

ASHP Guidelines on Handling Hazardous Drugs

ASHP published its first guidance on hazardous drugs (HDs) in 1983 as part of the 1983-84 ASHP Practice Spotlight: safe handling of cytotoxic drugs.^{1,2} This was followed by technical assistance bulletins (TABs) in 1985 and 1990, and the ASHP Guidelines on Handling Hazardous Drugs in 2006.³⁻⁵ The 2006 guidelines were created to harmonize with the National Institute for Occupational Safety and Health (NIOSH) Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings issued in 2004.⁶ The ASHP 2006 HD guidelines were current to 2005.

In 2007, the United States Pharmacopeial Convention (USP) revised USP Chapter 797 Pharmaceutical Compounding—Sterile Preparations⁷ to harmonize with the NIOSH 2004 Alert. It became effective May 1, 2008, establishing many of the NIOSH recommendations as enforceable requirements. On February 1, 2016, USP published a new general chapter, Chapter 800, Hazardous Drugs—Handling in Healthcare Settings.⁸ Unlike the other publications regarding HDs noted above, USP Chapter 800 is not a guidance document but an enforceable standard, containing both best practice recommendations and mandates for reducing the occupational exposure of healthcare workers who handle nonsterile and sterile HDs. The standards set by USP Chapter 800 are applicable in all settings in which HDs are compounded and administered and where healthcare workers may contact HD residue, not just hospitals and clinics.

This is a prepress version of guidelines that will appear in final form in *AJHP* at a future date. Those guidelines will replace this preliminary version when they are final.

With the ever-increasing number of publications on this topic, the inclusion of older material in these guidelines has been limited to landmark or other crucial studies. The ASHP 1990 TAB and 2006 guidelines provide historic overviews of this topic. Sections of USP Chapter 800 are discussed in this document but the ASHP Guidelines on Handling Hazardous Drug are not intended to modify, interpret, or be a substitute for the provisions of USP Chapter 800. These updated guidelines include information from the literature, NIOSH, and USP, and are current to October 2017.

Purpose

Significant advances in the awareness of safe handling of HDs have been made since the previous version of these guidelines was published in 2006. NIOSH has created a topics page to maintain a bibliography of NIOSH HD documents, publications on occupational exposure to antineoplastic and other HDs, and research on safe handling drawn from the published literature.⁹ After more than 30 years of published guidance, the international research shows that occupational exposure to HDs continues, that negative reproductive outcomes continue, and that barriers to adherence to safe handling guidance remain. The purposes of these updated guidelines are to (1) inform the reader about new and continuing concerns for healthcare workers handling HDs, and (2) provide information on recommendations and requirements, including those regarding controls and equipment that have been developed since the publication of the 2006 ASHP guidelines.

Because newer studies have shown that contamination is widespread in healthcare settings and that more workers than previously thought are exposed, these guidelines should

be implemented wherever HDs are received, stored, prepared, transported, administered, or disposed.⁸⁻¹¹

Comprehensive reviews of the literature covering anecdotal and case reports of surface contamination, worker exposure, and risk assessment are available from NIOSH,^{6,9,12} the Occupational Safety and Health Administration (OSHA),^{13,14} and individual authors.¹⁵⁻²⁰ The primary goal of this document is to provide recommendations for the safe handling of HDs. These guidelines represent the research and recommendations of many groups and individuals who have worked tirelessly over decades to reduce the potential harmful effects of HDs on healthcare workers. The research available to date, as well as the opinions of thought leaders in this area, is reflected in the guidelines. Where possible, recommendations are evidence based. In the absence of published data, professional judgment, experience, and common sense have been used.

Background

Healthcare workers may be exposed to HDs at many points during manufacture, distribution, receipt, storage, transport, compounding, and administration, as well as during waste handling and care of treated patients.⁶ All workers involved in these activities, as well as in equipment maintenance and repair, have the potential for contact with uncontained drug. One study of worker contact with surfaces contaminated with HDs identified a number of job categories not traditionally expected to be exposed.¹¹ Unit clerks, transport workers, ward aides, dietitians, and oncologists were observed touching contaminated surfaces. A follow-up study documented cyclophosphamide in the urine of these workers, concluding that workers in the drug

administration setting, even those who were not responsible for administering the drugs to patients (i.e., volunteers, oncologists, ward aides, and dietitians), had the largest proportion of samples exceeding the limit of detection (LOD) for cyclophosphamide.²¹ These results suggest that it is reasonable to expand the list of potentially exposed workers. Recent studies have also begun to examine the impact on families and caregivers of home treatments with HDs.²²⁻²⁴ However, the scope of these guidelines is limited to workers in healthcare settings.

Exposure to HDs in the workplace has been associated with acute and short-term reactions, as well as long-term effects. Anecdotal and case reports in the literature range from skin-related and ocular effects to flu-like symptoms and headache.^{6,17} Reproductive studies on healthcare workers have shown an increase in fetal abnormalities, fetal loss, and fertility impairment resulting from occupational exposure to these potent drugs.²⁵⁻²⁸ An extensive study published in 2012 documented increased spontaneous abortions in nurses exposed to HDs in the workplace.²⁶ An increase in learning disabilities among offspring as a result of occupational exposure to these potent drugs has also been reported.²⁷

Antineoplastic drugs and immunosuppressants are some of the types of drugs included on lists of known or suspected human carcinogens by the National Toxicology Program²⁹ and the International Agency for Research on Cancer.³⁰ Although the increased incidence of cancers for occupationally exposed groups has been investigated, with varying results,³¹⁻³⁴ two related studies described evidence of drug uptake (drug being incorporated into workers' bodies) and chromosomal changes in oncology workers exposed to workplaces contaminated with HD residue.^{35,36} The DNA of exposed workers showed a statistically significant increase in frequency of damage to chromosome 5 or 7 and an increase in frequency of damage to chromosome 5

alone. As signature lesions in chromosomes 5, 7, and 11 have been shown to be associated with chemotherapy treatment-related myelodysplastic syndrome (MDS) and acute myeloid leukemia (t-AML), these results provide additional evidence of harmful effects from occupational exposure to HDs.³⁷⁻³⁸ These conclusions are bolstered by recent meta-analyses of comet assay, micronuclei and chromosomal aberration data in healthcare workers that have shown increases in chromosomal damage in workers exposed to antineoplastic drugs.³⁹⁻⁴¹

Continuing exposure. Prior to the publication of the 2004 NIOSH Alert, a 1999 study done in three cancer treatment centers in the U.S. and three in Canada provided strong evidence of surface contamination with antineoplastic HDs in compounding and infusion areas.⁴² Measurable amounts of cyclophosphamide, ifosfamide, and fluorouracil were detected in 75% of the pharmacy wipe samples and 65% of the infusion area wipe samples. The levels of contamination were higher in the pharmacy areas than in the drug infusion areas. The number of positive wipe sampling results was related to the amount of drug prepared and administered.

A NIOSH-sponsored study of three university-based U.S. cancer centers published in 2010 reexamined HD contamination and other risk points from the 1999 study.^{10,42} The 2010 study measured surface contamination of at least one of the five drugs (cyclophosphamide, ifosfamide, fluorouracil, paclitaxel, and cytarabine) in 75% of the pharmacy wipe samples and 43% of the infusion wipe samples. The study confirmed that HD contamination is generally widespread, even with engineering controls such as Class II biological safety cabinets (BSCs); that pharmacy areas have more contaminated surfaces; and that the contamination is in higher concentrations than in nursing areas. Most importantly, this study confirmed that there had

been little progress in reducing HD contamination in similar healthcare settings in the U.S. in the 10 years between the studies.

A series of multi-site studies on HD contamination has been published by a research team in British Columbia.^{11, 21, 43} Through interviews and observations, 11 job categories having potential for HD exposure by dermal contact with potentially contaminated surfaces were identified within six medical sites.¹¹ In addition to those workers traditionally thought to be exposed, workers who had possible dermal contact with HDs included receiving staff, unit clerks, ward aides, and even volunteers. In investigating contaminated surfaces, the researchers noted that although the BSC had the highest frequency of contact in the compounding area, the pen inside the BSC and the isopropyl alcohol (IPA) spray bottle were frequently touched.¹¹ Intravenous (IV) pumps, countertops, and waste containers were the most contacted surfaces in the infusion areas. The team collected surface wipe samples at the participating sites, using cyclophosphamide as the marker drug.¹¹ Of the 275 surface samples collected, 35% were above the LOD.¹¹ As in the 2010 U.S. study,¹⁰ the pharmacy compounding areas had the greater number of contaminated wipes (47 of 85) and the highest concentration of drug.¹¹ Additional surface wipe sampling done at the same six medical sites⁴³ produced a total of 438 samples from 55 categories of surfaces in five drug handling stages (delivery, preparation, transport, administration, and waste), with 159 (36%) having concentrations above the LOD. The most-contaminated surfaces by stage were the drug delivery elevator button, drug preparation pen (possibly from the BSC), transport bin for drug pick up, drug administration IV pump, and waste elevator button.⁴³ In the original study,¹¹ the BSC was noted to be the most frequently touched item in the drug preparation area; however, the pen used in the BSC was the most

contaminated. Other items such as a marker and tweezers kept in the BSC were also heavily contaminated, probably resulting in glove contamination during each contact. While routine cleaning of the BSC surface was reported, miscellaneous items, such as the pen, were probably not included in that cleaning. Measureable HD contamination on elevator buttons is concerning for workers, and visitors may also be exposed to this risk.

In addition, this research team sought to determine whether healthcare workers from the earlier studies were at risk of cyclophosphamide uptake through dermal contact with contaminated surfaces or by other means.²¹ Participants identified from the prior studies as potentially exposed agreed to collect urine samples to quantify the urine concentration of non-metabolized cyclophosphamide. Cyclophosphamide levels greater than the LOD were found in 55% of urine samples.²¹ Participants from departments where drug preparation and drug administration do not take place (e.g., shipping/receiving, transport, nutrition, and materials management) had the highest average urinary concentration levels of cyclophosphamide.²¹ When the results were stratified by job title, unit clerks had the highest average urinary cyclophosphamide concentration. The authors identified two factors associated with cyclophosphamide uptake: (1) whether a worker had a duty to handle antineoplastic HDs, and (2) whether a worker received training on safe drug handling and concluded that interventions to minimize this risk should be more broadly applied.

A review of studies of healthcare worker exposure to antineoplastic HDs published in the U.S., Canada, and Europe after publication of the 2004 NIOSH HD Alert found no decrease in contamination.⁴⁴ In addition, separating the publications by origin, the review found that only 9 of 71 such studies were done by U.S. researchers, and most of those were sponsored by

medical device manufacturers. U.S. critics of HD safe handling guidance often note the lack of evidence of exposure as well as the recommendations to mitigate it. The exceptionally small number of U.S. studies found in this literature review may indicate a basic lack of interest in conducting such research in the U.S.

Routes of exposure. Numerous studies have shown the presence of HDs in the urine of healthcare workers.^{10,21,45-47} A review of 20 studies from 1992 to 2011 examining biomarkers of exposure in healthcare workers handling antineoplastic HDs found drug in workers' urine in 17 of the 20 studies.¹⁹ One of the review's studies⁴⁷ is described as showing no response in 50 subjects, but the study does note that all subjects demonstrated post-shift exposure to platinum. A study by Wick,⁴⁶ which was not included in the review, demonstrated that six of eight participants' 24-hr urine samples were above the LOD for cyclophosphamide and ifosfamide. Hon²¹ collected 201 urine samples from 103 subjects, including those in job categories with low expectation of exposure; 55% had levels greater than the LOD for cyclophosphamide, with unit clerks having the highest average level.

HDs may enter the body through inhalation, dermal absorption, accidental injection, ingestion of contaminated foodstuffs, or mouth contact with contaminated hands. Inhalation was previously suspected as the primary route of exposure, but one or more of these routes might be responsible for workers' exposure. More recent studies, especially those looking at healthcare workers not directly involved with HD compounding and administration, support the theory that dermal contact with contaminated surfaces is the primary route.^{18,19,21, 48-50}

An alternative to dermal absorption, where HDs go through unprotected skin after contact with contaminated surfaces, is that surface contamination transferred to hands may be

ingested via the hand-to-mouth route.^{51,52} Researchers have looked at hand sampling as a measure of exposure.⁵¹ Using a technique of wipe sampling, similar to that done for work surfaces, healthcare workers' hands may be swabbed to check for HD contamination.⁵¹ One study of workers at six sites analyzed a total of 225 wipe samples; 20% were above the LOD of cyclophosphamide.⁵² Contaminated hands may transfer HD residue to other surfaces and other workers as well as contribute to hand-to-mouth transfer. Hand sampling may offer an alternative to surface sampling in monitoring HD contamination and exposure.

