE—sister chromatid exchange
SDS—safety data sheet
SOP—standard operating procedure
SWFIR—sterile water for irrigation
TAX—paclitaxel
USP—U.S. Pharmacopeial Convention
UV—ultraviolet
WHO—World Health Organization

Interventions to Reduce Worker Exposure

Key Points

- Adherence to a hierarchy of controls can reduce worker exposure to HDs.
- Engineering controls, such as ventilated cabinets and closed-system drug-transfer devices (CSTDs), can reduce exposure during compounding and manipulation of HDs.
- Administrative controls set the policies and expectations for a safety program to guide work practices and decrease worker exposure to HDs.
- Work practice controls are another way to reduce HD contamination and worker exposure.
- To meet industry standards, HCWs must use PPE (i.e., gowns, double gloves, eye and face protection) when handling HDs.

Nurses, pharmacists, and other workers involved in health care should not risk their own health while performing routine medication handling activities. Policies, procedures, and equipment for delivering drugs to patients have always been designed for patient safety. Some examples include procedures requiring sterile equipment for preparing and administering drugs that must remain sterile, accurate measurement for correct dosing, and safety equipment to control the rate of infusions.

The potential for HCW harm from occupational exposure to HDs was not considered until the late 1970s (Falck et al., 1979). This information led to the development of policies, procedures, and equipment aimed at protecting workers from the most likely routes of HD exposure. Early recommendations were based on information and technology available at the time. Current recommendations now have more than 30 years of evidence to support their use. Recommendations include engineering controls, PPE, medical and environmental monitoring, hazard identification, and the need for a comprehensive HD program (Crickman & Finnell, 2016). Guidelines for the safe handling of HDs are harmonized among all organizations with an interest in HD safety. Although they vary in the focus of their guidelines, ASHP, NIOSH, OSHA, and USP are in agreement about the best practices for the protection of HCWs from HD exposure. The following section outlines the ONS guidelines for minimizing occupational exposure to HDs.

Hierarchy of Controls

OSHA defines *industrial hygiene* as "the science of anticipating, recognizing, evaluating, and controlling workplace conditions that may cause workers' injury or illness" (OSHA, 1998, para. 2). Industrial hygiene professionals use the hierarchy of controls (see Figure 1) to determine how to implement feasible and effective controls for hazardous agents or HDs.

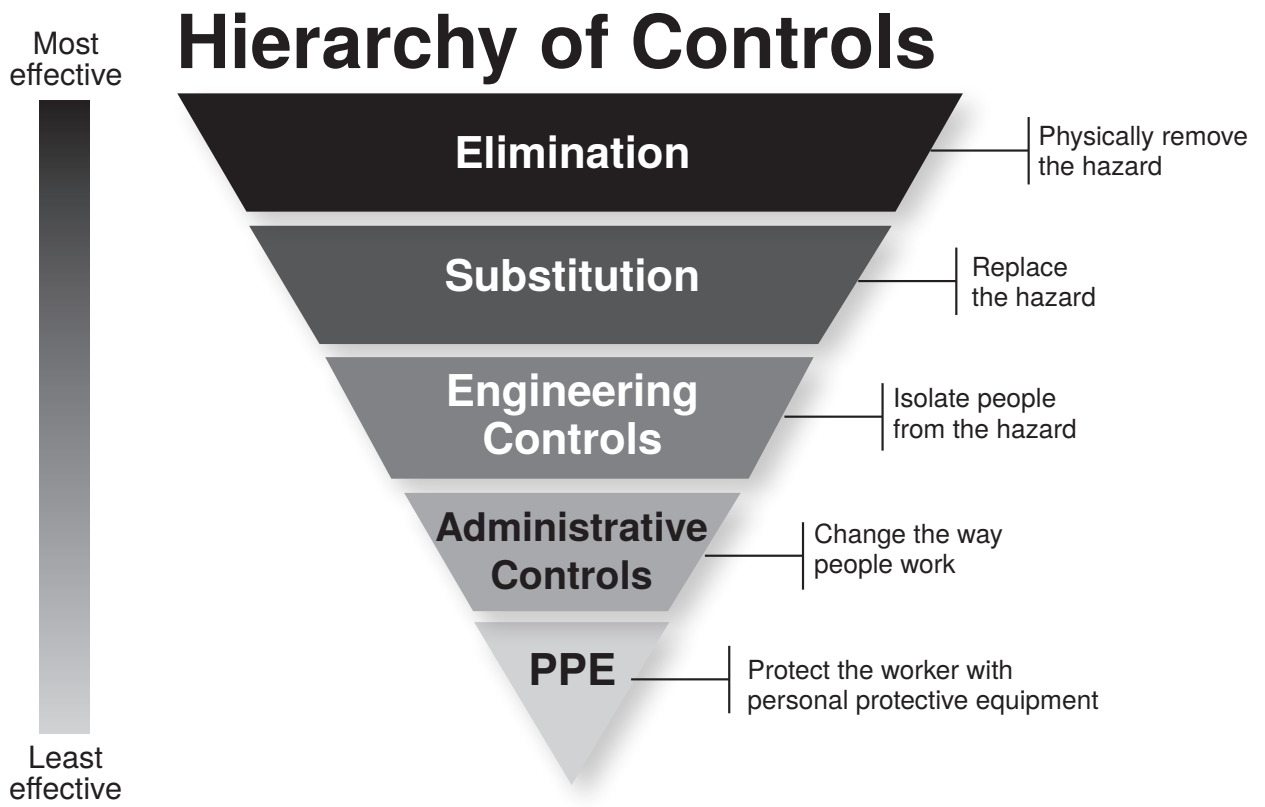
These steps involve elimination or substitution, engineering controls, administrative controls including work practices, and PPE. As elimination of HDs or substitution of non-HDs for HDs is not an option, the recognized methods of decreasing employee exposure to HDs are by implementing engineering controls, administrative controls, and PPE.

Engineering controls reduce worker exposure at the source by eliminating the hazard or by isolating the worker from the hazard. Engineering controls include machines and equipment designed to either contain the hazard or provide appropriate ventilation. Because engineering controls do not eliminate the risk, PPE must be added to provide barrier protection from the hazard. Specific work practices that change the way work is performed may effectively reduce worker exposure. Administrative controls reduce workers' exposure by establishing appropriate, and mandatory, work procedures; restricting access to potentially contaminated areas; and scheduling risky tasks so that the fewest number of employees are exposed. This section will discuss how the hierarchy of controls applies to HD handling in the healthcare environment.

Engineering Controls

Engineering controls for compounding sterile HD doses must be designed to protect the sterility of the drug and to provide containment of drug residue generated during the compounding process. USP is a public standards–setting authority for medicines and healthcare products manufactured or sold in the United States. USP sets standards for the "quality, purity, strength, and consistency" of drugs and solutions (USP, n.d., para. 1). USP General Chapter 797, "Pharmaceutical Compounding—Sterile Preparations," was revised in 2008 to include specific standards for the compounding of hazardous sterile preparations (USP, 2017a). The next revision of USP General Chapter 797 will eliminate the content on HD sterile compounding, which will reside solely in the newly created USP General Chapter 800, "Hazardous Drugs—Handling in Healthcare Settings" (USP,

Figure 1. Hierarchy of Controls



Note. From "Hierarchy of Controls," by National Institute for Occupational Safety and Health, 2016. Retrieved from http://www.cdc.gov/niosh/topics/hierarchy.

2016a). The USP General Chapter 797 standards of cleanliness, training, and environmental monitoring for sterile compounding still must be followed. USP General Chapter 800 addresses the standards for the compounding of sterile and nonsterile HDs, including active pharmaceutical ingredients (APIs) and manipulating nonsterile doses, such as crushing tablets (USP, 2016a). USP General Chapter 800 provides for product protection (e.g., maintaining the sterility and quality of the HD dose) as well as providing protection for the HCW and the environment. USP General Chapter 800 applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs (e.g., pharmacies, hospitals and other healthcare institutions, patient treatment clinics, physicians' practice facilities). Personnel who may potentially be exposed to HDs include but are not limited to pharmacists, pharmacy technicians, nurses, physicians, physician assistants, and home healthcare workers. USP General Chapter 800 identifies the requirements for engineering controls and ventilation, receipt, storage, compounding, and dispensing of HDs but extends beyond USP General Chapter 797 to include standards for the administration of HD doses. Standards in USP General Chapter 800 must be implemented by December 1, 2019.

USP General Chapter 797 adopted the term *primary engineering control*, or *PEC*, to describe ventilated devices that provide a clean environment, where air is filtered through high-efficiency particulate air (HEPA) filters, for compounding sterile drugs. The quality of the air is measured by the number of particles per cubic meter; the lower the particulate count, the cleaner the compounding environment. The International Organization for Standardization (ISO, 2015) rates the environment based on the particle count, with a lower ISO class number indicating a cleaner environment. An ISO Class 5 environment is required for compounding sterile IV drugs (USP, 2016a, 2017a). USP General Chapter 800 has modified the terminology to emphasize the containment qualities required of ventilated engineering controls for handling HDs. It divides engineering controls for containment into three categories representing primary, secondary, and supplemental levels of control. Both sterile and nonsterile HDs must be compounded in a C-PEC to minimize HCW exposure and environmental contamination when directly handling HDs. Only sterile HDs must be

compounded in C-PECs that maintain an ISO Class 5 environment for the protection of the final dose from microbial contamination. The containment secondary engineering control (C-SEC) is the room in which the C-PEC is placed. Supplemental engineering controls (e.g., CSTDs) are adjunct controls to offer additional levels of protection. USP General Chapter 800 requires sterile and nonsterile HDs to be compounded within a C-PEC located in a C-SEC. C-SECs will be discussed in a later section.

USP General Chapter 800 addresses the special requirements for HD storage and compounding (see Figure 2). NIOSH (2004a), in its alert on HDs, uses the term *ventilated cabinet* to describe the type of engineering control that minimizes worker exposure by containing airborne HD contaminants. For sterile doses of HDs, the appropriate engineering controls include Class II and III BSCs and compounding aseptic containment isolators (CACIs), as these cabinets provide both product and personnel protection (ASHP, 2006; NIOSH, 2004a; USP, 2016a, 2017a). Compounding of nonsterile doses of HDs or other activities where containment ventilation is desired may be done in a non–ISO Class 5 ventilated control, such as a fume hood (containment ventilated enclosure, Class I BSC). If nonsterile activities are done in the ISO Class 5 C-PEC, full decontamination for HD residue and cleaning and disinfection for particulates are required prior to resuming sterile compounding (Controlled Environment Testing Association [CETA], 2007; USP, 2016a). It must be recognized that C-PECs do not eliminate the generation of contamination and may have limitations in their containment.