Hazard assessment. The risk to workers from handling HDs is the result of a combination of the inherent toxicity of the drugs and the extent to which workers are exposed to the drugs in the course of their daily job activities. Both hazard identification (the qualitative evaluation of the toxicity of a given drug) and an exposure assessment (the amount of worker contact with the drug) are required to complete a hazard assessment. As the hazard assessment is specific to the safety program and safety equipment in place at a work site, a formal hazard assessment may not be available for most practitioners. An alternative is a performance-based, observational approach. Observation of current work practices, equipment, and the physical layout of work areas where HDs are handled at any given site will serve as an initial assessment of appropriate and inappropriate practices.⁶

NIOSH defines a risk assessment as characterization of potentially adverse health effects from human exposure to environmental or occupational hazards. Risk assessment can be divided into five major steps: hazard identification, dose-response assessment, exposure assessment, risk characterization, and risk communication.⁴

USP Chapter 800 introduced a new term, *assessment of risk*, that allows an entity to perform an evaluation of risk to determine alternative containment strategies and/or work practices to those described in USP Chapter 800 for some dosage forms of HDs that may not pose a significant risk of direct occupational exposure.⁸ An *assessment of risk* may only be used for drugs on the NIOSH list that are *neither* HD active pharmaceutical ingredients (APIs) *nor* antineoplastics requiring HD manipulation. According to USP Chapter 800, the assessment of risk must, at a minimum, consider the type of HD, the dosage form, the risk of exposure, the packaging involved, and how the drug will be manipulated.

If an *assessment of risk* is done, the entity must document the alternative containment strategies and/or work practices specific to the drugs and dosage forms so as to minimize healthcare workers' exposure. The *assessment of risk* must be reviewed and documented at least every 12 months. An *assessment of risk* should not be confused with a *risk assessment*, as the hazard identification step is not done by the entity. USP Chapter 800 describes the requirements and restrictions of an *assessment of risk*.⁸

Definition of HDs

The 1990 ASHP TAB proposed criteria to determine which drugs should be considered hazardous and handled within an established safety program.⁴ The TAB's definition of HDs was revised by the NIOSH Working Group on Hazardous Drugs for the 2004 alert.⁶ These definitions are compared in Table 1.

NIOSH. The NIOSH 2004 HD Alert contained an appendix of HD lists compiled from information provided by four organizations that had generated lists of HDs for their respective

institutions, as well as a list from the Pharmaceutical Research and Manufacturers of America (PhRMA).⁶ NIOSH adopted a mechanism both to review its HD criteria and to update its HD list every 2 years by reviewing the existing drugs on the HD list and examining newly approved drugs, and drugs with new FDA warnings against the NIOSH HD criteria. The review process for the addition of the new listings is described in the Federal Register.⁵³

From 2004 through 2012, NIOSH has recommended standard precautions or universal precautions be taken in handling HDs. In 2014, with the addition of many non-antineoplastic drugs and drugs in tablet and/or capsule form to the list, NIOSH noted that no single approach could cover the diverse potential occupational exposures to the drugs.⁵⁴ This change required development of a new format for the 2014 NIOSH list of HDs, which for the first time divided HDs into three groups:

- **Group 1:** Antineoplastic drugs (AHFS Classification 10:00) [ASHP/AHFS DI 2013]. Many of these drugs may also pose a reproductive risk for susceptible populations.
- **Group 2:** Non-antineoplastic drugs that meet one or more of the NIOSH criteria for an HD. Some of these drugs may also pose a reproductive risk for susceptible populations.
- **Group 3:** Drugs that primarily pose a reproductive risk to men and women who are actively trying to conceive and women who are pregnant or breast-feeding (some of these drugs may be present in breast milk).

The 2016 NIOSH HD list retains this three group format.⁵⁵ The most current NIOSH list of HDs, along with other NIOSH HD documents, may be found on the NIOSH Hazardous Drug Exposures in Healthcare Topics Page.⁵⁶

USP Chapter 800. In 2016, USP Chapter 800 adopted the NIOSH HD list as the list of antineoplastic and other HDs that an organization, wishing to comply with USP Chapter 800, must begin with.⁸ This list may be modified to include only the drugs that they handle and must be reviewed at least every 12 months. The list must be dynamic: whenever a new agent or dosage form is used by the organization, it should be reviewed against the list. The NIOSH HD criteria must be used to identify HDs that enter the market after the most recent version of the NIOSH HD list and to assess any investigational drugs used by the organization.

OSHA. The OSHA *Hazard Communication Standard* (HCS) was updated in 2012 to align with the United Nations Globally Harmonized System of Classification and Labeling of Chemicals (GHS).⁵⁷ The revised HCS defines a hazardous chemical as any chemical that is classified as a physical or health hazard, a simple asphyxiant, combustible dust, pyrophoric gas, or hazard not otherwise classified.⁵⁸ It further defines a health hazard as a chemical that is classified as posing one of the following hazardous effects: acute toxicity (any route of exposure), skin corrosion or irritation, serious eye damage or irritation, respiratory or skin sensitization, germ cell mutagenicity, carcinogenicity, reproductive toxicity, specific target organ toxicity (single or repeated exposure), or aspiration hazard. The criteria for determining whether a chemical is classified as a health hazard are detailed in Appendix A to §1910.1200—Health Hazard Criteria.⁵⁹ In addition, the HCS requires that drugs that pose a health hazard (with the limited exception of those in solid, final forms for direct administration to the patient, such as tablets or pills) be included on lists of hazardous chemicals to which employees are exposed. As a federal standard, the HCS is the definitive document establishing compliance with all phases of this right-to-know legislation, including the definition of *hazardous* and the requirements for

the Safety Data Sheet (SDS). In addition, HCS requires that the hazards of all chemicals produced or imported into a workplace are classified, and that information concerning the classified hazards is transmitted to employers and employees.⁵⁷

A list of HDs in use in the facility is required by the OSHA HCS and by USP Chapter 800.^{8,57} The Joint Commission, in Elements of Performance for Medication Management (MM).01.01.03, requires that hospitals identify in writing their high-alert and hazardous medications.⁶⁰

HDs as Sterile Preparations

Many HDs are designed for parenteral administration, requiring aseptic reconstitution or dilution to yield a final sterile preparation. As such, the compounding of these products is regulated as sterile pharmaceutical compounding by USP Chapter 797.⁷ The intent of USP Chapter 797 is to protect patients from improperly compounded sterile preparations (CSPs) by regulating facilities, equipment, and work practices to ensure the sterility of extemporaneously compounded sterile preparations. USP Chapter 797 addresses not only the sterility of a preparation but also the accuracy of its composition. Because many HDs are very potent, there is little margin for error in compounding.

HDs, as CSPs, are regulated by both USP Chapter 797 and USP Chapter 800 for compounding environments.^{7,8} Compounding of nonsterile HDs must meet the criteria in USP Chapter 795, Pharmaceutical Compounding—Nonsterile Preparations,⁶¹ as well as USP Chapter 800.⁸ With the adoption of USP Chapter 800, the HD section will be removed from USP Chapter 797.

USP Chapter 800 has changed the requirements for HD handling, storage, and compounding environments to emphasize containment, including the containment primary engineering control (C-PEC), the device in which compounding takes place, and the containment secondary engineering control (C-SEC), the room in which the C-PEC is placed.⁸ Major revisions in engineering controls adopted by USP Chapter 800 include a requirement that certain areas be under negative pressure relative to surrounding areas to contain HDs and minimize risk of exposure.⁸ External ventilation (i.e., exhausting to the outside) is advocated to achieve negative pressure. Because HDs are also compounded in areas adjacent to patients and family members (e.g., in chemotherapy infusion centers), inappropriate environmental containment puts them, as well as healthcare workers, at risk.⁸

Recommendations

The recommendations below stem from the dedicated and thoughtful efforts of numerous groups and individuals over many years. Where possible, the recommendations are evidence based. In the absence of published data, the professional judgment and opinions of thought leaders have been relied upon. In this document, the term “must” is used to denote a requirement of generally applicable laws, regulations, or practice standards; the term “should” indicates a generally accepted recommendation that is not drawn from an authoritative reference. Healthcare professionals are encouraged to rely on their professional judgment, experience, and common sense in applying these recommendations to their unique circumstances, as no set of guidelines on this topic can address all the needs of every healthcare facility.

Safety Program

Policies and procedures for the safe handling of HDs must be in place for all situations in which these drugs are used throughout a facility. A comprehensive safety program must be developed that deals with all aspects of the safe handling of HDs. This program must be a collaborative effort, with input from all affected departments, such as pharmacy, nursing, medical staff, environmental services, transportation, maintenance, employee health, risk management, industrial hygiene, clinical laboratories, and safety. New research indicates that HD contamination is more widespread than generally believed and that worker exposure extends beyond the primarily accepted occupations.^{11,21} It is important to make all affected workers aware of the potential risks and to train them in appropriate safety precautions.⁶²

Per USP Chapter 800, each facility handling HDs “must have a designated person who is qualified and trained to be responsible for developing and implementing appropriate procedures; overseeing entity compliance with this chapter and other applicable laws, regulations, and standards; ensuring competency of personnel; and ensuring environmental control of the storage and compounding areas.”⁸ As many HDs are also hazards that are identified in the revised HCS, the requirements of the HCS must also be met.⁵⁷ A fundamental element of this safety program is the SDS, formerly the Material Safety Data Sheet (MSDS), mandated by the HCS.⁶³ Employers are required to have an SDS available for all hazardous agents, including hazardous drugs, in the workplace. A comprehensive safety program must include a process for monitoring and updating the SDS database. When an HD is purchased for the first time, an SDS must be received from the manufacturer or distributor. The SDS should

define the appropriate handling precautions, including protective equipment, controls, and spill management associated with the drug. SDS collections are available online through the specific manufacturer or through safety-information services. In the event an online service is used, a proper contingency plan must be in place to access this vital information in the event of a system failure.

Drugs that have been identified as requiring safe handling precautions should be clearly labeled at all times during their transport, storage, and use. HCS requires a list of hazardous chemicals be present in the workplace as part of the written hazard communication program.⁶⁴ The HCS applies to all workers, including those handling HDs at the manufacturer and distributor levels. Employers are required to develop and implement employee training programs regarding workplace hazards and protective measures.⁶⁴

USP Chapter 800 requires that “all personnel who handle HDs are responsible for understanding the fundamental practices and precautions and for continually evaluating these procedures and the quality of final HDs to prevent harm to patients, minimize exposure to personnel, and minimize contamination of the work and patient-care environment.”⁸ HCS and USP Chapter 800 require employee training to the tasks they will perform as part of the safety program.^{8,57} Personnel competency must be demonstrated every 12 months and documented.⁸

The outside of the vials of many commercial HDs are contaminated when they are received in the pharmacy.^{50, 65-68} In one study, the contamination extended to the inside of the packing cartons and onto the package inserts placed around the vial within the carton.⁶⁸

This study found cyclophosphamide contamination on 100% of the cyclophosphamide vials, the outside outer packaging, and inside outer packaging that was sampled.⁶⁸ Package leaflets (inserts) were also sampled, with 90-100% of samples found to be above the LOD. In addition, the researchers sampled primary packaging containing tablets (blister packages) of 50 mg cyclophosphamide tablets. Cyclophosphamide was quantified in all wipe samples from the tablet blister packages.⁶⁸

Such contamination on packaging presents an exposure risk to anyone opening drug cartons or handling the vials, including workers receiving open or broken shipping cartons or selecting vials to be repackaged at a distribution point (e.g., a worker at the drug wholesaler selecting HDs for shipping containers or a pharmacy worker dividing an HD in a multidose container for repackaging into single-dose containers). These activities present risks, especially for workers who too often receive inadequate safety training.⁶² Environmental services staff and patient care assistants who handle drug waste and patient waste are also at risk and are not always included in the safe handling training required by safety programs. Safety programs must identify and include all workers who may be at risk of exposure.^{11,43,62}

New packaging techniques for HD vials include a film wrapper on the vials and reinforcement of the bottom of the vials with a plastic disk. Studies of specialty packaging methods have shown that these resist breakage and that the wrapper is less contaminated than detected in previous studies of the glass of the vial itself.^{67,69} The packaging (cartons, vials, ampules) of HDs should be properly labeled by the manufacturer or distributor with a distinctive identifier that notifies personnel receiving them to don appropriate personal protective equipment (PPE) during their handling. Sealing these drugs in plastic bags at the

distributor level provides an additional level of safety for workers who are required to unpack cartons. USP Chapter 800 requires policies and procedures (P&Ps) and standard operating procedures (SOPs) for labeling, packaging, and transport of HDs.⁸ It should be noted that USP Chapter 800 does not apply to manufacturers or distributors. Distributors may provide special packaging and labeling if requested by their customers.

Labeling, Packaging, Storing, and Transport of HDs from Point of Receipt

The safety program should address the entire lifecycle of HD handling, including receipt, storage, and transportation. Drug packages, bins, shelves, and storage areas for HDs must bear distinctive labels identifying those drugs as requiring special handling precautions.

Receipt of HDs. According to USP Chapter 800, HDs listed as antineoplastic HDs on the current NIOSH HD list^{55,56} and all HD APIs must be unpacked in areas that are neutral/normal or negative pressure relative to the surrounding areas.⁸ HDs must not be removed from their external shipping containers in sterile compounding areas or in any area that is under positive pressure to the surrounding areas.⁸ During receipt of HDs, visual examination of cartons for outward signs of damage or breakage is an important initial step in the receiving process. Policies and procedures must be in place for handling damaged cartons or containers of HDs (e.g., returning the damaged goods to the distributor using appropriate containment techniques).⁸ These procedures should include the use of PPE, which must be supplied by the employer. HD spill kits must be available in the receiving area.⁸ The spill kit should contain complete PPE, including a NIOSH-certified respirator, in the event no ventilation protection is available where damaged HD containers are handled.^{8,70,71} As required by OSHA, a complete

respiratory program, including proper training and fit-testing, must be completed by all staff required to use respirators.⁷⁰ Surgical masks do not provide adequate protection from the harmful effects of these drugs.

USP Chapter 800 has a table listing the summary of requirements for receiving and handling damaged HD shipping containers.⁸ USP Chapter 800 prefers that damaged shipping containers be transported to a C-PEC designated for nonsterile compounding prior to opening.⁸

Storing HDs. Segregation of HD inventory from other drug inventory improves control and reduces the number of staff members potentially exposed to the danger.⁵ USP Chapter 800 requires that HDs listed as antineoplastic HDs on the current NIOSH HD list^{55,56} that require manipulation (more than counting or repackaging of final dosage forms) and HD APIs to be stored separately from non-HDs.⁸ HDs should be stored so as to prevent contamination and personnel exposure. These HDs must be stored in areas with sufficient external exhaust ventilation (i.e., negative-pressure rooms) having at least 12 air changes per hour (ACPH).⁸ The non-antineoplastic, reproductive-risk-only, and final HD dosage forms of antineoplastic HDs, as contained on the current NIOSH HD list,^{55,56} may be stored with other inventory per USP Chapter 800, if the facility's assessment of risk and policy allow it.⁸

HDs placed in inventory should be protected from potential breakage by storage in bins that have high fronts and on shelves that have guards to prevent accidental falling.⁵ USP Chapter 800 notes that HDs must be stored to prevent spillage or breakage if the container falls.⁸ Special care must also be taken to secure shelves and other storage containers in the event of earthquakes or other natural disasters as appropriate. The bins must also be appropriately sized to properly contain all stock. Care should be taken to separate HD inventory

to reduce potential drug errors (e.g., pulling a look-alike vial from an adjacent drug bin). To reduce transfer of HD residue from vials and cartons, all staff members must wear gloves tested to ASTM D6978 for resistance to chemotherapy (i.e., chemotherapy gloves). NIOSH notes that single chemotherapy gloves are sufficient in receiving, unpacking, and placing HDs into storage, unless there is a spill.⁵⁵ Because many studies have shown that HD residue on the drug vial itself is routine and that contamination has been reported in significant amounts,⁶⁵⁻⁶⁹ staff should consider wearing double chemotherapy gloves when receiving, unpacking, stocking and inventorying these drugs and selecting HD packages for further handling.^{5,20} Per NIOSH 2016 recommendations, a gown and respiratory protection should also be used when spills or leaks are of concern (e.g., if a carton appears damaged) during HD receiving, unpacking, and storage activities.⁵⁵

Transport of HDs. All transport of HD packages must be done in a manner to reduce environmental contamination in the event of accidental dropping.⁵ HD packages must be placed in sealed containers and labeled with a unique identifier. Carts or other transport devices must be designed with guards to protect against falling and breakage. All individuals transporting HDs must have safety training that includes spill control and have spill kits immediately accessible.^{5,57} Staff handling HDs or cleaning areas where HDs are stored or handled must be trained to recognize the unique identifying labels used to distinguish these drugs and areas.⁵⁷ Warning labels and signs must be clear to non-English readers. All personnel who work with or around HDs must be trained to appropriately perform their jobs using the established precautions and required PPE.⁵⁷

Environment

It has long been shown that HD contamination is widespread in healthcare settings, even when primary compounding controls are in place.^{6,10,11,21,42-46} USP Chapter 800 focuses on containment of HD contamination, which is illustrated in the new terminology of ventilation controls.⁸ Many prior recommendations for controlled, ventilated areas for storage and handling HDs will become mandates when USP Chapter 800 becomes effective.⁸ Similar to NIOSH and ASHP recommendations, USP Chapter 800 requires that HDs be handled within a program that promotes patient safety, worker safety, and environmental protection.^{5,6,8} Facilities must identify all areas where HDs are stored or handled.^{5,6,8} As staff members in some jobs may not be proficient in English, using signs with verbal and pictorial warnings is preferred.⁵⁷ HDs should be handled in restricted areas where access is limited to authorized personnel trained in handling requirements. Break rooms and refreshment areas for staff, patients, visitors, and others should be located away from areas of potential HD contamination to reduce unnecessary exposure to staff, visitors, and others. USP Chapter 800 requires that specific areas are designated for defined HD tasks, including receipt and unpacking, storing HDs, and compounding nonsterile and sterile HD preparations.⁸ USP Chapter 800 also requires that certain HD areas have negative pressure from surrounding areas to contain HDs and minimize risk of exposure.⁸

Compounding. Only individuals trained in the compounding of HDs should do so.^{5,6,8} HDs should be compounded in a controlled area where access is limited to authorized personnel trained in handling requirements.^{5,6} Sterile and non-sterile HDs must be compounded in environments that have a negative pressure to all adjacent areas.⁸ Positive-

pressure environments for HD compounding must not be used because of the potential spread of airborne contamination from contaminated packaging, poor handling technique, and spills.⁵ Ventilation controls for sterile and nonsterile compounding are covered in the *Ventilated Engineering Controls* section below.

Administration. Only individuals trained in the administration of HDs should do so.^{5,6,8} Nurses who administer HDs and care for patients receiving chemotherapy should meet the requirements of the Oncology Nursing Society (ONS) position statement on administration.⁷² During administration, access to the administration area should be limited to patients receiving therapy and essential personnel. Eating, drinking, applying makeup, and the presence of foodstuffs should be avoided in patient care areas while HDs are administered. For inpatient therapy, where lengthy administration techniques may be required, hanging or removing HDs should be scheduled to reduce exposure of family members and ancillary staff and to avoid the potential contamination of dietary trays and personnel.

Because much of the compounding and administration of HDs throughout the U.S. is done in outpatient or clinic settings with patients and their family members near the compounding area, care must be taken to minimize environmental contamination and to maximize the effectiveness of cleaning (decontamination) activities. The design of such areas must include surfaces that are readily cleaned and decontaminated. Upholstered and carpeted surfaces should be avoided, as they are not readily cleaned. Several studies have shown floor contamination and the ineffectiveness of cleaning practices on both floors and surfaces.^{10,36,37,40,73,74}

HDs may also be administered in nontraditional locations, such as the operating room, which presents challenges in training of personnel and in proper containment of the drugs and drug residue. Intracavitary administration of HDs (e.g., into the bladder, peritoneal cavity, or chest cavity) frequently requires equipment for which locking connections may not be available. Inhalation of some HDs to treat certain diseases also has the potential for significant worker exposure as well as environmental contamination, as closed system administration is problematic. All staff members who handle HDs should receive safety training that includes recognition of HDs and appropriate spill response. HD spill kits, containment bags, and disposal containers must be available in all areas where HDs are handled.

Ventilated Engineering Controls

Engineering controls protect workers by removing hazardous conditions or by placing a barrier between the worker and the hazard. To safely handle HDs, ventilated engineering controls are required for primary and secondary containment of sterile and nonsterile forms of these drugs. For compounding sterile preparations, USP Chapter 797 designated primary engineering controls, buffer areas, and clean rooms as ventilated engineering controls that provided appropriate air quality.⁷ USP Chapter 800 applies to both sterile and nonsterile compounding of HDs and has modified USP Chapter 797 terminology to emphasize the key requirement in handling HDs, which is containment.⁸ USP Chapter 800 divides ventilated engineering controls for containment as containment primary engineering controls (C-PEC) used for the actual compounding, and containment secondary engineering controls (C-SEC), in which the C-PEC is placed.⁸ These guidelines only present a summary of USP General Chapter 797 and 800 and are not meant to interpret the standards and best practices described in those documents.

Containment Primary Engineering Controls (C-PECs)

A C-PEC is defined in USP Chapter 800 as a ventilated device designed and operated to minimize worker and environmental exposures to HDs.⁸ A C-PEC functions by controlling emissions of airborne contaminants through the following⁸:

- The full or partial enclosure of a potential contaminant source.
- The use of airflow capture velocities to trap and remove airborne contaminants near their point of generation.
- The use of air pressure relationships that define the direction of airflow into the cabinet.
- The use of HEPA filtration on all potentially contaminated exhaust streams.

The C-PEC required is dictated by the type of compounding being performed, as well as other factors.

Nonsterile compounding. For nonsterile HD compounding, a C-PEC that provides personnel and environmental protection, such as a Class I BSC or containment ventilated enclosure (CVE) must be used. A C-PEC for nonsterile use does not require unidirectional airflow because the critical environment does not need to be ISO classified.⁸ A Class II BSC or a compounding aseptic containment isolator (CACI) may be used if they are dedicated to nonsterile compounding. The C-PECs used for manipulation of nonsterile HDs must be either externally vented (preferred) or have redundant high-efficiency particulate air (HEPA) filters in series as a containment system to exhaust into the work area.⁸ HEPA filters do not trap vapors and should not be used for handling vaporous HDs, either as nonsterile APIs or in other nonsterile forms.^{6,75} USP Chapter 800 allows a C-PEC that is usually used for sterile

compounding (e.g., Class II BSC or CACI, as defined by USP Chapter 797, as revised in 2008) to be used for occasional nonsterile HD compounding if it is decontaminated, cleaned, and disinfected before resuming sterile compounding in that C-PEC.⁸ As cleaning and decontaminating a C-PEC has not been shown to be very effective, this is not a preferred option.^{73,74,76,77} The C-PEC used for nonsterile compounding must be placed in a C-SEC that has at least 12 ACPH, is externally vented, and is at negative pressure relative to adjacent areas.⁸

Sterile compounding. To compound sterile HDs, as with any sterile compounding, the standards in USP Chapter 797 must be followed.⁷ Sterile HDs must be compounded in a C-PEC that provides ISO Class 5 or better air quality and unidirectional airflow. A Class II or Class III BSC or a CACI are appropriate ventilated engineering controls for compounding sterile HDs.⁸ C-PECs for sterile compounding must be located in a C-SEC that is either an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified containment segregated compounding area (C-SCA).⁸ USP Chapter 800 requires C-PECs used for compounding of sterile HDs to be externally vented to the outside.⁸

Class II BSCs. Class II BSCs have been used to provide product, personnel, and environmental protection while compounding sterile HDs for over three decades. As specific and sensitive analytical methods have been developed to measure representative, or marker HDs, studies have shown continuing HD contamination on surfaces in HD work areas and detected HDs in the urine of healthcare workers exposed to these drugs while compounding in a Class II BSC.^{10,16, 42,46} The exact cause of contamination has yet to be determined, but it is probably a combination of issues. Studies have shown that (1) there is contamination on the outside of vials received from manufacturers and distributors,⁶⁵⁻⁶⁹ (2) work practices required

to maximize the effectiveness of the Class II BSC are neglected or not taught;^{78,79} and (3) the potential vaporization of HD solutions may reduce the effectiveness of the HEPA filter in providing containment.^{75,80} Studies of surface contamination have discovered deposits of HDs on the floor in front of the Class II BSC, indicating that drug may have escaped through the open front of the BSC onto contaminated gloves or the final product, or into the air.^{10,42,46} Workers must understand that the Class II BSC does not prevent the generation of contamination within the cabinet and that the effectiveness of such cabinets in containing HD contamination depends on operators' use of proper technique and strict adherence to policies and procedures.