Biosafety Cabinets

BSCs are classified as Class I, Class II, or Class III. The Class II BSC was adopted in the early 1980s as a valuable tool in reducing occupational exposure while compounding sterile doses of HDs. Originally designed to handle biologics in a laboratory setting, the Class II BSC has HEPA-filtered, vertical-flow unidirectional air supply in the work area of the cabinet, creating the necessary ISO Class 5 environment for sterile compounding. It has a glass shield extending across the front of the cabinet with a front opening of 8–10 inches, through which the operator accesses the work area. Inward airflow through this opening combines with the downward airflow and is removed from the work area through front and rear grills. The front air barrier is designed to create a protective air curtain containing contamination generated in the work area within the cabinet. The mixed contaminated air is either recirculated within the cabinet or exhausted to the workroom or outside environment through HEPA filters. The type of Class II BSC (A1, A2, B1, or B2) is determined by the percentage of contaminated air that is recirculated within the cabinet, the amount of air coming out of the cabinet, and where that air is exhausted. NIOSH (2004a) recommends not using a recirculating cabinet and exhausting all contaminated air to the outside through HEPA filters and a ducted connection. USP General Chapter 800 requires that all of the contaminated air coming out of the Class II BSC be vented to the outside. This requires an auxiliary exhaust system in addition to HEPA filters. The A2, B1, and B2 cabinets may be connected to outside exhaust systems. HEPA fil-

Figure 2. U.S. Pharmacopeial Convention Chapter 800 Summary of Requirements for Sterile Antineoplastic Hazardous Drugs*

Storage Area	**C-PEC ISO Class 5**	**C-SEC With ISO Class 7 Buffer Area With ISO Class 7 Ante Area**	**C-SEC With Unclassified C-SCA**
• Separate • Vented outside • Negative pressure • At least 12 ACPH • Dedicated refrigerator for antineoplastic HDs in area with above characteristics	• Usually Class II BSC or CACI • Must be vented outside • Must be located in C-SEC • Must operate continuously	• Fixed walls • HEPA-filtered supply air • Must be vented outside • Must have 30 ACPH • Buffer area must be negative pressure to adjacent areas. • Ante area must be positive pressure to adjacent areas. • Sink must be in ante room 1 meter away from entrance to the HD buffer room. • BUD as described in USP General Chapter 797	• Must be vented outside • Must have 12 ACPH • Must be negative pressure to adjacent areas • Sink in C-SCA must be 1 meter away from C-PEC, or sink immediately outside C-SCA. • BUD as described in USP Chapter 797 for C-SCA

* Not inclusive of other HD requirements

ACPH—air changes per hour; BSC—biosafety cabinet; BUD—beyond-use dating; CACI—compounding aseptic containment isolator; C-PEC—containment primary engineering control; C-SCA—containment segregated compounding area; C-SEC—containment secondary engineering control; HD—hazardous drug; HEPA—high-efficiency particulate air; ISO—International Organization for Standardization; USP—U.S. Pharmacopeial Convention

Note. Based on information from U.S. Pharmacopeial Convention, 2016a.

ters are not effective for containing volatile materials because they do not capture vapors and gases (Kiffmeyer et al., 2002; Larson, Khazaeli, & Dillon, 2003). The Class II BSC type B2 is a nonrecirculating, total exhaust cabinet and is appropriate for work with volatile HDs (NIOSH, 2004a; USP, 2016a).

The Class II BSC must meet the performance standards of NSF 49-2014, and manufacturers must test their cabinets to this standard (NSF International, 2014). The containment of the Class II cabinet is dependent on the airflow within the cabinet and the technique of the operator in accessing the work area through the front air barrier. Studies of workplace contamination have shown HD residue on the floor in front of the Class II BSC (Berruyer et al., 2015; Connor et al., 2010). These studies indicate a limitation in using this type of cabinet for drug compounding.

The Class II BSC also is designed to be decontaminated by fumigating with a vigorous disinfectant that permeates the contaminated air plenums of the cabinet. This process is not effective for removing drug and other chemical residue. Surface decontamination with detergent and physical wiping may be used to remove drug residue from the Class II BSC; however, many of the air plenums are not accessible to accomplish this (American Society of Hospital Pharmacists, 1990).

The Class II cabinets should remain on so that the blower operates continuously to prevent release of any drug residue from the contaminated plenums and under the work surface into the workroom. USP General Chapter 800 requires any C-PEC used to compound sterile HDs to be run continuously (USP, 2016a). If the Class II BSC must be turned off, it should first be cleaned and the front opening sealed with plastic and tape to prevent any contaminants from escaping. Class II BSCs should be serviced and certified by a qualified technician at least every six months and any time the cabinet is repaired or moved (American Society of Hospital Pharmacists, 1990; NIOSH, 2004a; USP, 2017b).

Class III BSCs may be used for sterile compounding of HDs because they provide product and environmental protection (ASHP, 2006; NIOSH, 2004a; USP, 2016a). Class III BSCs are totally enclosed with gas-tight construction. The entire cabinet is under negative pressure, and access to the work area for compounding activities is through attached gloves, which limits floor contamination in front of the cabinet. All of the air is HEPA filtered, and outside exhaust is mandatory through a duct with an auxiliary blower. The Class III cabinet has the same limitations on decontamination as the Class II cabinet. Generally, the cost of purchasing, installing, and maintaining this type of cabinet is prohibitive, and few, if any, are used for extemporaneous sterile compounding.

Compounding Aseptic Containment Isolators

USP General Chapter 800 includes a CACI as an accepted C-PEC for compounding sterile HDs (USP, 2016a). Unlike the Class II BSC, however, no uniform design or performance standards exist for CACIs used for pharmaceutical compounding. CETA has produced several application guides to help in the selection and use of CACIs in healthcare facilities (CETA, 2008a). In the absence of standards, manufacturers have produced varying designs and have marketed isolators for the purpose of pharmaceutical compounding with no evidence of effectiveness. One study examining the different isolator designs found extensive differences in the abilities of the various isolators to handle challenges to the airflow that would occur during pharmaceutical compounding (Peters, McKeon, & Weiss, 2007). The authors concluded that the performance of unidirectional-flow isolators supports their use in pharmacy and nursing operations, whereas the performance of turbulent-flow isolators does not (Peters et al., 2007). USP General Chapter 800 defines a CACI as having unidirectional airflow for compounding sterile preparations (USP, 2016a). Internationally, the CACI has not been adopted as the required C-PEC for compounding HDs. Testing standards for the CACI are available from CETA (2008b).

Floor and glove contamination with HDs has been shown when using CACIs in either positive or negative pressure mode (Mason et al., 2005). It was, in the authors' opinion, lower than in comparable Class II BSC studies. In a second study of two pharmacies where isolators were in use, wipe sampling for platinum compounds determined that all sampled surfaces were contaminated with detectable levels of platinum (Kopp et al., 2013). Contamination was detected on floors as well as gloves. The study did not control for vial contamination, which could be a significant source of the platinum residue. Both studies found platinum in the urine of exposed HCWs. These two studies document that isolators do not prevent HD contamination during compounding and do not contain it perfectly. No studies document that isolators eliminate the need for gowns. As USP mandates sterile gloves for sterile compounding, a sterile glove worn over the CACI fixed glove is required. Studies have shown that surfaces in and around isolators are contaminated with HDs (Crauste-Manciet, Sessink, Ferrari, Jomier, & Brossard, 2005; Kopp et al., 2013). It is prudent for the operator to always wear a glove when gathering drugs and supplies, accessing the pass-through handle, and loading and unloading the pass-through.

Containment Secondary Engineering Controls

The C-SEC is the room in which the C-PEC is placed. It incorporates specific design and operational parameters required to contain the potential hazard within the compounding room (USP, 2016a). The C-SEC for sterile compounding may either be an ISO Class 7 buffer room with an ISO Class 7 ante room (preferred) or an unclassified (i.e., requires no ISO air classification) containment segregated compounding area (C-SCA).

The C-SEC should improve the ability of the C-PEC to maintain the required ISO Class 5 air quality. The preferred C-SEC design is the ISO Class 7 buffer room that has fixed walls, negative pressure relative to all adjacent areas, and external ventilation with a minimum of 30 air changes per hour (ACPH) (USP, 2016a). The ISO Class 7 buffer area also requires an additional source of HEPA-filtered air (not solely from the C-PEC). Access to the ISO Class 7 buffer area must be through a second area, the ante area, which provides transition from non–compounding activities to sterile compounding. The ante area for the sterile compounding of HDs also must be ISO Class 7, as the pressure differentials required for HD containment (negative pressure) forces the air into the buffer area to prevent the escape of HD contamination from the compounding environment into the surrounding work area. USP General Chapter 800 requires the ISO Class 7 ante room to have fixed walls, a minimum of 30 ACPH of HEPA-filtered supply air, positive pressure relative to all adjacent unclassified areas, and an air quality of ISO Class 7 or better (USP, 2016a). A handwashing sink must be placed in the ante room at least one meter from the entrance to the HD buffer room to avoid contamination migration into the negative-pressure HD buffer room. With this configuration, sterile doses of HDs prepared in the C-PEC may have the beyond-use dating (BUD) described in USP General Chapter 797.

An alternate C-SEC configuration is an unclassified C-SCA that is externally vented. The C-SCA must have fixed walls, negative pressure to all adjacent areas, and a minimum of 12 ACPH. A handwashing sink must be placed at least one meter from the C-PEC and may be either inside the C-SCA or directly outside the C-SCA. No nonsterile to sterile compounding may be done in a C-SCA. Sterile doses of HDs prepared in a C-PEC (either a Class II BSC or a CACI) within a C-SCA must not exceed the BUD described in USP General Chapter 797 for compounded sterile preparations prepared in a segregated compounding area (USP, 2016a).

Only authorized, trained staff may have access to the C-SEC, and only after removing all jewelry and cosmetics and properly garbing and washing (USP, 2017b). No eating, drinking, smoking, chewing gum, applying of cosmetics, or storing of food should occur in the ante or buffer areas (ASHP, 2006; OSHA, 2016).

Supplemental Engineering Controls

USP General Chapter 800 describes supplemental engineering controls (e.g., CSTDs), which are adjunct controls that provide an additional level of protection during compounding or administration of HDs (USP, 2016a). NIOSH recommends using needleless systems, glove bags, and CSTDs to limit the potential for generating aerosols and exposing workers to sharps while transferring HDs and HD solutions from packaging to dosing equipment and to patients (NIOSH, 2004a). The persistent presence of HD contamination in compounding and administration areas, despite adherence to HD safe handling guidelines, has generated an interest in supplemental engineering controls, especially for administration areas where primary engineering controls are not available. The device most frequently discussed in this category is the CSTD. The CSTD is defined both by NIOSH and USP General Chapter 800 as a drug-transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system (NIOSH, 2004a; USP, 2016a). NIOSH and USP General Chapter 800 recommend the use of CSTDs in compounding HDs, but both note the CSTD must be used only in conjunction with ventilated engineering controls (e.g., C-PECs). USP General Chapter 800 requires the use of a CSTD during administration of antineoplastic HD doses when the dosage form allows and when the CSTD is known to be physically and chemically compatible with a specific HD in use (USP, 2016a).