Class II BSCs types A2, B1, or B2 are acceptable under USP Chapter 800 for compounding sterile HDs.⁸ USP Chapter 800 notes that the type A2 cabinet, which recirculates a portion of the HD-contaminated air through HEPA filters while exhausting the remainder to the outside, can be reliably integrated with ventilation systems and accommodates the pressurization requirements of USP Chapter 800 for the C-SEC. Class II type B2 BSCs exhaust all air from the cabinet through an outside ventilation system, recirculating none of the HD-contaminated air within the cabinet.⁸¹ USP Chapter 800 notes that these are typically reserved for use with volatile components. Class II type A1 BSCs are not appropriate for HDs, as they are not designed for integration with an outside ventilation system to exhaust to the outside.⁸¹ Class II type A2 and B1 BSCs recirculate a portion of the contaminated air but are designed to connect to an outside ventilation system and exhaust the predominant amount.⁸¹ A new Class II BSC, the type C1, is currently available, but is not certified by NSF International.^{82,83} The Class II type C1

cabinet is a recirculating cabinet with outside exhaust capabilities. It may be useful in handling HDs, but additional testing and validation are needed to document this.

Most Class II BSCs recirculate contaminated air within the cabinet through HEPA filters, which may not trap all HDs, allowing them to pass into the HEPA-filtered air.^{75,80,83} The Class II BSC is designed with air plenums that are unreachable for surface decontamination; the plenum under the work tray collects room dirt and debris that mix with HD residue when the cabinet is operational.⁴ Drafts, supply-air louvers, and other laminar flow equipment placed adjacent to the Class II BSC can interfere with the containment properties of the inflow air barrier, resulting in contamination of the work environment.^{81,84} Additional information on classes and types of BSCs is available through the Centers for Disease Control and Prevention (CDC).⁸¹ More information on the design and use of Class II BSCs is available from the NSF International (NSF)/American National Standards Institute (ANSI) standard 49.⁸³ Recommendations for use of Class II BSCs are listed in Appendix A.

Alternatives to Class II BSCs. USP Chapter 800 identifies the Class III BSC or the CACI as acceptable ventilated engineering controls for compounding sterile HDs. These offer alternatives to the open-front Class II BSC.⁸

Class III BSC. By definition, a Class III BSC is a totally enclosed, ventilated cabinet of leak-tight construction.⁸¹ Operations in the cabinet are conducted through fixed-glove access. The cabinet is maintained under negative air pressure. Supply air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double HEPA filtration or by HEPA filtration and incineration. Class III cabinets are not exhausted through the general exhaust system. The Class III BSC is designed for use with highly toxic or infectious material. Because of the costs of

purchasing and operating a Class III BSC, it is not commonly used for extemporaneous compounding of sterile preparations.⁵

CACI. A CACI is a form of compounding isolator specifically designed for compounding pharmaceutical ingredients or preparations that provides worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment with unidirectional airflow for compounding sterile preparations.^{7,8} Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile HDs are prepared, the exhaust air from the compounding isolator should be appropriately removed by properly designed building ventilation.^{7,8}

Unlike Class II BSCs, which have a standard to which they are designed and validated,⁸³ there have been few performance measures for the compounding isolator. USP Chapter 797 created performance criteria for the CACI, including unidirectional airflow,⁷ and the Controlled Environment Testing Association (CETA) has established several performance guides, testing requirements, and servicing instructions that may be used with CACIs to ensure their effectiveness for the compounding of HDs.⁸⁵⁻⁸⁸

For compounding sterile preparations, the filtered air and airflow must achieve an ISO class 5 environment within the CACI.^{7,89} The totally enclosed design may reduce the escape of contamination during the compounding process, and the CACI may be less sensitive to drafts and other laminar airflow equipment. Issues unique to CACIs include pressure changes when accessing the fixed-glove assembly, pressure changes in the main chamber when accessing the

antechamber (compounding isolator pass-through) and ergonomic considerations associated with a fixed-glove assembly. Compounding isolators must be continuously monitored for leaks in the gloves and the fixed-glove assembly. Glove changes must be done routinely and facilities must have policies for the frequency of such changes. As in all sterile HD compounding, the glove closest to the sterile preparation must be sterile.

CACIs, like Class II BSCs, do not prevent the generation of contamination within the cabinet workspace, and their effectiveness in containing contamination depends on proper technique.^{41,90,91} The potential for the spread of HD contamination from the antechamber and main chamber of the CACI to the workroom may be reduced by surface decontamination, but no wipe-down procedures have been studied. Surface decontamination may be more readily conducted in CACIs than in Class II BSCs; however, opening the front of the CACI to improve access may allow surface contamination to escape the enclosure. Cleaning the enclosure through the glove ports generally requires tools and may be difficult for some operators. (See *Decontamination, deactivation, and cleaning* below for more information.)

Recirculating CACIs depend on high-efficiency (HEPA or ultra-low penetrating air [ULPA]) filters. These filters may not sufficiently remove volatile HD contamination from the airflow. CACIs that discharge air into the workroom, even through high-efficiency filters, present exposure concerns similar to those of unvented Class II BSCs. If there is a possibility that the HDs handled in them may vaporize, it will not be contained in a filter. USP Chapter 800 requires outside exhaust.⁸ CACIs used for compounding HDs should be at negative pressure or use a pressurized air lock to the surrounding areas to improve containment. Some compounding isolators rely on a low-particulate environment rather than laminar-airflow technology to

protect the sterility of the preparations and are not recommended for compounding sterile hazardous preparations.⁸ Recommendations for use of Class III BSCs and CACIs are summarized in Appendix B.

Containment Secondary Engineering Controls (C-SECs)

USP Chapter 800 requires that C-PECs used to compound sterile and nonsterile HDs be located in a C-SEC, which may be either an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified C-SCA.⁸ The C-SEC must be vented to the outside, be physically separated from non-HD preparation areas, have appropriate ACPH, and be at negative pressure to all adjacent areas. If the negative pressure in the C-SEC is supplied either all or in part by the C-PEC, the C-PEC must operate continuously.⁸ The C-PEC must also operate continuously if used for sterile compounding.⁸ The allowance for HD compounding in a C-SCA is new, as this was not allowed in USP Chapter 797 and will be allowed only after USP Chapter 800 takes effect.^{7,8} The beyond-use date (BUD) of all CSPs compounded in a C-SCA, however, must be limited as described in USP Chapter 797.^{7,8}

Containment Supplemental Engineering Controls

USP Chapter 800 describes a third level of control, a containment supplemental engineering control, which provides adjunct controls to offer an additional level of protection during compounding or administration of HDs.⁸

Closed system drug-transfer devices. The device most frequently discussed in this category is the closed system drug-transfer device (CSTD). The NIOSH definition of a CSTD,

adopted by USP Chapter 800, is 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.^{6,8} The continued discovery of HD contamination in compounding and administration areas, despite adherence to HD safe handling guidelines, has generated an interest in CSTDs, especially for administration areas where C-PECs are not available during HD administration. The initial CSTD, developed in Europe, was tested in 1996-97 during compounding and administration by three nurses for one year in an outpatient setting. Compared to surface contamination of similar work areas reported in the literature, the closed system was more effective than the BSC in reducing contamination during preparation.⁹²

In originally defining the CSTD in 2004, NIOSH did not specify design or performance criteria for what constitutes an effective CSTD.⁶ A number of devices marketed as CSTDs have appeared since 2004. These devices are designated by the FDA as Class II medical devices, not requiring premarket approval.⁹³ 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 manufacturer’s 510(k) submission, the FDA clears the new device for sale in the U.S.⁹³ Many devices marketed for IV compounding or administration have been cleared by the FDA 510(k) process under various product codes. Many of the devices marketed and used for HD compounding are not CSTDs by definition and may not be appropriate for HD use. FDA created a product code, ONB, specifically for a closed antineoplastic and HD reconstitution and transfer system.⁹⁴ Although applications under this code are not independently tested by the FDA, the application process is more stringent for the manufacturer and the code specifically addresses antineoplastics and HDs. Products that are

marketed as CSTDs but have not been cleared by FDA under the product code ONB should not be considered CSTDs.

Although some CSTDs have been shown in peer-reviewed studies to limit the potential of generating aerosols and reduce HD contamination in the workplace, not all marketed CSTDs have been studied, and no surrogate or marker HD has been shown to be superior in measuring CSTD effectiveness or has been universally adopted for that purpose. The NIOSH topics page includes an expanded bibliography of publications related to CSTDs.⁹⁵ In the absence of a performance standard, NIOSH is attempting to develop protocols to test the containment performance of both the physical barrier type of CSTD and those designed to operate using air-cleaning technologies.^{96,97} Difficulties encountered in this attempt include the selection of surrogates to represent HDs and the method to capture and analyze the surrogates. The NIOSH protocols are a positive step in evaluating these devices. As other products become available, they should meet the definition of CSTDs established by NIOSH⁶ and should be required to demonstrate their effectiveness in independent studies.⁸ CSTDs (or any other ancillary devices) are not a substitute for using a ventilated cabinet.^{6,8}

The use of ventilated engineering controls during compounding HDs provides protection for the worker as well as the sterile preparation. During administration of HDs, there are no similar controls available. For these reasons, USP 800 has determined that CSTDs should be used when compounding HDs and that CSTDs must be used when administering antineoplastic HDs when the dosage form allows and the device is physically or chemically compatible with the HD to be used.⁸

USP Chapter 800 notes that there is no certainty that all CSTDs will perform adequately, and without a standard for evaluating CSTD containment, users will have to rely on independent, peer-reviewed studies and demonstrated contamination reduction to evaluate performance claims.⁸

Personal Protective Equipment (PPE)

PPE provides worker protection to reduce exposure to HD aerosols and residues. However, in the hierarchy of controls, PPE is the least effective measure for protecting workers.⁹⁸ Additional PPE may be required to handle the HDs outside of a C-PEC, such as treating a patient or cleaning a spill. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE for possible scenarios that may be encountered in healthcare settings in Table 5.¹² NIOSH has also created a Workplace Solution on PPE containing detailed recommendations with references.⁹⁹ Disposable PPE must not be re-used. Reusable PPE, such as a face shield or cartridge respirator, must be decontaminated and cleaned after use. USP Chapter 800 has an extensive discussion of PPE and its appropriate use but requires that the entity develop SOPs for PPE based on its own safety plan and assessment of risk.⁸ The following summary of PPE use is not designed to replace or interpret the best practice mandates of USP.^{7,8}

Removal of PPE. PPE used to compound HDs, to dispose of HDs, and to clean up an HD spill should be considered contaminated with HD residue. PPE used to administer HDs, to perform patient care, or to discard patient waste should be considered contaminated with HD residue and potentially contaminated with infectious material. Removal of PPE must be done cautiously to avoid transferring contamination to skin, the environment, or other surfaces that may be touched with uncovered skin. Wearing double gloves provides an additional barrier to

possible contamination transfer as the hands are covered until the last item of PPE is removed. After any handling of HDs, the outer gloves should be removed one at a time with the contaminated glove fingers touching only the outer surface of the other glove, never the inner surface. The first glove should be removed and then turned inside out. Still wearing the inner, clean glove, personnel should place the fingers underneath the wrist of the second, outer glove and roll the glove down, turning it carefully inside out to avoid touching the outside. The face shield, if worn, should be removed next, while avoiding contact with the front. Personnel should then remove the gown, using care to avoid transfer of contamination to clothes and skin. They should then turn the gown inside out, fold it tightly, and discard it as trace waste. Other PPE (e.g., hair coverings, face mask, shoe coverings) should then be carefully removed, from least contaminated to most contaminated. The inner gloves should be removed last and discarded in the HD disposal container. Hands should be washed with soap and water.