Numerous studies have shown that surface contamination with HD residue occurs in areas where HDs are compounded and administered even when ventilated engineering controls are in place (see Table 5). Clinical studies done with one CSTD, the PhaSeal® system, showed significant reduction in surface contamination in HD compounding areas when the CSTD was used compared to the standard needle-and-syringe technique (Miyake, Iwamoto, Tanimura, & Okuda, 2013; Sessink, Connor, Jorgenson, & Tyler, 2011; Sessink, Trahan, & Coyne, 2013; Siderov, Kirsa, & McLauchlan, 2010). A number of other CSTD systems, with various methods of capturing HD residue during compounding, have been marketed since 2004. Several have been studied and reported on in peer-reviewed literature (Clark & Sessink, 2013; De Ausen, Defreitas, Littleton, & Lustik, 2013; Queruau Lamerie et al., 2012; Vyas, Turner, Clark, & Sewell, 2016; Zock,

Soefje, & Rickabaugh, 2011). There is no standard testing method or performance standard for devices marketed as CSTDs. FDA considers these Class II medical devices and clears them for sale in the United States using FDA's 510(k) process (U.S. FDA, 2015). The FDA 510(k) process does not establish independent performance standards for devices submitted as "substantially equivalent," nor does it test or approve these devices. Based on a successful review of the 510(k) submission, the FDA "clears" the new device for sale in the United States (U.S. FDA, 2015). Many devices marketed for IV compounding or administration are not CSTDs by definition and may not be appropriate for HD use. In 2014, FDA created Product Code ONB specifically for a "closed antineoplastic and hazardous drug reconstitution and transfer system" (U.S. FDA, 2014). While applications under this code are not independently tested by FDA, the application process is more stringent for the manufacturer. Products that are marketed as CSTDs but have not been cleared by FDA under the Product Code ONB should not be considered CSTDs.

All of the CSTD systems cleared by FDA under Product Code ONB are designed to protect the key areas of compounding and administration where studies have identified drug escaping into the environment: vial penetration with a needle; leakage from a syringe with a needle or when removing a needle; transfer into an IV solution bag; spiking an IV container with an IV set; priming the IV set for patient administration; administration of IV push doses; and removal of IV sets from bags, primary sets, or manifolds. Each system offers an access "cap" that locks onto the vial top and provides protection when reconstituting or removing drug from the vial. The cap has a spike or a cannula that penetrates the vial septum and an external, closed device that mates with a specific syringe adapter. This connection between the vial cap and syringe adapter allows needle-safe or needle-free access to the vial. Two of the existing systems use an adapter that contains either covered or recessed spikes allowing transfer of fluid from the syringe and vial. Other systems use a closed male Luer lock instead of a needle-safe adapter that attaches to the syringe. This closed male Luer mates with the specific needle-free adapter on the vial cap opening valves and allows the transfer of fluid between the syringe and vial. Each system has a bag access device that is attached to an IV bag before any drug is added. Each system's bag access device is equipped with the proprietary adapter that allows it to mate with the syringe adapter, either the spiked, needle-safe injector or the needle-free, closed male Luer. The bag adapters allow a closed connection between the drug in the syringe and the IV bag and a dry connection to the spike of any IV set. Bag adapters allow connecting the IV set and priming the IV line prior to adding drug or, alternatively, to spike at the patient's area using the dry-spike option and back-priming the IV set (usually a secondary set) from the primary nondrug fluid. The closed male Luer connectors are designed to mate with the specific needle-free adapter on IV tubing (Y-sites), creating closed, leak-resistant connections to the patient's line for either IV push administration or additional protection at a tubing-to-tubing connection. The needle-safe systems offer adapters for Y-sites to allow protection for IV push administration or when connecting additional tubing. The use of these tubing-to-tubing connection devices allows safe removal of either the syringe or secondary tubing from the patient's primary IV setup.

Additional devices are being developed for both oral and difficult parenteral administration situations (Haifler et al., 2010; Wakui et al., 2013). The NIOSH Workplace Safety and Health Topics page includes an extensive bibliography of publications related to CSTDs and is available online at www.cdc.gov/niosh/topics/antineoplastic/sampling.html.

Because the CSTD systems have components that are used in the administration of HD doses as well as in the compounding, these devices reduce the potential exposure of nursing staff during administration. Using CSTDs should result in reduction of environmental surface contamination with HDs and should reduce exposure of all staff assigned to areas where HDs are compounded or administered (Clark & Sessink, 2013; De Ausen et al., 2013; Queruau Lamerie et al., 2012, 2013; Vyas et al., 2016; Zock et al., 2011).

Administrative Controls

Administrative controls form the backbone of any safety program. These establish the awareness of an issue and provide clear direction for reducing exposure. Administrative controls include policies, procedures, scheduling practices, staff education and training, validation of competency, and medical surveillance. The safety program must be well established, and staff performance expectations should be clearly defined.

Organizations should have policies and procedures or standard operating procedures related to safe handling of HDs (USP, 2016a). Policies should address all aspects of handling of HDs and drug waste for the protection of employees, patients, visitors, and the environment from exposure, including the following:

- Addressing the safe receipt, storage, transport, compounding, administration, spill control, and disposal of HDs and HD waste
- Requiring all employees handling HDs to wear PPE

- Prohibiting eating, drinking, smoking, chewing gum or tobacco, applying cosmetics, and storing food in areas where HDs are used
- Requiring training and documentation of training for all employees who handle HDs in any capacity, including understanding of health risks, handling, receiving, compounding, administering, spill control, and drug and patient waste management
- Having written policies that describe the HD spill cleanup procedure
- Requiring the availability of spill kits
- Having written policies that address medical surveillance of employees involved in the handling of HDs

Quality improvement programs should include monitoring of compliance with HD policies and procedures (USP, 2016a). A Japanese study demonstrated that when a continuous monitoring system for adherence to safety policies was implemented, there was a reduction in HD contamination of wipe samples and urine samples related to 80% or better compliance with their monitoring checklist (Yoshida et al., 2013).

The risks of exposure to HDs in the workplace must be made clear to all staff at every level, including aides, housekeepers, and laundry service workers, as well as healthcare professionals. USP General Chapter 800 emphasizes administrative controls for the safe compounding of HDs by mandating conditions that protect HCWs and other personnel in the preparation and storage areas (USP, 2016a). USP General Chapter 800, OSHA, and NIOSH require extensive training of all personnel who handle HDs in the safety procedures and equipment necessary to perform the specific task; this includes the C-PEC, PPE, and any emergency procedures associated with acute exposure or spill control. The effectiveness of training must be verified prior to beginning any work with HDs, and ongoing training must be documented at least annually. Training in work practices also must include the following: aseptic manipulation; negative pressure technique; correct use of safety equipment; containment, cleanup, and disposal procedures for breakages and spills; and treatment of personnel for contact and inhalation exposure. (See the Staff Education and Training section for a full discussion of education and training for HD handlers.)

Administrative controls also should include a medical surveillance program (NIOSH, 2004a; OSHA, 2016; USP, 2016a). Medical surveillance involves collecting and interpreting data to detect changes in the health status of working populations potentially exposed to hazardous substances. NIOSH provides direction for establishing such a program in its publication *Medical Surveillance for Health Care Workers Exposed to Hazardous Drugs* (NIOSH, 2013). Clear policies should be established for workers regarding reproductive risks and alternative duty, as well as reasonable scheduling patterns to reduce the potential for exposure. (See the Medical Surveillance of Healthcare Workers Handling Hazardous Drugs section for details about medical surveillance for HD handlers.)

Work Practice Controls

Another way to reduce occupational exposure to HDs is to use appropriate work practices. Work practices must be designed to minimize the generation of HD contamination and maximize the containment of inadvertent contamination that occurs during all routine tasks involving HDs and in the event of a breakage or spill. Work practice controls are an extension of other aspects of the hierarchy of controls. They are similar to administrative controls in that they represent the use of established procedures. Work practices often involve the consistent and appropriate use of engineering controls and PPE to minimize exposure.

A critical examination of the existing work practices is necessary to identify potential opportunities for HD exposure. Certain work practices can result in surface contamination with HDs, such as the following:

- Exiting and reentering a Class II BSC to obtain additional equipment without changing gloves
- Failing to wipe off HD vials/ampoules prior to compounding to remove drug residue
- Inadequate cleaning of spills on equipment or other surfaces
- Priming IV tubing with HDs instead of a nondrug solution or priming tubing outside the C-PEC
- Failing to wash hands with soap and water after HD handling activities
- Contamination of self or environment while removing PPE

Many possible causes of surface contamination exist. Direct observation of nurses', pharmacists', and others' techniques of preparation, handling, and administration may yield information about potential sources of contamination and its spread. If potential sources of surface contamination are not identified, they cannot be eliminated.

The following work practices are likely to result in decreased surface contamination:

- Gather all necessary supplies before placing hands in the C-PEC.
- Wear double gloves that have been tested for HD permeation using American Society for Testing and Materials (ASTM) Standard D6978-05 (2013), as recommended by both NIOSH and USP General Chapter 800 for HD handling activities (NIOSH, 2016; USP, 2016a).

- Change gloves every 30 minutes or sooner if warranted by permeation data on the HD.
- Change gloves immediately if torn or knowingly contaminated.
- Remove contaminated gloves carefully, turning them inside out to protect bare hands from coming into contact with the outside of the gloves.
- Wash hands with soap and water after removing gloves and prior to donning new gloves. Do not use waterless hand cleaners; wash with soap and water.
- Place waste generated in compounding (e.g., outer gloves, vials, gauze) in a sealed plastic bag before removing it from the C-PEC.
- Discard the sealed bag containing used equipment in a puncture-proof HD waste receptacle placed immediately outside the C-PEC.
- Avoid reaching into sealed bags used to transport drugs without PPE. Visually examine the contents of the sealed bag. If visible leakage is present, do not open the outer bag. To reduce the risk of exposure, verify the dose at the administration site. For example, one RN wearing PPE can remove the drug container from the bag while another nurse performs a double check without touching the drug container. An alternative is to use clear sealable bags for transport so that the doses can be verified without removing the drug containers from the bag. This practice might not be possible if ultraviolet light–blocking bags are used.
- Use a plastic-backed pad to protect work surfaces where HD containers are set down.
- Use locking connections on all IV delivery devices.
- Use and dispose of sharps carefully.
- Do not "unspike" IV bags. Discontinue and discard infusion bags with tubing intact.
- Place HD disposal containers near the workspace.
- Keep the lid closed on HD disposal containers except when placing contaminated materials in them.
- Avoid touching equipment (e.g., infusion pumps, computer keyboards, telephones) when wearing gloves used to handle HD containers.
- Clean countertops and other surfaces in the work area after completion of HD handling.
- Clean potentially contaminated surfaces (e.g., infusion pumps, computer keyboards, telephones) regularly to reduce overall HD contamination in the work area.

Personal Protective Equipment

The use of PPE is necessary for HCWs to prevent occupational exposure to HDs. Since the widespread use of PPE, employee exposure to HDs has decreased. Studies have demonstrated that gloves provide protection against skin contact with tested HDs, and preventing skin exposure decreases symptoms in people with occupational contact with HDs (Fransman et al., 2014; Friese, Himes-Ferris, Frasier, McCullagh, & Griggs, 2012; Friese, McArdle, et al., 2015; Hon, Teschke, Demers, & Venners, 2014; Yoshida et al., 2013). For HD handling, ONS defines PPE as gloves tested for use with HDs, gowns made of materials shown to resist permeation by HDs, respirators, and face shields or goggles (Polovich et al., 2014).

Gloves

Designated chemotherapy gloves should be worn during all HD handling activities. Glove thickness, type, and time worn are major determinants of their permeability by HDs. ASTM (2013) has developed a standard for testing gloves against permeability by a selected group of HDs. Gloves are not tested for all known HDs because of the cost and lack of assays for many drugs; however, for gloves to be labeled for use with chemotherapy, they must be tested with the following seven drugs from different classifications:

- Carmustine
- Cyclophosphamide
- Doxorubicin
- Etoposide
- 5-FU
- Paclitaxel
- Thiotepa

Two additional HDs may be selected from a list provided by ASTM for permeation testing. All drugs used for testing must be purchased from pharmaceutical drug manufacturers or authorized distributors and prepared using the manufacturer's recommendations.

The test results are reported as the amount of time it takes for the drugs to permeate from the outer surface to the inner surface of the glove. Gloves used in handling HDs should have a minimum permeation time of 30 minutes. The glove-specific standard is ASTM D6978-05 (2013), in which the minimum limit of detection is 0.01 mcg/cm^2/min. Another ASTM standard, ASTM F739-12e1, is not specific to gloves and has a minimum limit of detection of 0.1 mcg/cm^2/min, which is only one-tenth as stringent as the newer standard (ASTM, 2012). HDs used in testing gloves often are listed on the glove box along with the permeation results. Alternatively, study results may be found in information provided by glove manufacturers. Not all HDs have assays that allow them to be tested, so testing representative HDs is currently the only solution. Gloves not tested for use with any HDs should not be used for HD handling because their ability to protect against chemical permeation is unknown.

Powder-free gloves are required for HD handling because powder may absorb contaminants, be dis-

persed, and increase the possibility of surface contamination (USP, 2016a). On January 19, 2017, FDA issued a ban on the sale, distribution, and manufacturing of all powdered gloves. This ban was approved to protect patients and HCWs from illness or injury resulting from powder exposure (e.g., inflammation, granulomas, respiratory allergic reactions) (U.S. FDA, 2016). OSHA (2016) has recommended changing gloves every 30–60 minutes and immediately if contamination occurs. However, based on the ASTM permeability testing, the maximum recommended wear time for gloves is 30 minutes. Certain drugs may permeate more quickly (e.g., carmustine, thiotepa). If using these drugs, change gloves according to the permeation time listed on the glove packaging. Gloves should be removed immediately if torn, punctured, or knowingly contaminated. Visual inspection of gloves to assess for pinhole leaks is a prudent practice, as variability of glove integrity within lots has been identified.

Double gloving is recommended for all activities involving HDs except for handling intact, unit-dose oral agents, when one pair of chemotherapy-tested gloves is acceptable (NIOSH, 2016). USP General Chapter 800 requires double gloving for HD compounding, administration, and all cleaning and decontamination activities. NIOSH recommends double gloves for spill control as well as for disposal of HD waste and patient waste (NIOSH, 2016). USP General Chapter 800 requires that the outer glove be sterile when compounding sterile HDs (USP, 2016a). Studies have found that thicker gloves increase the resistance to permeation and offer a higher level of protection and that double gloving significantly reduces perforations in the gloves (Landeck, Gonzalez, & Koch, 2015). For extended exposure to chemotherapy drugs, double gloving, the use of thicker gloves, and frequent changing of gloves increase their protective power (Caillot, Côte, Abidi, & Fabry, 1999). Villa et al. (2015) reported hand contamination for surgeons using double latex gloves during preoperative hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin but not with triple gloves. Korinth et al. (2007) noted that double-layer natural rubber gloves were effective in preventing permeation of mitomycin C under in vitro conditions similar to HIPEC exposure.

Concerns about latex sensitivity have prompted testing of alternative glove materials, including nitrile and neoprene, against different HDs (Capron, Destree, Jacobs, & Wallemacq, 2012; Dolezalova et al., 2009; Wallemacq et al., 2006). Studies show that nitrile has high resistance to permeation by multiple HDs (Capron et al., 2012; Dolezalova et al., 2009; Wallemacq et al., 2006). Testing has been done at various temperatures, in static and dynamic conditions, and while examining the effects of alcohol and isopropyl alcohol (IPA) on HD permeation (Capron et al., 2012; Wallemacq et al., 2006). Nitrile has been found to resist permeation in most studies; however, researchers using a different method determined that doxorubicin can penetrate nitrile gloves (Boccellino et al., 2010).

The likelihood of permeation through two layers of gloves during normal HD handling is small; however, wearing two pairs of gloves helps to protect the HCW's hands from contamination that can occur when removing gloves. The inner glove should be worn under the gown cuff, and the outer glove should be placed over the gown cuff. This technique ensures that skin on the wrist area is not exposed and facilitates correct sequencing (i.e., outer glove, gown, inner glove) during removal of PPE (ASHP, 2006). An additional benefit of double-gloving is that removing the outer gloves after handling HDs minimizes the chance of transferring HD contamination to surfaces in the workplace. Figure 3 presents a summary of recommendations for glove use in HD handling.

Figure 3. Recommendations for Glove Use in Hazardous Drug Handling

- Use gloves that have been tested to ASTM D6978-05 (2013), *Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs.*
- Select powder-free gloves.
- Inspect gloves for visible defects.
- Wear double gloves for compounding, administration, spill control, disposal, and cleaning.
- Change gloves every 30 minutes unless permeation testing has noted a shorter time for the drug being handled.
- Change gloves immediately if damaged or contaminated.

Note. Based on information from American Society of Health-System Pharmacists, 2006; National Institute for Occupational Safety and Health, 2016; U.S. Pharmacopeial Convention, 2016a.

Gowns

Gowns must be disposable and shown to resist permeation by HDs (USP, 2016a). Disposable gowns made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials. Gowns must close in the back (i.e., no open front), be long sleeved, and have closed cuffs that are elastic or knit. Gowns must not have seams or closures that could allow HDs to pass through. Gowns; head, hair, and shoe covers; and two pairs of chemotherapy gloves are required for compounding sterile and nonsterile HDs (USP, 2016a). Gowns shown to resist permeation are required when administering HDs (USP, 2016a).

In drug preparation areas, gowns must be changed per the manufacturer's information for permeation of

the gown. If no permeation information is available for the gowns used, change gown every two to three hours or immediately after a spill or splash (USP, 2016a). Gowns worn in HD handling areas must not be worn to other areas in order to avoid spreading HD contamination and exposing other HCWs. Disposable gowns must not be reused. Used gowns should be carefully removed immediately and discarded appropriately after each use.

Laboratory coats and other cloth fabrics absorb fluids, so they provide an inadequate barrier to HDs and should not be used. Washing of nondisposable clothing accidentally contaminated with HD residue should only be done according to facility policy, as drug residue may be transferred to other clothing. Potentially contaminated clothing must not be taken home under any circumstances (USP, 2016a).

No standard currently exists for testing gowns for permeation by HDs. Some manufacturers are using the ASTM standard F739-12e1, the standard test method for permeation of liquids and gases through protective clothing materials under conditions of continuous contact, for testing HD gowns. As there are no specific challenges to this standard, the drugs and concentrations from the ASTM glove standard (D6978-05 [2013]) are used. This practice has not been studied for effectiveness or safety. Gowns selected for HD use should be made of polyethylene-coated polypropylene or other laminate material. Gowns selected for HD use should be tested as impervious to HDs.

Eye and Face Protection

A plastic face shield should be worn in situations where eye, mouth, or nasal splashing is possible (such as during a bladder instillation of HDs). Goggles protect the eyes, but not the face, against spraying. Surgical masks provide a barrier to splashes, droplets, and sprays around the nose and mouth (USP, 2016a) but do not provide respiratory protection. They should not be relied upon for protection against aerosolized powders or liquids, such as during drug preparation or administration in nontraditional areas. For HD preparation, the C-PEC provides eye and face protection (American Society of Hospital Pharmacists, 1990; OSHA, 2016; USP, 2016a). For HD administration, working below eye level greatly reduces the likelihood of eye and facial splashing. Special work practices and additional PPE may be necessary to protect HCWs while performing higher-risk tasks (Korinth et al., 2007; Villa et al., 2015).

Areas where HDs are handled should have a sink with an eyewash station. Two functionally equivalent and cost-effective alternatives to an eyewash station are an IV bag of 0.9% sodium chloride solution (normal saline) connected to IV tubing or an irrigation bag of water or normal saline with attached tubing, which can be used to flush the eyes (ASHP, 2006). To protect sterility, tubing should be connected immediately before use.

Respiratory Protection

Respiratory protection is necessary when drug aerosols are present, such as when administering aerosolized HDs or cleaning up spills. Surgical masks do not provide respiratory protection from drug exposure and must not be used when respiratory protection from HD exposure is required. A surgical N95 respirator provides the respiratory protection of an N95 respirator and, like a surgical mask, provides a barrier to splashes, droplets, and sprays around the nose and mouth (USP, 2016a).

For most activities requiring respiratory protection, a fit-tested, NIOSH-certified N95 or a more protective respirator, such as that worn for tuberculosis protection, is sufficient to protect against airborne particles. These respirators offer no protection against gases and vapors. Use an appropriate full facepiece chemical cartridge-type respirator (see Approval of Respiratory Protective Devices, 2012) for events such as large spills when an IV bag breaks or a line disconnects and leaks, or where there is known or suspected airborne exposure to vapors or gases (NIOSH, 2008). Check the SDS for appropriate respiratory protection to use based on the agent involved (NIOSH, 2004b).