Gloves. Gloves are essential when handling HDs. Glove use has been more clearly described by USP and NIOSH as the definition of HDs has expanded to include non-antineoplastic HDs and reproductive-risk-only HDs and the catalog of formulations of HDs similarly enlarged to encompass APIs used in compounding, final dosage forms of compounded HD preparations, and manufactured HD products.^{8,55}

Although double-gloving is required by USP Chapter 800 in only select circumstances,⁸ wearing two pairs of gloves allows removal of the outer glove while the skin of the hand and wrist is still covered. Changing the outer glove while retaining the inner glove, during any HD handling, is a work practice that provides added protection against skin contact with HDs. Many studies have shown that areas where HDs are handled have significant surface contamination

and workers are at risk of absorbing HDs through uncovered skin any time they come into contact with this contamination.^{10,11,21, 43,46} A single, thicker glove, tested as a chemotherapy glove, may provide the same protection as two pairs of chemotherapy gloves against permeation during compounding and administration, but it does not provide the protection of never having exposed skin in a contaminated area. Double gloving and good work practices provide better protection. Facilities writing policies and procedures, especially detailing work practices, should consider requiring wearing double chemotherapy gloves when receiving and stocking HDs, selecting HD packages for further handling, handling drug waste and patient waste, cleaning spills, performing routine cleaning with detergents and disinfectants, and any situation in which an exposed hand or wrist may create a risk of touch contamination with HD residue on surfaces. NIOSH allows single gloves for receiving, unpacking and placing HDs in storage.⁵⁵ Because broken cartons and containers of HDs represent a major risk of worker exposure while receiving and unpacking, any package that does not appear intact should be handled with two pairs of chemotherapy gloves. Workers should visually examine the shipping container or tote for damage, as described in USP Chapter 800, and then determine the appropriate PPE.⁸ NIOSH also allows single gloves for handling intact, unit-dose oral agents, when no cutting or crushing is required.⁵⁵ NIOSH recommends double gloves for spill control and for cleaning and disposal of HD waste and patient waste.⁵⁵ USP Chapter 800 and Table 5 of the current NIOSH HD list should be consulted for specific information about glove use.^{8,55}

ASTM International has developed testing standards for assessing the resistance of medical gloves to permeation by chemotherapy drugs, ASTM D6978-05 (2013).¹⁰⁰ This standard tests gloves for resistance to permeation to a group of HDs selected for characteristics of

toxicity, diluent, and ability to permeate standard gloving material, among others. Gloves are not tested for all known HDs because of the cost and lack of assays for many drugs, so these drugs act as markers for permeability. Gloves passing this ASTM standard may be labeled as “chemotherapy gloves.” ASTM F739-12e1 (2012) is also a permeation standard, but it is neither specific to gloves nor to chemotherapy drugs and should not be used to test chemotherapy gloves.¹⁰⁰⁻¹⁰² The performance requirement of ASTM F739-12e1 is only one tenth that of ASTM D6978-05, and ASTM F739-12e1 is performed at room temperature rather than body temperature, which results in less drug permeation being measured and less-protective gloves to be marketed as chemotherapy gloves.¹⁰⁰⁻¹⁰² Staff purchasing gloves and staff using them for handling HDs must verify that the gloves are tested against ASTM D6978. USP Chapter 800 requires that chemotherapy gloves must meet ASTM D6978.⁸

Many guidance documents have recommended gloves both for sterile compounding and for any handling of HDs be powder-free to avoid powder particulates from contaminating sterile processing areas and to prevent absorption of HD contaminants, which may increase the potential for dermal contact.⁵ This issue was resolved when the FDA issued a ban on powdered gloves effective January 18, 2017.¹⁰³ The FDA states that the use of powder on medical gloves presents numerous risks to patients and healthcare workers, including inflammation, granulomas, and respiratory allergic reactions.¹⁰³

As latex sensitivity is a concern to healthcare workers and patients, gloves made of nitrile and neoprene have been tested against different HDs, with nitrile demonstrating a high resistance to permeation by multiple HDs.¹⁰⁴⁻¹⁰⁶ In a review of glove standards and studies done in the E.U. and U.S., Landeck¹⁰⁷ determined that for gloves used for extended exposure to HDs,

double gloving, the use of thicker gloves, and frequent glove changes increased worker protection. The authors recommend regular glove changes every 15–20 minutes with constant exposure to chemotherapy drugs.¹⁰⁷

USP Chapter 800 requires that gloves selected for use with HDs must meet ASTM D6978-05 (or its successor) and that two pairs of chemotherapy gloves are required for compounding sterile and nonsterile HDs. For sterile compounding, the outermost glove must be sterile.^{7,8} During sterile compounding in a Class II BSC, two pairs of ASTM D6978-approved gloves are required, with the outermost pair being sterile. During sterile compounding in a Class III BSC or a CACI, both of which are equipped with attached gloves or gauntlets, the gauntlet, sleeve and fixed glove assembly must be cleaned and disinfected prior to sterile compounding using an appropriate cleaner and disinfectant applied with a sterile wiper. The fixed glove, if disposable, must be changed prior to compounding and sanitized per the manufacturer's instructions. A pair of sterile ASTM D6978-approved gloves must be placed in the passthrough and brought into the C-PEC work area and donned over the glove connected to the gauntlet or over the fixed glove assembly. The outermost glove must be sterile. Supplies of sterile ASTM D6978-approved gloves must be kept near the C-PEC to allow changing of the outermost glove as needed.

USP Chapter 800 notes that chemotherapy gloves should be worn for handling all HDs, including non-antineoplastic HDs and for reproductive-risk-only HDs, and that two pairs of chemotherapy gloves are required for administering antineoplastic HDs.⁸ Gloves should be inspected for visible defects before donning. When double gloves are worn with a gown, the

inner glove should be placed underneath the gown cuff and the outer glove over the gown cuff. There should be no skin exposed at the wrist.

Based on the ASTM D6978 permeability testing, the maximum recommended wear time for gloves is 30 minutes. Certain drugs may permeate more quickly (e.g., carmustine, thiotepea).¹⁰⁰ When handling these drugs, gloves should be changed according to the permeation time listed on the glove packaging. Gloves should be removed immediately if torn, punctured, or knowingly contaminated. The same wear-time restrictions apply to the outermost glove in the Class III BSC or CACI.

When compounding in a Class II BSC, gloves (at minimum the outermost gloves) must be changed whenever it is necessary to exit and re-enter the BSC. Gloves worn during the administration of HDs must be removed at the completion of administration, if gloves are visibly damaged or contaminated, and before leaving the administration area to prevent the spread of HD residue to other areas. For the aseptic protection of sterile preparations, the outermost sterile gloves must be sanitized with an appropriate disinfectant (e.g., sterile IPA 70%) by wiping with a sterile wiper saturated with the disinfectant, when reentering the BSC. Personnel should never spray anything on contaminated gloves or any other potentially contaminated surface, as this may generate aerosols and spread HD contamination.¹⁰⁸

When removing HD gloves, the contaminated glove fingers must only touch the outer surface of the glove, never the inner surface. If the innermost glove becomes contaminated, both pairs of gloves must be changed. Both the innermost and outermost gloves should be considered contaminated, and glove surfaces must never contact the skin or any surface that may be touched by the unprotected skin of others. HD contamination may be distributed to

other surfaces during compounding, other handling, or during glove removal and may be a source of surface contamination and subsequent dermal absorption of HDs by workers not actively involved in the compounding, administration, or other tasks involving HDs, or who are not wearing PPE.^{11,21,109} Gloves used to compound HDs in the Class II BSC should be placed in a sealable plastic bag for containment within the C-PEC before disposal as contaminated waste. The outermost glove attached to the Class III BSC or CACI fixed glove or gauntlet must be removed from the assembly and placed in a sealable plastic bag for containment within the C-PEC before disposal as contaminated waste. During compounding, HD contamination may be transferred to the gloves or gauntlets and then transferred to the surfaces of all items within the C-PEC. Fixed glove and gauntlet surfaces must be cleaned after HD compounding to avoid the potential spread and cross-contamination of HD residue to other surfaces. All final preparations must be surface decontaminated while wearing ASTM D6978-approved gloves to avoid spreading contamination, and the clean inner glove must be used to apply labels.

Proper hand hygiene must be practiced before donning and after removing any PPE. Hands should be cleaned with soap and water after PPE is removed. Sanitizing gels should not be used until hands are thoroughly cleaned of HD residue, as rubbing gels into hands may increase the dermal absorption of any HD residue.¹¹⁰

Recommendations for use of gloves are summarized in Appendix C.

Gowns. Gowns are worn during the compounding of HD preparations to protect the preparation from the worker, the worker from the preparation, or both.⁵ Any sterile compounding requires PPE to protect the aseptic compounding environment from the biological contamination that is presented by the worker. The requirements of both USP

Chapters 797 and 800 must be met for sterile compounding.^{7,8} USP Chapter 800 requires gowns; head, hair, and shoe covers; and two pairs of chemotherapy gloves for compounding sterile and nonsterile HDs.⁸ HD compounding in an enclosed environment, such as a Class III BSC or a CACI, has not been exempted from the gowning requirement. USP Chapter 800 further requires that gowns that show resistance to permeability by HDs be worn when administering injectable antineoplastic HDs. Additional gown policies, as for other PPE, must be established by the entity and delineated in their procedures.

The selection of gowning materials depends on the goal of the process. Personal protective gowns are recommended during the handling of HD preparations to protect the worker from inadvertent exposure to extraneous drug particles on surfaces or generated during the compounding process and leakage of any liquid forms of HDs. HD gowns must be disposable and shown to resist HD permeability. Disposable gowns made of polyethylene-coated polypropylene (e.g., spunbond/meltblown/spunbond) provide better protection than uncoated gowns.^{5,8} Basic characteristics for HD gowns include that they close in the back with no open front, have long sleeves with tight-fitting elastic or knit cuffs to fit over gloves, and have no seams or closures to allow powder or liquid HD residue to pass through.^{5,8} Washable garments (e.g., laboratory coats, scrubs, and cloth gowns) absorb fluids and provide no barrier against HD absorption and permeation.^{5,8} To avoid spreading contamination, potentially contaminated clothing must never be taken home.⁸

There is no specific standard for gowns or gowning materials to be tested for permeation by HDs. ASTM F739-12e1 is a test method for permeation by liquids and gases through protective clothing materials under conditions of continuous contact, but it does not

specify drugs or concentrations to be tested and has no performance standard for an acceptable resistance to HD permeation.¹⁰¹ Some gowns are tested using the ASTM F739 parameters and the chemotherapy drugs and concentrations from D6978.¹⁰⁰ This practice has not been studied for effectiveness or safety. HD gowns should be coated and labeled as impervious per manufacturer testing.

Gowns should be changed per manufacturer's recommendations. If there is no specific information, coated gowns should be changed every 2–3 hours.^{5,8} Gowns must be changed immediately after a spill or splash. Contamination of gowns during glove changes must be a consideration. If the inner pair of gloves requires changing, a gown change may be needed. Gowns worn as barrier protection in the handling of HDs must never be worn outside the immediate handling areas. Gowns worn during administration should be changed when leaving the patient-care area and immediately if contaminated. Gowns should be removed carefully and properly disposed of as trace-contaminated waste to avoid becoming a source of contamination to other staff and the environment.^{5,6} Gowns used for cleaning or spill management and other uses may be more heavily contaminated. These gowns should be contained in sealable bags and discarded as bulk hazardous waste.