Removal of Personal Protective Equipment

After handling and disposal of HDs, the HCW should remove the outer gloves one at a time, turning them carefully inside out to avoid touching the outside, which is considered contaminated. The face shield, if worn, should be removed next, while avoiding contact with the front. Remove the gown, using care to pull it away from the body, not pulling it over the head, to avoid transfer of contamination to clothes and skin. Turn the gown inside out, fold it tightly, and discard it. Remove the respirator/mask (if worn), avoiding touching the facepiece. Finally, remove the inner gloves and discard in the disposal container. Wash hands with soap and water.

Drug Compounding

Key Points

- The USP General Chapter 800 details safe handling precautions to be followed for HDs in all practice settings including drug receipt, storage, compounding, and administration.
- These standards will be required beginning December 1, 2019.
- Compounding of HD doses must take place in a C-PEC appropriate to the needs of the setting.
- CSTDs are recommended during compounding, and required for administration, when the dosage form allows.
- Safe work practices can minimize the risk of exposure during drug compounding.

USP General Chapter 797 uses the term *compounded sterile preparations* (*CSPs*) to refer to all dosage forms that must be sterile when they are administered to patients and manufactured sterile products whether or not they are prepared strictly according to the instructions appearing in manufacturers' approved labeling (product package inserts) (USP, 2017b). Compounding includes preparing, mixing, and transferring drug between containers. USP General Chapter 797 further defines the conditions in which sterile compounding should take place to ensure the protection of patients. In the 2008 revision to USP General Chapter 797, sterile compounding of HDs also is addressed, and compounding conditions have been modified to ensure the protection of the workers (USP, 2017b). USP General Chapter 800 replaces General Chapter 797 for HD compounding and extends the standards to nonsterile as well as sterile compounding (i.e., to include the use of HD API powders and crushing commercial HD tablets). USP General Chapter 800 identifies the requirements for engineering controls, ventilation, receipt, storage, compounding, and dispensing of HDs but extends beyond USP General Chapter 797 to include standards for the administration of HD doses. USP General Chapter 800 will become official December 1, 2019.

Drug compounding represents a significant risk of exposure to HDs because the drug vials are potentially contaminated with HD residue, higher concentrations of drugs are handled, and multiple manipulations are required. The goal of using engineering controls, PPE, and meticulous work practices is to reduce the opportunities for worker exposure during drug compounding and related activities.

Many groups have published updated guidelines for special precautions in all HD-related activities, including ASHP (2006) and ONS (Polovich et al., 2014). OSHA addressed this worker hazard in the 1980s and recently placed an update on the OSHA Safety and Health Topics webpage (OSHA, 2016). NIOSH produced a significant update on handling HDs in its 2004 *Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings* (NIOSH, 2004a). As noted, USP General Chapter 800 addresses compounding sterile and nonsterile doses of HDs (USP, 2016a). USP General Chapter 800 is an enforceable standard that mandates certain precautions during the receiving, storing, compounding, transporting, and administering of HD doses. The standards in USP General Chapter 800 are intended to apply to all healthcare personnel who may be exposed to HDs in their workplace and all healthcare settings where HDs are handled (e.g., hospitals and other healthcare institutions, pharmacies, patient treatment clinics, physicians' practice facilities, other locations and facilities) (USP, 2016a).

General Information

All procedures for compounding HD doses, such as reconstituting, mixing, and transferring drug, must take place in a C-PEC. A C-PEC for HD sterile compounding is defined in USP General Chapter 800 as a device that provides an ISO Class 5 environment for the exposure of critical sites when compounding any sterile preparation (USP, 2016a). Critical sites per USP General Chapter 797 include any location where sterile component or fluid pathway surfaces (e.g., vial septa or injection ports) or openings (e.g., opened ampoules, needle hubs) are exposed and are at risk of direct contact with air, moisture (e.g., oral and mucosal secretions), or touch contamination (USP, 2017b). For compounding sterile HDs, the appropriate C-PECs include Class II and Class III BSCs and CACIs (ASHP, 2006; NIOSH, 2004a; USP, 2016a). These devices protect the environment and the operator from HD residue, as well as provide the needed "clean" (i.e., ISO Class 5) environment for sterile compounding. An extensive discussion of engineering controls may be found in the Hierarchy of Controls section.

It must be accepted that C-PECs do not eliminate the *generation* of contamination during HD compounding and may not be entirely effective in containing HD aerosols and residue. Secondary controls such as PPE and stringent work practices are required to maximize the usefulness of all C-PECs. Worker train-

ing on the correct techniques in utilizing the C-PEC and other safety devices is critical in establishing an effective safe handling program.

NIOSH and USP agree that HDs should be stored separately from non-HDs (NIOSH, 2004a; USP, 2016a). USP General Chapter 800 mandates that antineoplastic HDs requiring manipulation other than counting or repackaging of the final dosage must be stored separately from non-HDs in a manner that prevents contamination and personnel exposure (USP, 2016a). These HDs must be stored in a separate negative-pressure room that is vented to the outside, with at least 12 ACPH (USP, 2016a). Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator in a negative-pressure area with at least 12 ACPH (e.g., storage room, buffer room, C-SCA). If a refrigerator is placed in a negative-pressure buffer room, an exhaust located adjacent to the refrigerator's compressor and behind the refrigerator should be considered (USP, 2016a). HDs must be compounded within a C-PEC located in an externally vented C-SEC, which may be an ISO Class 7 buffer with an ISO Class 7 ante room, or an unclassified C-SCA (USP, 2016a). Per USP General Chapter 800, HD compounding areas must be physically separated from non-HD compounding, have appropriate ACPH, and be at negative pressure to all adjacent areas. The external venting and negative pressure are to contain any contamination generated in the storage or compounding of HDs and limit it from spreading out of the immediate work area (NIOSH, 2004a; USP, 2016a). Discussions of buffer areas, ante areas, and C-SCAs can be found in the Hierarchy of Controls section in this handbook.

Containment Primary Engineering Control Work Practices

The Class II BSC, Class III BSC, and CACI require somewhat different techniques for accessing and operating the C-PECs for compounding HDs. As the Class III BSC is rarely used, this discussion will be limited to the Class II BSC and the CACI. The CACI has attached sleeves and gloves that limit the movement of the operator and require all drugs and supplies to be placed into and completed doses removed from the cabinet through transfer chambers, also known as *pass-throughs*. Training and practice are standard requirements for the use of all equipment.

Cleaning and disinfection of the C-PEC is required prior to beginning sterile compounding. To remove HD residue, a surface decontamination is required (see Figure 4). Disinfectants, especially alcohol, do not deactivate HDs (Benvenuto et al., 1993; Dorr, 2001; Hansel et al., 1997). While nothing has been shown to deactivate all HDs, many of the HD SDSs recommend sodium hypochlorite (bleach) solution as an appropriate deactivating agent (Johnson & Janosik, 1989). Researchers have shown that strong oxidizing agents, such as sodium hypochlorite, are effective deactivators of many HDs (Benvenuto et al., 1993; Hansel et al., 1997). Sodium hypochlorite with a detergent and neutralizer is commercially available as Surface Safe™, and it has been used to decontaminate C-PECs. The oxidizing bleach solution is combined with a detergent on a wiper that provides physical cleaning action along with some deactivation. The neutralizer protects the stainless steel surfaces and also deactivates certain HDs that are not affected by bleach. A non-chlorine bleach liquid sporicidal disinfectant containing hydrogen peroxide and peracetic acid has been shown by testing by an independent laboratory to remove some HDs from stainless steel surfaces (Contec Healthcare, 2016a, 2016b). Researchers examined a range of solutions on 10 HDs to simulate cleaning glass surfaces and stainless steel surfaces (Queruau Lamerie et al., 2013). The authors tested "elimination-type" solutions whose main action is to dissolve chemical products on the surface and "degradation type" solutions that react with the chemical structure of compounds, leading to their degradation and the formation of expected noncytotoxic compounds (Queruau Lamerie et al., 2013). Sodium hypochlorite showed the highest overall effectiveness, surfactants had good results for some drugs, and surfactant mixed with 20% IPA had the highest global effectiveness. Although the study demonstrated that all decontamination agents reduce HD contamination on work surfaces, none remove it totally (Queruau Lamerie et al., 2013). Further research is needed to establish an application and rinsing process to maximize the cleaning effect and minimize damage to surfaces.

Decontamination is recommended at least daily for a C-PEC that runs 24 hours per day but is used only for one shift; a C-PEC that is used throughout the 24 hours must be decontaminated two or three times daily (ASHP, 2006). USP General Chapter 800 requires that the C-PEC must operate continuously if it supplies some or all of the negative pressure in the C-SEC or if it is used for sterile compounding. Decontamination must be done if a spill has occurred or if there has been visible residue generated during compounding. Disinfection of the C-PEC with sterile 70% IPA must be done prior to any sterile compounding and every 30 minutes during continuous compounding (USP, 2017b). Apply spray to the wipers, not the C-PEC surface, whenever HD compounding has taken

place in a C-PEC to avoid spreading the HD residue. All wipers used to decontaminate or disinfect a C-PEC used for HD must be contained and discarded as HD waste.

Universally, good organization will improve compounding regardless of the type of C-PEC. Select and assemble the drug and all supplies and solutions prior to accessing the C-PEC. With a Class II BSC, this reduces the need to enter and exit the cabinet, which may cause HD contamination to migrate from the cabinet to the surrounding work area. As the closed CACI does not allow quick access to the work area, lack of organization results in extended compounding time.

USP General Chapter 797 requires that drugs and supplies brought into the C-PEC be wiped down or sprayed with sterile 70% IPA to reduce the particulate load and related microbial contamination (USP, 2017b). HD drug vials have been shown to be contaminated with drug residue when they are received from the manufacturer or distributor (Power et al., 2014; Schierl et al., 2010). Removing this contamination is necessary to avoid placing HD residue into the CACI

Figure 4. "Bugs" Versus "Drugs": What Are Decontamination and Cleaning?

Cleaning and *surface decontamination* are very general terms that signify the removal of contamination. In sterile compounding of HDs, contamination may take the form of viable organisms (*bugs*) or HD residue (*drugs*). **Disinfection** neutralizes viable organisms; **deactivation** neutralizes chemical residue. No one agent has been found that does this reliably and consistently. Residue left on compounding surfaces from either disinfection or deactivation must be removed by physically wiping with appropriate wipers and rinsing agents (a no-residue cleaner or sterile water for irrigation).

Desired Effect	Considerations and Concerns	Possible Agents
Disinfection: removal of viable organisms ("bugs") Disinfectants are classified as low, intermediate, and high level based on which organism they kill and the concentration and contact time required.	Disinfectants are used to remove viable organisms from surfaces in the compounding area and to sanitize gloves during sterile compounding. Disinfectants may be hampered by the presence of blood or other biologic fluids or other residue that requires removal ("cleaning") prior to or in conjunction with disinfection. Certain disinfectants incorporate a detergent into the solution. Low- or no-residue disinfectants are preferred to avoid the need for rinsing. Controlled Environment Testing Association (2007) and USP 1072 (U.S. Pharmacopeial Convention, 2016b) provide information on different levels of disinfectants and sterilants that are useful against a variety of organisms and may be used in rotation with sterile isopropyl alcohol to improve surface decontamination.	Disinfectants • Intermediate level – Sterile 70% IPA – Iodophor – Phenolic – Accelerated hydrogen peroxide (efficacy based on concentration plus contact time) • High level – Chlorine (efficacy based on concentration plus contact time) – PeridoxRTU® is a high-level disinfectant and sporicide. Independent lab testing shows some HD removal (Contec Healthcare, 2016b).
Sanitization Sterile gloves are easily contaminated (by both "bugs" and "drugs") and should be sanitized with a disinfectant as needed during compounding. Spraying any solution in the C-PEC or onto HD-contaminated surfaces (e.g., gloves) can spread HD residue.	Hand or glove sanitizers should be available in the sterile compounding area. With HD compounding, gloves also are contaminated with HD residue. DO NOT handle sanitizers with dirty gloves. Use wipers to touch bottles. NEVER spray the sanitizer onto the gloves (or other surfaces), as this will transfer the HD residue (Kiffmeyer et al., 2013). Spray or place gel on the wiper and wipe off (sanitize) the gloves. Contain and discard all wipers used on potentially HD-contaminated surfaces as HD waste.	Hand/glove sanitizers • Alcohol-based gels • Disinfectant gel • Sterile 70% IPA spray
Deactivation ("drug") Removes chemical residue by degradation or inactivation. Some HDs are potent chemicals with resistance to deactivation.	Deactivating agents may be strong chemicals that present their own problems in clinical use. No one agent has been shown to inactivate or neutralize all HDs. Some chemicals are effective against some HDs. Some HDs, however, degrade to mutagenic by-products upon treatment with some chemicals. Residue from deactivation still must be removed from the affected surfaces.	Deactivating agents • SDSs list agents to use in response to a spill. Many list sodium hypochlorite (bleach) as effective. Concentration and contact time must be considered. • Package inserts for HDs list some agents that degrade HDs. Sodium thiosulfate deactivates certain HDs. Mechlorethamine, for example, is neutralized with 5% sodium thiosulfate and 5% sodium bicarbonate solution for 45 minutes.

(Continued on next page)

Figure 4. "Bugs" Versus "Drugs": What Are Decontamination and Cleaning? *(Continued)*

Desired Effect	Considerations and Concerns	Possible Agents
Surface decontamination (drug and other residue) Removes contamination (residue) from a nondisposable surface to a disposable one using detergent and good wipers followed by rinsing.	Low-sudsing and low-residue detergents may be used to remove contamination from surfaces in the C-PEC or adjacent surfaces (e.g., counters, storage bins, floors). All cleaning must be done wearing double gloves, and all disposable wipers, towels, gauze pads, and other items must be contained in sealable plastic bags and then discarded as hazardous waste. Surface decontamination must be followed by rinsing. Disinfect all C-PEC surfaces prior to compounding. The amount of HD contamination placed into the Class II BSC or isolator may be reduced by surface decontamination (i.e., wiping down) of HD vials. Researchers examined a range of solutions to simulate cleaning glass surfaces (e.g., glass vials). Sodium hypochlorite (e.g., Surface Safe™) showed the highest overall effectiveness; surfactants had good results for some drugs. Queruau Lamerie et al. (2013) found that surfactant mixed with 20% IPA had the highest global effectiveness. Further research is needed to establish an application and rinsing process.	Detergents • High-pH soap-type cleaners are recommended in SDSs and other literature. • Dilute all cleaners according to manufacturer instructions. • Prepare cleaners and disinfectants carefully. • Use only freshly prepared cleaners and disinfectants.

BSC—biosafety cabinet; C-PEC—containment primary engineering control; HD—hazardous drug; IPA—isopropyl alcohol; SDS—safety data sheet; USP—U.S. Pharmacopeial Convention

Note. Based on information from American Society of Health-System Pharmacists, 2006; Benvenuto et al., 1993; Contec Healthcare, 2016b; Controlled Environment Testing Association, 2007; Hansel et al., 1997; Johnson & Janosik, 1989; Kiffmeyer et al., 2013; U.S. Pharmacopeial Convention, 2015.

or Class II BSC work area and then transferring it to other surfaces. While various cleaning and decontamination solutions were tested on glass with 10 different HDs, the researchers (as discussed previously) noted that none totally removed the residue (Queruau Lamerie et al., 2013). In addition, several of the solutions might be problematic with drug labels. More research on vial cleaning is needed. There are general principles that may be applied to vial cleaning: use low-linting wipers that meet the intent of USP General Chapter 797 for sterile compounding; use fresh wipers and discard as HD contaminated waste; do not reuse wipers; spray the wiper, not the drug vial, to avoid transfer of the HD residue into the air or onto other surfaces; and use fresh gloves for wiping and change gloves before compounding to avoid transfer of HD residue from the glove surfaces. While Surface Safe is appropriate for decontaminating the C-PEC, it may damage the label if applied directly to the drug vial, creating a safety issue for patients if the drug and dose are not visible. Sterile 70% IPA and sterile water for irrigation (SWFIR) do not damage the vial label and should be adequate, if used as noted here, in reducing the HD residue.

Only those items needed for immediate compounding should be placed in the work area of the Class II BSC or the main chamber of the CACI. Overcrowding should be avoided inside the C-PEC because excess supplies can block the airflow, which may breach the containment properties of the Class II BSC. This also may interfere with the HEPA-filtered, unidirectional air in either the Class II BSC or CACI, compromising sterile compounding (ASHP, 2006; American Society of Hospital Pharmacists, 1990; USP, 2015). Excess supplies in the Class II BSC or main chamber of the CACI may become contaminated from HD residue generated during the compounding process (Sessink, Boer, Scheefhals, Anzion, & Bos, 1992). This contamination may then be transferred out of the C-PEC. Place only those items necessary for drug preparation, a small disposable sharps container, and a heavy-duty zipper-lock bag (for disposal of syringes, vials, and gloves) in the Class II BSC before beginning work. The CACI may be equipped with waste outlets that allow the waste to be discarded directly from the main chamber. Containing waste in small zipper-lock bags before placing in HD waste containers provides more robust containment. Items not needed immediately may be left in the transfer chamber of the CACI and accessed as needed. Care must be taken to avoid HD transfer from used gloves.

While USP General Chapter 800 recommends placing a plastic-backed preparation mat on the work surface of the C-PEC (USP, 2016a), the practice of covering the working surface of the C-PEC with a plastic-backed, absorbent, disposable drape is problematic for both sterile compounding and for HD containment. The drape can negatively affect the contain-

ment airflow of the Class II BSC (Minoia et al., 1998) and possibly the clean airflow in a CACI with unidirectional air. In-house testing by one manufacturer concluded that the use of a ChemoPlus™ preparation mat used on the work surface of a Class II BSC does not harm the containment performance as long as the mat remains on the work surface and never blocks the front or rear work zone grills (NuAire, Inc., 2005). USP General Chapter 797 is currently silent on the addition of a nonsterile mat into the C-PEC. If used, the mat should be changed immediately if a spill occurs and regularly during use and should be discarded at the end of the daily compounding activity. The mat must be considered contaminated with HD residue. It must be handled carefully and discarded as HD waste.

Good work practices for all sterile products, as well as HD doses, require frequent handwashing prior to donning gloves. Hands must be washed after removing gloves with soap and water. Two pairs of ASTM-tested gloves must be used for sterile HD compounding (USP, 2016a). When used for sterile compounding, the outer chemotherapy gloves must be sterile (USP, 2015, 2016a). Chemotherapy gloves should be changed every 30 minutes unless otherwise recommended by the manufacturer's documentation and must be changed when torn, punctured, or contaminated.

Studies have shown that gloves are routinely contaminated with HD residue during compounding and that transfer of this contamination to other surfaces is common (Sessink et al., 1992). One study found detectable levels of platinum on isolator gloves (Kopp et al., 2013). USP General Chapter 797 requires frequent sanitization of gloves during sterile compounding. While this is also needed with sterile HD compounding, care must be taken not to handle spray bottles with contaminated gloves. Use wipers to act as a barrier between dirty gloves and other surfaces; spray the wipers, not the gloves with disinfectant; and wipe the gloves and discard the wipes as HD waste. Wearing two pairs of gloves during compounding allows the outer pair to be changed as needed while reducing the exposure to the worker as the inner pair remains intact.

Limitations Specific to the Class II Biosafety Cabinet

The effectiveness of the Class II BSC in protecting the HCW and environment is related to the airflow. Although the cabinet is designed to direct airflow and potential drug contamination away from the worker, this is a very technique-dependent process. Workers should avoid moving their hands in and out of the cabinet during compounding because a disturbance in the airflow may result in directing drug aerosols outside the cabinet. This should be kept in mind whenever there is the possibility of releasing drugs into the environment, such as when an HD container is open and during all drug-transferring activities.

Personal Protective Equipment in a Containment Primary Engineering Control

The use of a Class II BSC does not eliminate the need for PPE, and no studies have documented that a CACI reduces the transfer of HD contamination to the operator during the loading and unloading of HDs, supplies, and finished doses. As spills are possible during any HD handling, PPE must be used to prevent worker exposure. Gowns tested to protect from HD permeation and double gloves tested to ASTM Standard D6978-05 (2013) are universally recommended for HD handling (ASHP, 2006; NIOSH, 2004a, 2016; Polovich et al., 2014; USP, 2016a). USP General Chapter 797 requires extensive garbing (gown, gloves, mask, hair and shoe covers) to reduce the transfer of microbial-laden particulates from the worker to the environment and sterile product (USP, 2015). USP General Chapter 800 requires two pairs of gloves, the outer one sterile, for compounding sterile preparations (USP, 2016a). When wearing double gloves, tuck the cuff of the inner glove under the gown sleeve and the cuff of the outer glove over the gown sleeve. Change the outer gloves immediately whenever contamination is suspected. Change both gloves if the outer glove is torn, punctured, or contaminated by an obvious spill. At the completion of each batch, remove the outer gloves and seal them in a zipper-lock bag. Remove the gown before removing the inner pair of gloves.