Researchers have looked at gown contamination with fluorescent scans, high-performance liquid chromatography, and tandem mass spectrometry.^{111,112} In one study, researchers scanned nurses and pharmacists wearing gowns during the compounding and administration of HDs.¹¹¹ Of a total of 18 contamination spots detected, 5 were present on the gowns of nurses after drug administration. No spots were discovered on the gowns of pharmacists after compounding. In contrast, researchers using a more sensitive assay placed

pads in various body locations, both over and under the gowns used by the subjects during compounding and administration of cyclophosphamide and ifosfamide.¹¹² Workers wore short-sleeved nursing uniforms, disposable or cotton gowns, and vinyl or latex gloves. More contamination was found during compounding than administration. Contamination found on the pads placed on the arms of preparers is consistent with the design and typical work practices used in a Class II BSC, where the hands and arms are extended into the contaminated work area of the cabinet. Remarkably, one preparer had contamination on the back of the gown, possibly indicating touch contamination with the Class II BSC during removal of the final product. Pads were used in two additional studies to assess HD contamination on the workers' bodies.^{113,114} Pads placed on the arms and chest of workers compounding and administering showed evidence of touch contamination with HD residue on the studied areas. Without protective gowns, the HD residue may have contaminated skin or worker clothing, resulting in drug uptake or transfer.

Recommendations for use of gowns are summarized in Appendix D.

Eye and face protection. Many HDs are irritating to the eyes and mucous membranes. Appropriate eye and face protection must be worn when there is a risk of spills or splashes, when HD waste materials are handled, or when working outside of a C-PEC (e.g., administration in the surgical suite, working at or above eye level, or cleaning a spill). Face shields should be used in combination with goggles to provide a full range of protection against splashes to the face and eyes. Although face shields provide improved skin protection, face shields alone do not deliver full eye and face protection.^{8,99} Goggles must be used when eye protection is required.⁸ Eyeglasses alone or safety glasses with side shields do not sufficiently protect the

eyes from splashes and therefore are not suitable when handling HDs. A full-face piece respirator provides complete eye and face protection.⁸

Respirator protection. Staff unpacking HDs that are not contained in plastic should wear an elastomeric half-mask with a multi-gas cartridge and P100 particulate filter.⁸ All workers who may use a respirator must be fit-tested by a certified fit-tester and instructed on the utilization of the appropriate respirator according to the OSHA Respiratory Protection Standard.^{70,71} A respirator of the correct size and suitable to the aerosol size, physical state (i.e., particulate or vapor), and concentration of the airborne drug must be available at all times. Surgical masks do not provide respiratory protection and therefore should on no occasion be used when respiratory protection is required for HDs.^{6,8} N95 respirators offer no protection against gasses and vapors and negligible protection against direct liquid splashes.⁷¹ 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.⁸

Shoe and hair covering. Shoe and hair coverings must be worn throughout the sterile compounding process to minimize particulate contamination of the critical work zone and the preparation.⁷ With the potential for HD contamination on the floor in the compounding and administration areas, donning two pairs of shoe coverings, as the contamination-control mechanism, must occur. Contaminated shoe covers must never be worn outside of the immediate HD area to avoid spreading contamination.⁸ The outer shoe covers must be removed with gloved hands when exiting the compounding area. Gloves are required, and care must be taken, when removing hair or shoe covers, to prevent contamination from spreading to uncontaminated areas. Hair and shoe coverings used in the HD handling areas must be

contained, along with used gloves, and discarded as trace contaminated waste in the appropriate waste receptacle. Shoe coverings that are overtly contaminated, as in spill cleanup, should be disposed of as hazardous waste.

Work Practices

Compounding sterile HDs. Work practices for the compounding of sterile HDs differ somewhat with the use of a specific C-PEC. Good organizational skills are essential to minimize contamination and maximize productivity. All activities not requiring a critical environment (e.g., checking labels, doing calculations) should be completed before accessing the C-PEC. All items needed for compounding must be gathered before beginning work to eliminate the need to exit the C-PEC once compounding has begun. Two pairs of ASTM D6978-approved gloves should be worn to gather HD vials, due to the frequent findings of HD residue on vials, and one or two pairs of ASTM D6978-approved gloves may be worn to gather other supplies. All areas where HDs are received, stored, handled, and wasted have been shown to be contaminated with HD residue. Prudent practice is to wear two pairs of gloves.^{6,8,10,11,20,21,43} After completing tasks, these gloves should be carefully removed and discarded as contaminated waste. Fresh ASTM D6978-approved gloves must be donned before aseptic manipulation. For compounding sterile HDs, the ASTM D6978-approved glove closest to the sterile preparation must be sterile.

Only supplies and drugs essential to compounding the dose or batch should be placed in the work area of the C-PEC. C-PECs should not be crowded to avoid unnecessary HD contamination and disrupting airflow. Luer-Lok connections on syringes and on all

compounding and ancillary devices must be used whenever possible for manipulating HDs, as they are less likely to separate during compounding and administration.

Spiking an i.v. set into a solution containing HDs or priming an i.v. set with HD solution in an uncontrolled environment must be avoided. One recommendation is to attach and prime the appropriate i.v. set to the final container in the C-PEC before adding the HD. CSTDs should achieve a dry connection between the administration set and the HD's final container. This connection allows the container to be spiked with a secondary i.v. set and the set to be primed by backflow from a primary non-HD solution. This process may be done outside the C-PEC, reducing the potential for surface contamination of the i.v. set during the compounding process. Only CSTDs that have been tested to achieve a dry connection may be considered for use with this technique. Personnel should avoid placing the i.v. set on the surface of the C-PEC during compounding to reduce the transfer of HD residue from the surface of the C-PEC to the surface of the i.v. set. Care must also be taken to avoid contaminating the tubing with HD residue from the surface of the gloves. A new i.v. set must be used with each dose of HD. Once attached, the i.v. set must never be removed from an HD dose, thereby preventing the residual fluid in the bag, bottle, or tubing from leaking and contaminating personnel and the environment.

Transport bags must never be placed in the C-PEC work area during compounding, to avoid inadvertent contamination of the outer surface of the bag by transfer of HD residue. Final HD preparations must be surface decontaminated after compounding is complete. In any type of C-PEC, clean ASTM D6978-approved gloves must be worn when labeling and placing the final HD preparation into the transport bag. Handling final preparations and transport bags with

gloves contaminated with HD residue will result in the transfer of the contamination to other workers. Personnel should don clean ASTM D6978-approved gloves whenever there is a doubt as to the cleanliness of the inner or outer gloves.

Working in any C-PEC. With or without ancillary devices (e.g., CSTDs), none of the available ventilated engineering controls can provide 100% protection for the worker. Personnel must recognize the limitations of the equipment and address them through appropriate work practices.^{4,5} PPE use with C-PECs is addressed by USP⁸ and NIOSH⁵⁵ (see also *PPE* above). The effectiveness of C-PECs in containing HD contamination depends on proper technique.⁴⁷ HD contamination from the work area of the CACI (e.g., on the surfaces of the final preparation) may be brought into the antechamber or airlocks of the CACI, and ultimately into the workroom environment. Surface decontamination of the preparation before removal from the CACI's main chamber should reduce the HD contamination that could be transferred to the workroom, but no wipe-down procedures for final preparations have been studied. Surface contamination may be removed by using isopropyl alcohol, sterile water, peroxide, or sodium hypochlorite solutions on disposable pads and wiping the surface of the final preparation, provided the packaging is not permeable to the solution and the labels remain legible and intact.

Recommendations for working in C-PECs are summarized in Appendix E.

Class II BSCs. Class II BSCs use unidirectional, vertical-flow, HEPA-filtered air (ISO class 5) as their controlled aseptic environment. Before beginning an operation in a Class II BSC, personnel should follow the hand washing and PPE requirements of USP Chapter 797 and 800.^{7,8} For cleaning the Class II BSC, nonsterile ASTM D6978-approved gloves are appropriate.

Sterile ASTM D6978-approved gloves must be available near the Class II BSC to allow changes of gloves during sterile HD compounding. The Class II BSC work surface should be cleaned of surface contamination with detergent, sodium hypochlorite, and neutralizer, or an independently tested alternative cleaner. Between cleanings, the compounding surface must be disinfected with sterile 70% isopropyl alcohol applied with a sterile wiper, never using a spray. For the Class II BSC, the front shield must be lowered to the proper level to protect the face and eyes. The operator should be seated so that his or her shoulders are at the level of the bottom of the front shield. All drugs and supplies needed to aseptically compound a dose or batch should be gathered and disinfected with sterile 70% alcohol before being placed in the direct compounding area (DCA) of the C-PEC. Exiting and reentering the work area should be avoided. Being careful not to place any sterile objects below them, i.v. bags and bottles may be hung from the bar. All items must be placed well within the Class II BSC, away from the unfiltered air at the front barrier. By design, the intended work zone within the Class II BSC is the area between the front and rear air grilles. The containment characteristics of the Class II BSC are dependent on the airflow through both the front and back grilles; these grilles should never be obstructed. Due to the design of the Class II BSC, the quality of HEPA-filtered air is lowest at the sides of the work zone, so manipulations should be performed at least six inches away from each sidewall in the horizontal plane. A small waste-sharps container may be placed along the sidewall toward the back of the BSC. Per USP Chapter 800, a plastic-backed preparation mat should be placed on the work surface of a C-PEC prior to compounding HDs.⁸ One study has suggested that a plastic-backed absorbent preparation pad in a Class II BSC may interfere with airflow,¹¹² but another study determined that use of a flat firm pad that did not

block the grilles of the cabinet had no effect on airflow.¹¹⁵ The use of a large pad that might block the front or rear grilles must be avoided. In addition, because a pad may absorb small spills, it may become a source of HD contamination for anything placed upon it. Preparation pads are not readily decontaminated and must be replaced and discarded after preparation of each batch and frequently during compounding. The mat should be changed immediately if a spill occurs.⁸ Equipment for HD compounding must be dedicated. Work practices for sterile compounding of HDs must adhere to USP Chapters 797 and 800.^{7,8} More information on the design and use of Class II BSCs is available from the CDC⁸¹ and NSF/ANSI Standard 49-2016.⁸³

Class III BSCs and CACIs. At least one pair of ASTM D6978-approved gloves should be worn to prepare for work in a Class III BSC or a CACI. Using two pairs of gloves allows changing only the outer pair while handling vials and supplies. Wearing gloves, workers must gather all drugs and supplies needed to aseptically compound an HD dose or batch, sanitize them, and ready them for placement into the antechamber of the compounding isolator. Supplies and drugs in the antechamber are disinfected with sterile 70% isopropyl alcohol when taken into the main chamber (the DCA) of the compounding isolator, where the drug and supplies are used to compound the dose. The contaminated supplies are removed using the closed trash system of the compounding isolator, if so equipped, or sealed into a transport bag and removed via the antechamber for disposal as contaminated waste. The dose is then labeled and placed into a sealable bag for transport in the antechamber. The transport bag is never placed in the DCA of the compounding isolator to avoid contaminating the outer surface.

For sterile compounding, the gloves closest to the sterile preparation must also be sterile.^{7,8} Sterile gloves must be placed into the antechamber to be transferred into the DCA.

Additional work practices may include cleaning off the gloves or gauntlets and final preparation after initial compounding and before handling the label and sealable transport bag. Care must be taken when transferring products out of the antechamber and disposing of waste through the antechamber or trash chute to avoid accidental contamination.

Aseptic technique. Stringent aseptic technique, described by Wilson and Solimando¹¹⁶ in 1981, remains the foundation of any procedure involving the use of needles and syringes in manipulating sterile dosage forms. This technique, when performed in conjunction with negative pressure technique, minimizes the escape of drug from vials and ampules. Needleless devices have been developed to reduce the risk of blood-borne pathogen exposure through needle sticks. None of these devices has been tested for reduction of HD contamination, and the appropriateness of these devices in the safe handling of HDs has not been determined. CSTDs have been developed to reduce the release of HD residue during compounding but not all HDs or all types of sterile compounding are compatible with CSTDs. Stringent aseptic technique using needles and syringes is a necessary skill, especially for those occasions when no ancillary device is available or appropriate.