Compounding of Sterile Hazardous Drug Doses

Aseptic technique is required for compounding all parenteral drugs to maintain the sterility. CSPs are addressed in USP General Chapter 797 along with specific training and methods to document competency of aseptic technique (USP, 2017b). Appropriate actions to provide safe CSPs for patients are assumed and will not be addressed here. Meticulous aseptic technique for compounding HDs in ampoules and vials has been described in the literature (Wilson & Solimando, 1981).

Luer-lock syringes and access devices (e.g., needles, needleless devices) must always be used in HD compounding to prevent inadvertent separation of the devices and the resulting leakage. Syringes should never be more than three-quarters full when containing the HD dose to prevent separation of the plunger from the syringe barrel during compounding or transport (ASHP, 2006; American Society of Hospital Pharmacists, 1990; OSHA, 2016).

HDs supplied in ampoules (e.g., arsenic trioxide) require special precautions both to prevent microbial contamination and to avoid drug leakage from this open system. When opening ampoules, tap down any drug from the top of the ampoule and wrap a sterile gauze pad around the neck. Break the ampoule carefully using a single sharp motion aiming the ampoule into a corner of the C-PEC away from the HEPA filter; do not aim at the operator or open front of the Class II BSC. The gauze will reduce the risk of injury from the sharp edges of the glass as well as contain drug contamination from spilling. A filtering device must be used to prevent glass particles from being drawn into the syringe. Using a filtering straw reduces the needlestick risk associated with withdrawing the drug with a filter needle. The straw, however, has no cover so care must be taken to keep the packaging for removal and disposal of the straw into a sealed containment bag.

Many HDs are supplied in vials that may require reconstitution. When adding liquid to an HD drug vial or when withdrawing HD doses from vials, use caution to avoid pressure buildup inside the vial that can result in aerosols or leakage. Needleless dispensing devices with hydrophobic filters often are used to equilibrate any pressure in the vial, although no evidence is available to support their effectiveness in reducing HD exposure. No filter will prevent the escape of vapors. These devices are not closed systems and may have open channels into the drug vial. Only devices cleared by FDA as Product Code ONB should be considered CSTDs (U.S. FDA, 2014). In general, these other devices do not lock onto the vial and may dislodge during use, resulting in large spills. Other devices, if used, should be attached to one vial only and discarded with the empty vial into a containment disposal bag.

Negative Pressure Technique

When adding diluent to a vial or withdrawing liquid from a vial, use the negative pressure technique described by Wilson and Solimando (1981). Whether the syringe contains air or liquid, do NOT push on the plunger when the needle is in the vial. Use a syringe that is large enough to manipulate excess air, and after making the initial puncture with the needle, pull BACK on the plunger, drawing air into the syringe and creating negative pressure in the vial. This "vacuum" will draw the liquid into the vial without pushing the plunger and pressurizing the HD vial. Repeat the process until the diluent is transferred to the vial and the air is in the syringe. If possible, keep the needle in the vial while swirling to reconstitute the HD. If the volume of the dose may be removed from the vial without removing the needle or correcting the air volume, do so, as a second puncture in the vial septum presents an opportunity for leakage. If the needle must be removed from the vial, place the vial upright on the work surface and move the needle into the air space above the drug. Withdraw just enough air into the syringe that there is a pull on the plunger, demonstrating the negative pressure in the vial. Hold onto the vial and plunger and remove the needle from the vial septum. This technique should avoid generating positive pressure or leaking drug around the needle or access device.

When withdrawing liquid from a vial, draw up slightly less air into the syringe than the volume of the dose to be withdrawn. After the initial puncture, draw back on the plunger, creating negative pressure in the HD vial. Invert the vial to allow liquid to enter the syringe, repeating the process until the correct dose is transferred to the syringe. Once the dose volume has been transferred to the syringe, hold the syringe plunger firmly and place the vial upright on the work surface. Move the needle into the air space above the drug and draw back slightly on the plunger, bringing air into the syringe JUST to the top of the syringe hub, not into the syringe. This clears the HD liquid from the needle. Hold the plunger firmly as the vacuum in the vial will strain to equilibrate the pressure. Remove the needle from the vial septum. Transfer the dose into an appropriate IV delivery system. Do not recap HD-contaminated needles unless the needle must be removed. If the dose is to be delivered in the syringe, use a single-handed technique to recap the needle to avoid a needle stick. Remove the needle and cap, and replace with a syringe cap for transport. Do not transport drug-filled syringes with needles attached.

Wipe down the outside of the drug container (bag or syringe) with moist gauze. Wipe entry ports with alcohol and apply a closure, either hard plastic or foil seal is appropriate, to prevent any leakage from the port. Seal the drug syringe or container with the attached tubing in a plastic zipper-lock bag that will contain any spilled drug if the container leaks. The outer bag containing HDs should be free of drug residue to protect HCWs outside of the preparation area who transport and administer HDs.

Closed-System Drug-Transfer Devices

Connor, Anderson, Sessink, and Spivey (2002) demonstrated the potential for leakage in compounding HDs using a needle and syringe, as well as leakage in administration when attaching IV sets and priming lines.

CSTDs are designed to protect the sites shown to be prone to leakage during HD compounding and administration activities. Unlike C-PECs, CSTDs actually reduce the generation of HD contamination in the compounding process. CSTDs, as well as all other safety equipment, require training to be used properly and are not 100% effective. Closed systems are currently not available for use with ampoules. NIOSH and USP General Chapter 800 recommend the use of CSTDs in compounding HDs, but both state the CSTD must be used only in conjunction with ventilated engineering controls (i.e., C-PECs). USP General Chapter 800 requires the use of a CSTD during administration of antineoplastic HD doses when the dosage form allows and when the CSTD is known to be physically and chemically compatible with a specific HD in use. See the Hierarchy of Controls section for additional CSTD discussion.

Spiking IV Bags and Priming Lines

There is a risk of releasing drugs into the environment when spiking IV bags containing HD doses and when priming IV tubing with drug solution into an HD waste container or gauze pad. Vandenbroucke and Robays (2001) reported a 25% rate of leakage during the connection of tubing to an infusion bag. A risk of leakage also exists during the connection of the tubing to the patient side of the IV tubing when the tubing is primed with drug-containing solution. Guillemette et al. (2014) reported 100% of wipe samples in an oncology administration area as positive for marker drugs on the floor below the area for IV tube priming and the floor in front of the waste container.

The practice of spiking the IV bag and priming the tubing in the C-PEC prior to adding the HD is one way to avoid this exposure. USP General Chapter 800 requires HDs be administered safely using protective medical devices and techniques, noting that examples of protective techniques include spiking or priming IV tubing with a non-HD solution in a C-PEC (USP, 2016a). As studies have shown, the C-PEC work surface is laden with HD residue (Connor et al., 2010; Sessink et al., 2011, 2013). This practice could transfer contamination to the outside of the tubing, resulting in another opportunity for exposure. Priming in the C-PEC requires communication between the person compounding the drug and the person administering the drug so the appropriate administration set is selected. Practice settings that use multiple IV pumps and controllers might find this problematic. Some institutions have elected to attach a secondary set to all IV bags or bottles that contain HDs to avoid this issue. Secondary sets are compatible with most IV tubing with a proximal port and a needleless connector. Once spiked, the secondary set may be primed in the C-PEC or at the bedside using backflow priming from the primary IV solution. Secondary IV tubing used to deliver HDs must not be disconnected from the patient's primary pump tubing, unless a CSTD is used. The entire tubing setup must be discarded intact to avoid leakage and contamination of patient care areas with HD residue.

As an alternative, a CSTD component may be used that spikes into the IV bag in the C-PEC. This infusion adapter provides a dry-spike connection that may be accessed at the patient bedside with a secondary or primary set and eliminates the leakage associated with spiking. This device is ideal for backflow priming at the bedside. Use only a CSTD that has been tested as a dry-spike adapter. When priming the line in the C-PEC, another alternative is to use the closed male Luer connection available with the CSTD systems to lock off the distal end of the IV tubing (usually a secondary set). This provides a closed system for connecting the IV to the needleless Y-site and then allows the secondary set to be removed when the infusion is completed. Use only a CSTD that has been tested as a closed adapter to the Y-site connection. Removing standard IV sets from the patient's IV setup is known to be a significant source of exposure as drug remains in the tubing. This closed male Luer should prevent leakage on disconnection, allowing the dose and tubing to be discarded into a containment bag as needed rather than waiting until the entire setup may be discarded. This system is especially useful when administering an HD regimen that requires multiple IV bags of the same or different HDs for a course of therapy. See the Hierarchy of Controls section for additional discussion of CSTDs.

Nonsterile Hazardous Drugs

HDs should be delivered in the final dose and form for administration whenever possible to minimize exposure risk. Unit dose packaging is the preferred method of providing oral HDs; however, not all HDs are available in that form. Tablet coatings are not

designed to prevent active drug from leaching from the tablet, and some coatings are not robust enough to survive general handling. Powder from tablets or damaged capsules might represent an exposure risk. Any handling of tablets or capsules should be done wearing gloves tested for use with HDs, with the assumption that exposure is possible (ASHP, 2006; American Society of Hospital Pharmacists, 1990; NIOSH, 2016; OSHA, 2016).

Compounding of nonsterile doses of HDs (e.g., crushing or breaking oral HD doses to be made into liquids) or other activities where containment ventilation is desired (e.g., opening damaged HD containers) may be done in a non-ISO Class 5, ventilated C-PEC, such as a fume hood (Class I BSC) to avoid the inhalation of HD powder (USP, 2016a). The use of an ISO Class 5 C-PEC is discouraged for nonsterile compounding (USP, 2016a). If nonsterile activities must be done in the ISO Class 5 C-PEC, full decontamination for HD residue and cleaning and disinfection for particulates and microorganisms are required prior to resuming sterile compounding. For nonsterile HD compounding, a mask with face protection, a gown tested to protect from HD permeation, and double gloves tested to ASTM Standard D6978-05 (2013) are required.

Crushing tablets or opening capsules for administration (e.g., to mix in food or to administer through a feeding tube) increases the risk of exposure. Liquid formulations dispensed in an oral or enteral syringe are preferred.

HDs in an enteral feeding syringe should have a leakproof end cap when dispensed. If crushing of HDs must be done outside of the pharmacy, don full PPE, use a plastic-backed pad to protect the work environment, and use a pill crusher with a single-use plastic pouch to contain the powder. Multi-use pill crushers or mortars and pestles should not be used. Dispose of the plastic-backed pad and PPE according to guidelines. Decontaminate and disinfect the surfaces in the work area.

Safety Measures: Drug Labeling

All HD doses must be labeled in order to identify them. A label on the drug container itself and on the outside of the bag used for transport should alert the handler that special precautions are required (ASHP, 2006; American Society of Hospital Pharmacists, 1990; NIOSH, 2004a; OSHA, 2016; USP, 2016a). Attach a warning label stating, for example, "CAUTION: HAZARDOUS DRUG. HANDLE WITH PPE. DISPOSE OF PROPERLY."

Disposal of Compounding Supplies

All items used in the compounding of HDs are considered contaminated and should be discarded in a hazardous waste container. Discard needles and other sharps in the small sharps container inside the C-PEC or through waste ports, if applicable. Discard empty vials, used syringes, drapes, and other items used in drug compounding in the zipper-lock bag. Remove the outer gloves and place them in the zipper-lock bag. Decontaminate any containers stored in the C-PEC (e.g., sharps container) with an approved detergent solution before removing from the C-PEC and place into the lined hazardous waste container. Carefully remove the gown and then the inner gloves to avoid contaminating skin and clothing. Contain all PPE in zipper-lock bags and discard in the hazardous waste container. Seal the HD waste container if any waste is placed in it that is not contained in a secondary bag. Wash hands with soap and water before leaving the preparation area. Gloves and gowns should not be worn outside the drug preparation area.

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Appendix A. Handling of Hazardous Drugs Employee Agreement

All care providers (RN, MD, NP, PA, LPN, Tech, housekeeping staff, patient observer):

I have read the Handling of Hazardous Drugs policy and procedure, and I understand:

- ☐ There are possible risks to my health and the health of other staff members who work in the environment when I handle hazardous medications.
- ☐ Medications are classified as hazardous when they possess any of the following characteristics: genotoxicity, carcinogenicity, teratogenicity or fertility impairment. Investigational drugs are considered hazardous until proven otherwise.
- ☐ Safety data sheets (SDSs) are accessible to me if exposure occurs.
- ☐ Proper application of personal protective equipment and safe handling are required when handling hazardous medications to avoid risk to my health and the health of other staff members working in the environment.
- ☐ Proper apparel and safe handling are required when handling body fluids during the first 48 hours following the administration of a hazardous medication.
- ☐ Immediate action must be taken if direct contact occurs with any medication that is labeled as hazardous. If skin or eye contact occurs, the employee must complete the Employee Report of Incident form and report to Occupational Injury Clinic (OIC) or the ED (if the OIC is closed) after following the washing procedure.
- ☐ Procedures for the proper disposal of hazardous medications are required to avoid staff exposure and environmental contamination.

*Spill cleanup policy must be followed for the management and cleaning of any spilled hazardous medication.

RN, MD, NP, LPN only:

I have read the Handling of Hazardous Drugs policy and procedure; and I understand:

- ☐ The procedures for the administration of hazardous medications.
- ☐ The proper disposal of supplies used in the administration of hazardous medications.
- ☐ The proper use of closed-system drug-transfer devices for hazardous drug administration.
- ☐ The management of bulk waste for hazardous medications.

Employee _____

Signature Printed Name Employee # Date

Witness _____

Signature Printed Name Date

Appendix B. Hazardous Drug Administration Safe Handling Checklist

Name: _____ Date of Review and Exam: _____

PRIOR TO ADMINISTRATION	Yes	No	Initials
1. Gather equipment required for drug administration.			
2. Select appropriate gloves for hazardous drug administration.			
3. Select appropriate gown for hazardous drug administration.			
4. Identify situations when mask and face protection are required.			
5. Locate hazardous drug spill kit.			
6. Obtain hazardous waste container.			
7. Receive drug(s) from pharmacy in sealed bag.			
ADMINISTRATION			
1. Wash hands and don personal protective equipment before opening drug delivery bag.			
2. Visually inspect the contents of the delivery bag for leaks.			
3. Gather IV administration supplies including closed-system drug-transfer devices.			
4. For IV infusions • Ensure tubing is primed with a nondrug solution. • Utilize plastic backed absorbent pad under work area. Remove cap from IV tubing and connect to patient's IV device. • Utilize closed-system drug-transfer device when compatible. • Tighten locking connections. • When complete, don personal protective equipment and discontinue IV bag with tubing intact (do not unspike bag). • Utilize gauze pads when disconnecting from patient's IV device when a closed-system drug-transfer device cannot be used.			
5. For IV push medications • Utilize closed-system drug-transfer device when possible. • Tighten locking connection. • When complete, do not recap needle. • Discard syringe-needle unit in puncture-proof container.			
6. For intramuscular/subcutaneous injections • Utilize closed-system drug-transfer device when possible. • Attach needle to syringe. • Tighten locking connection. • When complete, do not recap needle. • Discard syringe-needle unit in puncture-proof container.			
7. For oral drugs (tablets/capsules) • If using bar code technology, scan medication prior to removing medication from packaging. • Don gloves. • Open unit-dose package and place into medicine cup (avoid touching drug or inside of package). • Avoid touching tablets/capsules.			
8. For oral drugs in liquid form • Obtain drug in final form in appropriate oral syringe. • Don double gloves, gown, and mask with face protection. • Use plastic-backed absorbent pad during administration. • Discard syringe in hazardous waste container after administration.			
POST-ADMINISTRATION			
1. Don personal protective equipment.			
2. Seal hazardous drug–contaminated supplies in sealable plastic bag for transport to hazardous waste container.			

(Continued on next page)

Appendix B. Hazardous Drug Administration Safe Handling Checklist *(Continued)*			
POST-ADMINISTRATION *(cont.)*	**Yes**	**No**	**Initials**
3. Place sealed plastic bag in hazardous waste container.			
4. Remove outer gloves.			
5. Close lid on waste container.			
6. Decontaminate equipment in the area appropriately.			
7. Remove and discard inner gloves.			
8. Wash hands thoroughly with soap and water.			

Appendix C. Hazardous Drug Administration Practicum for Registered Nurses

Objectives	Content	Teaching/Learning Strategies
Recall the properties and health risks of workplace exposure to hazardous drugs.	Characteristics of hazardous drugs • Carcinogenicity • Reproductive toxicity • Teratogenicity or developmental toxicity • Infertility • Organ toxicity at low doses • Genotoxicity • Drugs similar in structure or toxicity	Discuss clinical scenarios regarding potential exposure. • Case study: Nurse attempting to conceive or breastfeeding • Case study: Experienced nurse who chooses not to wear personal protective equipment, therefore placing others in the environment at risk • Case study: Explaining to patient and family why you are wearing personal protective equipment • Case study: Caregivers handling hazardous drugs and hazardous drug waste in the home Learner will interview nursing staff on their personal protective equipment practices in light of current evidence and will evaluate feedback in light of recommended practices. In advance of clinical experience, learner will download and review: • *Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings:* www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf • *Controlling Occupational Exposure to Hazardous Drugs:* www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html *Materials:* • *NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings:* www.cdc.gov/niosh/docs/2004-165 • Case studies
Outline potential routes of exposure in the clinical setting.	Potential routes of exposure include the following: • Skin or mucous membrane exposure • Needle sticks or sharps • Inhalation of aerosols, dust, or droplets • Ingestion Common exposure scenarios • Manipulation of vials • Opening ampoules • Expelling air from syringes • Drug administration by all routes • Spiking IV bags and changing IV tubing • Leakage of tubing or IV bags or syringes • Contamination of objects in the environment • Handling body fluids of patients who have received hazardous drugs • Cleaning up hazardous drug spills	Learner will have discussion and question and answers with instructor. Review clinical setting for possible exposure scenarios by walking through and observing administration of chemotherapy, disposal, and removal of personal protective equipment. Learner will journal about practices observed and identify potential areas for improvement.

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Appendix C. Hazardous Drug Administration Practicum for Registered Nurses *(Continued)*

Objectives	Content	Teaching/Learning Strategies
Demonstrate safe handling, administration, and disposal of hazardous drugs in accordance with recommended best practices.	Overview of appropriate drug storage, transportation, handling, and disposal procedures • National Institute for Occupational Safety and Health Alert regarding safe handling of hazardous drugs, drug handling, and disposal • Review and practice safe handling techniques using personal protective equipment, including gloves, gowns, respirator, and eye and face protection. • Rationale for personal protective equipment use • Review of work practice controls to minimize environmental contamination, such as not spiking at the bedside, working below eye level, use of personal protective equipment, closed-system devices, using gauze under syringe at injection ports, using Luer-lock connections, safe priming of IV tubing with a nondrug solution, washing exposed surfaces with detergent and water, and proper disposal technique. • Standard precautions, including double gloving and disposable gowns, when handling excreta of patients who have received hazardous drugs in previous 48 hours • Use of mask with face protection when splashing is possible • Use of plastic-backed absorbent pads for patients at home or in the workplace • Linen handling procedures • Hazardous drug spill management procedures	Clinical observation with patients receiving chemotherapy Under supervision of instructor, perform the following: • Return demonstration of appropriate personal protective equipment use while administering hazardous drugs • Return demonstration of work practice controls to minimize environmental contamination • Return demonstration of proper disposal technique utilizing hazardous waste receptacles • Instruction of patient and family on safe handling practices, including handwashing, personal protective equipment, safety of children and pets, and management of linens and contaminated objects • Location of hazardous drug spill kit and review of contents *Materials:* • *NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings:* www.cdc.gov/niosh/docs/2004-165 • Oncology Nursing Society *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice,* Appendix 3, Clinical Practicum Evaluation (Polovich et al., 2014, p. 469) • Oncology Nursing Society *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice,* Appendix 1, Safe Management of Chemotherapy in the Home, Evaluation (Polovich et al., 2014, p. 466). • Spill kit matching game to identify use of each component In advance of clinical experience, learner will download and review *CDC Workplace Solutions, Personal Protective Equipment for Health Care Workers Who Work with Hazardous Drugs:* www.cdc.gov/niosh/docs/wp-solutions/2007-117/pdfs/2007-117.pdf
Explain medical surveillance as a component of a safe handling program.	Definition of medical surveillance • Comprehensive program to minimize workplace exposure • Engineering controls • Work practices • Personal protective equipment Elements of a medical surveillance program • Health surveys • Laboratory work • Physical exam • Rationale for follow-ups	Discussion with preceptor Visit to occupational health for medical surveillance program enrollment In advance of clinical experience, learner will download and review *CDC Workplace Solutions, Personal Protective Equipment for Health Care Workers Who Work with Hazardous Drugs:* www.cdc.gov/niosh/docs/wp-solutions/2007-117/pdfs/2007-117.pdf