In reconstituting HDs in vials, it is critical to avoid pressurizing the contents of the vial. Pressurization may cause the drug to spray out around the needle or through a needle hole or a loose seal, aerosolizing the HD into the work zone. Pressurization can be avoided by creating a slight negative pressure in the vial. Too much negative pressure, however, can cause leakage from the needle when it is withdrawn from the vial. The safe handling of HD solutions in vials or ampules requires the use of a syringe that is no more than three-fourths full when filled with the solution, which minimizes the risk of the plunger separating from the syringe barrel.¹¹⁶ For

reconstitution, once the diluent is drawn up, the needle is carefully inserted into the upright HD vial stopper, being careful not to core the stopper. The syringe plunger is then pulled back (to create a slight negative pressure inside the vial), so that air is drawn into the syringe. Small amounts of diluent should be transferred slowly into the HD vial as equal volumes of air are removed. The needle should be kept in the vial, and the contents should be swirled carefully until dissolved. For a liquid HD, the vial is kept upright while a syringe and needle are prepared. A slightly smaller amount of air than the amount of the required HD dose is drawn into the syringe. The needle is inserted into the vial stopper, being careful not to core the stopper, and the vial is inverted with the syringe and needle inserted. The proper amount of drug solution should be gradually withdrawn while equal volumes of air are exchanged for solution. The exact volume needed must be measured while the needle is in the vial, and any excess drug should remain in the vial. With the vial in the upright position, the plunger should be drawn back past the original starting point to again induce a slight negative pressure before removing the needle. The needle hub should be clear of drug solution before the needle is removed.

If an HD is transferred to an i.v. bag, care must be taken to puncture only the septum of the injection port and avoid puncturing the sides of the port or bag. After the drug solution is injected into the i.v. bag, the i.v. port, container, and set (if attached by pharmacy in the C-PEC) should be surface decontaminated. Wearing clean gloves (or the inner glove), personnel should label the final preparation, including an auxiliary warning, and cover the injection port with a protective seal. The final container should be placed into a sealable bag to contain any possible leakage.⁴

To withdraw HDs from an ampule, the neck or top portion should be gently tapped.¹¹⁶ After the neck is wiped with sterile 70% isopropyl alcohol, a 5- μ m filter needle or straw should be attached to a syringe that is large enough that it will be not more than three-fourths full when holding the drug. The fluid should then be drawn through the filter needle or straw and cleared from the needle and hub. After this, the needle or straw is exchanged for a needle of similar gauge and length; any air and excess drug should be ejected into a sterile vial (leaving the desired volume in the syringe); aerosolization should be avoided. The drug may then be transferred to an i.v. bag or bottle. If the dose is to be dispensed in the syringe, the plunger should be drawn back to clear fluid from the needle and hub. The needle should be replaced with a locking cap, and the syringe should be surface decontaminated and labeled.

Training and demonstration of competence. The OSHA HCS and USP Chapter 800 require employee training to the tasks they will perform as part of the safety program.^{8,57} The HCS details the requirements for worker information and training in paragraph H of the HCS regulation.⁵⁷ In the 2008 revision of USP Chapter 797, which includes HDs, the training requirements note that compounding personnel of reproductive capability must confirm in writing that they understand the risks of handling HDs.⁷ This requirement is also in USP Chapter 800.⁸ ONS provides an excellent example of a worker agreement to handle HDs in the 3rd edition of *Safe Handling of Hazardous Drugs*.¹¹⁰

Personnel must be trained before handling HDs as part of their job responsibilities.^{8,57} Staff handling HDs must demonstrate competency before commencing responsibilities and at least every 12 months thereafter.⁸ All staff who will be compounding HDs must be trained in the stringent aseptic and negative-pressure techniques necessary for working with sterile HDs

as well as all primary, secondary, and supplementary engineering controls.⁸ Once trained, staff must demonstrate competence by an objective method, and competency must be reassessed on a regular basis.¹¹⁷ Additional training should be carried out whenever new equipment or procedures are put in place. All training and competency testing must be clearly documented as part of the worker's safety record.^{8,57}

Compounding and handling of nonsterile HD dosage forms. Nonsterile compounding of HD dosage forms must adhere to USP Chapter 795 and USP Chapter 800.^{8,61} Best practices and mandates for other activities involved in handling of nonsterile HD forms (e.g., tablets, oral liquids) are provided in USP Chapter 800.⁸ Guidance for PPE when handling nonsterile HD dosage forms is available from NIOSH.⁵⁵

Although nonsterile dosage forms of HDs contain varying proportions of drug to nondrug (nonhazardous) components, there is the potential for personnel exposure to and environmental contamination with the hazardous components if HD are handled (e.g., packaged) by pharmacy staff. Most HDs are not available in liquid formulations; however, such formulations are often prescribed for small children and adults with feeding tubes. Recipes for extemporaneously compounded oral liquids may start with the parenteral form or an API, or they may require that tablets be crushed or capsules opened. Tablet trituration has been shown to cause fine dust formation and local environmental contamination.¹¹⁸ Healthcare personnel should avoid manipulating HDs (e.g., crushing tablets or opening capsules) if possible. Liquid formulations are preferred if solid oral dosage forms are not appropriate for the patient. If HD dosage forms do require manipulation such as crushing tablet(s) or opening capsule(s) for a

single dose, personnel must don appropriate PPE and use a plastic pouch to contain any dust or particles generated.

USP Chapter 800 requires that compounding of nonsterile HDs be performed in a C-PEC that provides environmental and personnel protection. A Class I BSC or CVE is acceptable equipment for this task. A CACI or a Class II BSC may also be used if they are dedicated to nonsterile compounding. USP Chapter 800 allows a C-PEC used for sterile HD compounding to be used for nonsterile HD compounding, provided that the C-PEC is decontaminated, cleaned, and disinfected before resuming sterile compounding in that same device. As noted above, cleaning and decontaminating a C-PEC has not been shown to be very effective, making this an undesirable solution.^{73,74,76,77}

Nonsterile HD dosage forms, like oral HD capsules or tablets, vary in their risk of causing occupational exposure. The level of risk, however, depends on the tasks required to prepare and dispense the doses. Manual counting of solid medications may be problematic if, for example, repeated handling of a large container of tablets has created a loose powder or residue of tablet dust. Exposure to the dust or residue may present a risk of powder inhalation or skin contact. USP Chapter 800 notes that an assessment of risk should be conducted to determine the appropriate containment strategies for the HD tasks required of the worker.⁸

There are risks associated with automatic pill counters, especially high-speed delivery devices. One study looked at a number of drugs dispensed in this manner and found measurable drug dust concentrations in the air surrounding such devices.¹¹⁹ Pill dust was generated in a variety of worker-related tasks, such as emptying and refilling the drugs in the device canisters.¹¹⁹ Cleaning the device or the canisters using compressed air produced the

highest amount of contamination in the air. The researchers found that workers directly involved with the automatic pill counters and those who hand-filled prescriptions were exposed to higher air concentrations of tablet fillers, like lactose, than workers who did other jobs such as administrative or office work.¹¹⁹ In studies of surface contamination with sterile HDs, measurable drug levels have been found in workers, most likely due to contact of uncovered skin with drug-contaminated surfaces.^{21,46} Drug residue generated in any task may be found on work surfaces and result in a potential occupational exposure. Work practices and cleaning procedures must be in place to at least reduce this exposure. Procedures for nonsterile HD compounding and other handling, as well as the appropriate use of equipment (C-PECs and other devices) for this purpose, must be developed to avoid the release of aerosolized powder or liquid into the environment during manipulation of HDs.

Recommendations for preparation and handling of nonsterile HD dosage forms are summarized in Appendix F.

Decontamination, deactivation, cleaning and disinfection. All guidelines agree that decontamination of areas where HDs are stored, compounded, administered, wasted, or otherwise handled is critical to reduce the levels of HD residue on various surfaces.^{5,6,8,110,120} All areas where HDs are handled and all reusable equipment and devices must be decontaminated. Decontamination occurs by inactivating, neutralizing, or physically removing HD residue from nondisposable surfaces (e.g., stainless steel C-PECs) and transferring it to absorbent, disposable materials (e.g., wipes, pads, towels) appropriate to the area being cleaned. The decontaminating, deactivating, cleaning, and disinfecting agents selected must be appropriate

for the type of HD contaminant(s), location, and surfaces to be cleaned. Consult manufacturer or supplier information for compatibility with cleaning agents used.⁸ Agents used for decontamination, deactivation, and cleaning should be applied through the use of wipes wetted with appropriate solution and not delivered as a spray to avoid aerosolizing and/or spreading HD residue.

Cleaning processes must be validated for solutions and methods by surface wipe sampling of HDs that have appropriate assays.^{73,74,76,77,121-124} Additionally, sterile compounding (ISO 5) areas and devices must be subsequently disinfected.^{7,8} Appropriate preparation of materials used in compounding before introduction into the C-PEC, including spraying (for non-HD-contaminated supplies) or wiping with sterile 70% isopropyl alcohol or appropriate disinfectant, is also necessary for sterile compounding.⁷

All personnel who perform decontamination, deactivation, cleaning, and disinfection activities must be trained in appropriate procedures to protect themselves and the environment from contamination.^{7,8} Proper PPE must be worn when performing these tasks (see *PPE* above). All disposable materials must be discarded to meet state and federal Environmental Protection Agency (EPA) regulations and the entity's policies.⁸

Decontamination, deactivation, and cleaning. Decontamination may be defined as cleaning or deactivating. Deactivating an HD is preferred, but no single process has been found to deactivate all currently available HDs from different surface materials.^{76,77,121} A 2013 study created terms to clarify the types of HD decontaminants tested on glass and stainless steel as elimination type (cleaners) and degradation type (deactivators).⁷⁶ Elimination-type solutions dissolve chemical products on surfaces, and degradation-type solutions react with the chemical

structure of HD compounds, leading to their degradation and formation of non-cytotoxic compounds. Elimination-type detergents, solutions, solvents, and surfactants and degradation-type cleaners were applied to stainless steel and glass surfaces that were contaminated with 10 HDs and removed.⁷⁶ Wipe samples were collected from the surfaces and analyzed for HD residue. All tested decontamination agents reduced the HD residue on the surfaces, but none totally removed it. Sodium hypochlorite was found to be very effective but damaged the stainless steel (no neutralizer was used in this study). Solutions containing anionic surfactants were very effective cleaners and had a high safety ratio but did not deactivate any HD. A second research team used similar solutions on gemcitabine and fluorouracil and found that these cleaning procedures were able to reduce HD contamination but did not completely eliminate it.¹²⁴ They concluded that it might be more effective to adapt cleaning procedures to the variety of drug compounds and surface types rather than continue with a singular approach.¹²⁴

The two studies also looked at removing HD contamination from glass surfaces.^{76, 124} The cleaning agents and application methods may be useful in decontaminating HD vials before placing them into the C-PEC. The outer surface of HD vials has been shown to be contaminated with HD residue.⁶⁵⁻⁶⁹ The amount of HD contamination placed into the C-PEC may be reduced by surface decontamination (i.e., wiping down) the HD vials. Care must be taken to avoid damaging the information on the vial label.

In a 2015 study, 70% IPA was compared to sodium dodecyl sulfate (SDS) in 20% IPA for the routine decontamination of 10 antineoplastic agents from the surfaces of UK-designed BSCs.⁷⁷ This study concluded that 70% IPA was only 49% efficient at achieving decontamination for the 10 antineoplastic agents tested. The SDS/20% IPA solution averaged 82% overall;

however, vincristine and epirubicin demonstrated cleaning efficacies lower than 20% to both tested solutions. Therefore, the use of alcohol for disinfecting stainless steel surfaces may result in the spread of contamination rather than any actual cleaning.⁷⁷ Additional considerations with SDS/IPA 20% include whether a rinse is needed with SDS and that 20% IPA is insufficient as a disinfectant, requiring additional application of an effective disinfecting solution.

Decontamination of C-PECs should be conducted per manufacturer recommendations. The SDS for many HDs recommend sodium hypochlorite solution as an appropriate deactivating agent.^{125,126} Researchers have shown that strong oxidizing agents, such as sodium hypochlorite, are effective deactivators of many HDs.¹²⁵ There are commercially available products that provide a system for decontamination and deactivation using sodium hypochlorite, detergent, and thiosulfate to neutralize the hypochlorite and deactivate other HDs.⁷³ Other non-chlorine bleach commercial disinfectant and sporicidal cleaners may provide appropriate decontamination from HDs.^{127,128} Although it is not possible to perform analysis for all of the HDs, a selection of different chemical HDs with different diluents may provide sufficient markers of the type of contaminants on a given surface. The manufacturer of the deactivating cleaner should provide independent laboratory analysis and documentation of effective cleaning. A decontamination (cleaning/deactivating) process should include one or more cleaning or deactivating agents and the method used to apply it and the use of a neutralizer or rinse step, if needed. The entire process should be validated by wipe sampling the various surfaces to determine whether the HD has been removed. As there are many types of chemical HDs, analysis of a number of them, preferably various types, would be needed to validate a given process.

A ventilated cabinet that runs continuously should be cleaned before the day's operations begin and at regular intervals or when the day's work is completed. USP Chapter 800 further states that the work surface of the C-PEC must be decontaminated between compounding of different HDs.⁸ The C-PEC must be decontaminated at least daily (when used), any time a spill occurs, before and after certification, any time power interruption occurs, and if the ventilation device is moved.⁸ Ventilated C-PECs (i.e. Class II and III BSCs and some CACIs) have air plenums that handle contaminated air. These plenums are designed for fumigation of the contamination from biological agents traditionally handled in the BSCs. The plenums are not designed for surface decontamination of drug or nonbiological residue, and many of the contaminated surfaces (plenums) cannot be reached for surface cleaning.^{4,5,81} The area under the C-PEC work tray should be cleaned at least monthly to reduce the contamination level in the BSCs and CACIs where appropriate.⁴

Disinfection. The selection and use of disinfectants in healthcare facilities is guided by several properties, such as microbicidal activity, inactivation by organic matter, residue, and shelf life. Many disinfectants registered by the EPA are one-step disinfectants, formulated to be effective in the presence of light to moderate soiling without a pre-cleaning step. However, when the surface to be disinfected has heavy soiling, a cleaning step is recommended prior to the application of the disinfectant. Trained compounding personnel are responsible for developing, implementing, and practicing the procedures for cleaning and disinfecting the DCAs written in the SOPs.⁷ A 2013 study demonstrated the importance of SOPs by demonstrating that the efficacy of chemical decontamination of HD work surfaces depends not only on the cleaning solution used but also on the cleaning protocol.¹²² It is necessary to adapt the protocol

to the surface to clean, and it must be standardized and validated.¹²⁴ Cleaning and disinfecting agents are to be used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues.⁷

Administration of HDs. Studies of infusion areas where HDs are administered have demonstrated significant HD surface contamination, which creates exposure risks for nurses, other workers, patients, and visitors to these areas.^{10,11,21, 46,129} A 2017 study¹²⁹ that measured surface contamination directly related to administration of HDs found the incidence and amount of contamination from marker drugs cyclophosphamide and 5-fluorouracil were higher than previously reported in studies looking at overall contamination in the infusion area.^{10,42} Practices for administration of HDs must protect patients, workers, and the environment.^{6,8,110,120} The need for more protection in the infusion area is addressed in USP Chapter 800, which provides direction on improved practices, including the required use of a CSTD for administration of antineoplastic HDs when the dosage form allows.⁸

Policies and procedures governing the administration of HDs must be jointly developed by nursing and pharmacy for the mutual safety of healthcare workers. These policies should supplement policies designed to protect patient safety during administration of all drugs. All policies affecting multiple departments must be developed with input from managers and workers from the affected areas. Extensive nursing guidelines for the safe and appropriate administration of HDs have been developed by the Oncology Nursing Society (ONS)^{110,120} and USP.⁸ Guidance on best practices for HD administration may also be found on the OSHA safety and health topics page on HDs.^{13,14}

Recommendations for reducing exposure to HDs during administration in all practice settings are listed in Appendix G.

Spill management. Policies and procedures must be developed to attempt to prevent spills and to govern cleanup of HD spills. Written procedures must specify who is responsible for spill management and must address the size and scope of the spill. Spills must be contained and cleaned up immediately by trained workers.

Spill kits containing all of the materials needed to clean up spills of HDs should be assembled or purchased (Appendix H). These kits should be readily available in all areas where HDs are routinely handled. A spill kit should accompany delivery of injectable HDs to patient care areas even though they are transported in a sealable plastic bag or container. If HDs are being prepared or administered in a nontraditional area (e.g., home setting, operating room, procedure area, radiology or unusual patient-care area), a spill kit and respirator must be obtained by the drug handler. Signs must be available to warn of restricted access to the spill area.⁸

Only trained workers with appropriate PPE and respirators should attempt to manage an HD spill. All workers who may be required to clean up a spill of HDs must receive proper training in spill management and in the use of PPE and NIOSH-certified respirators.^{70,71} Policies and procedures should describe how to establish access to workers trained to the OSHA Hazardous Waste Operations and Emergency Response Standard who may provide spill management in the event of a large spill.¹³⁰

The circumstances and handling of spills should be documented. Staff and nonemployees exposed to an HD spill should also complete an incident report or exposure form and report to the designated emergency service for initial evaluation.

All spill cleanup materials, including PPE used for spill management, must be disposed of as hazardous waste in accordance with EPA Resource Conservation and Recovery Act (RCRA) regulations.^{131,132} Spill cleanup materials must not be discarded as chemotherapy waste or biohazard waste. Additional information on spill control practices is available on the OSHA Safety and Health Topics page.^{13,14}

Recommendations for spill cleanup procedure are summarized in Appendix I.

Worker contamination. Procedures must be in place to address worker contamination, and protocols for medical attention must be developed before the occurrence of any such incident. OSHA requires suitable facilities for quick drenching or flushing of the eyes and body where workers may be exposed to injurious corrosive materials.¹³³ Limitations on having running water and drains in HD compounding areas conflict with these requirements. An alternative is to have a portable emergency eyewash station or emergency kits containing isotonic eyewash supplies and soap immediately available in areas where HDs are handled. Workers who are contaminated during the spill or spill cleanup or who have direct skin or eye contact with HDs require immediate treatment. OSHA-recommended steps for treatment are outlined in Appendix J.¹³³ Additional information on personnel contamination is available on the OSHA Safety and Health Topics page.^{13,14}

Hazardous Waste Containment and Disposal

In 1976, RCRA was enacted to provide a mechanism for tracking hazardous waste from its generation to disposal.¹³⁴ Regulations promulgated under RCRA are enforced by the Environmental Protection Agency (EPA) and apply to pharmaceuticals and chemicals discarded by pharmacies, hospitals, clinics, and other commercial entities. The RCRA outlines four characteristics of hazardous waste (D codes)¹³⁵ and contains lists of agents that are to be considered hazardous waste when they are discarded (P and U codes).¹³² Any discarded drug that is on one of the lists (a “listed” waste) or meets one of the criteria (a “characteristic” waste) is considered hazardous waste. EPA has provided some relief for pharmaceuticals over the years by excluding epinephrine salts and weak medicinal nitroglycerin from the list, although epinephrine base and other forms of nitroglycerin are still listed.¹³⁶ Not all states have adopted these exemptions, so state hazardous waste regulations and interpretations should be consulted. In addition to a few others, the listed drugs include warfarin, nicotine, dalfampridine (4-aminopyridine), and physostigmine, as well as seven current chemotherapy drugs: arsenic trioxide, chlorambucil, cyclophosphamide, daunomycin, melphalan, mitomycin C, and streptozocin.¹³⁷ They require handling, containment, and disposal as RCRA hazardous waste.

Every state except Iowa and Alaska is authorized to implement its own hazardous waste program, and these programs may be more stringent than the EPA. State and local regulations must be considered when establishing a hazardous waste and HD disposal policy for a given institution.¹³⁸

The RCRA allows for the exemption of empty containers from hazardous waste regulations. Empty containers are defined as those that have held U-listed or characteristic wastes and from which all wastes have been removed that can be removed using the practices

commonly employed to remove materials from that type of container and no more than 3% by weight of the total capacity of the container remains in the container.¹³⁹ Disposal guidelines developed by the National Institutes of Health (NIH) and published in 1984 coined the term “trace-contaminated” waste using the 3% rule.¹⁴⁰ Note that a container that has held an acute hazardous waste listed in §261.33(e), such as arsenic trioxide, is not considered empty by the 3% rule,¹⁴¹ and that spill residues from cleanup of hazardous agents are considered hazardous waste.¹³²

It is important that distinctions be drawn between HDs from an OSHA (HCS) and NIOSH employee exposure perspective and hazardous waste from an EPA perspective. USP Chapter 800 uses “antineoplastic hazardous drugs” to refer to those HDs generally used as chemotherapy in oncology treatment.⁸ For example, antineoplastic drugs listed in Table 1, Group 1 of the NIOSH 2016 HD list⁵⁵ are both employee hazards and hazardous to the environment based on their acknowledged toxicity. EPA hazardous waste regulations have not kept up with drug development, with over 100 chemotherapy drugs not listed by EPA.¹⁴² The recommendation, therefore, is to manage all antineoplastic drugs as hazardous waste through a permitted hazardous waste treatment, storage, and disposal facility. Assuming that an organization is no longer disposing of any waste drugs by discarding them down the sewer drain, those listed in Table 2, Group 2 and Table 3, Group 3 of the NIOSH HD list⁵⁵ could be managed as nonhazardous pharmaceutical waste through incineration at a permitted regulated medical waste or waste-to-energy facility. To emphasize the difference between HDs and hazardous waste, the term “chemotherapy” will be used to denote antineoplastic HDs. The healthcare organization always has the option to manage all NIOSH HDs as hazardous waste, of

course, if sorting is problematic. It is important to review state regulations for stricter definitions of hazardous waste; in Minnesota, for example, these drugs must be managed as hazardous waste.¹⁴³

Trace-contaminated chemotherapy drug waste. By the NIH definition of trace chemotherapy waste,¹⁴⁰ “RCRA-empty” containers, needles, syringes, trace-contaminated gowns, gloves, pads, and empty i.v. sets may be collected and incinerated at a regulated medical waste incinerator. Sharps used in the preparation of chemotherapy should not be placed in red sharps containers, since these are most frequently disinfected by autoclaving or microwaving, not by incineration, and pose a risk of aerosolization to waste-handling employees.

Bulk chemotherapy and RCRA drug waste. Although the use is not official, the terms “bulk” chemotherapy and RCRA drug waste have been used to differentiate containers that have held either (1) RCRA-listed or characteristic hazardous waste or (2) any chemotherapy drugs that are not RCRA empty or any materials from chemotherapy or hazardous waste drug spill cleanups. These wastes should be managed as hazardous waste.

Dual infectious-hazardous waste. If a situation arises where a syringe with a needle containing a listed chemotherapy drug cannot be used, it should be managed as a “dual” waste. A black needlebox labeled as both a hazardous and biohazardous waste should be used for containment. The contract with the hazardous waste disposal company should have this waste stream listed on the waste profile. The cost of this waste stream is typically higher than others, so it should be used only when needed.

Once hazardous waste has been identified, it must be collected, stored, and transported according to specific EPA and Department of Transportation (DOT) requirements.^{134,144} Properly labeled, leak-proof, and spill-proof containers of nonreactive plastic are required for areas where hazardous waste is generated. DOT Packing Group II containers are required for transportation.¹⁴⁵ Needles, scalpels, and waste contaminated with blood or other body fluids must not be mixed with hazardous waste.

Only individuals who meet OSHA-mandated hazardous waste awareness training may transport the hazardous waste containers from satellite accumulation areas in the pharmacy and nursing units to the storage accumulation sites.^{146,147} Hazardous waste must be properly manifested and transported by a federally permitted hazardous waste transporter to a federally permitted hazardous waste storage, treatment, and disposal facility.¹³¹ A licensed contractor may be hired to manage the hazardous waste program. The waste generator, however, may be held liable for mismanagement of hazardous waste. Investigation of a contractor, including verification of possession and type of license, should be completed and documented before a contractor is engaged.

In addition to determining what types of containers and what methods of sorting an organization will implement to properly manage both OSHA and EPA HD wastes, it is important to understand how generating hazardous waste impacts an organization as a whole. Additional departments need to be involved, such as laboratory and maintenance, which may also generate other types of RCRA hazardous wastes. EPA defines waste generation status by the total amount of hazardous waste generated per calendar month.¹⁴⁸ Small and large quantity generators are determined by the amount of P, U, and D-listed wastes that are discarded on a

monthly basis. The Hazardous Waste Generator Improvements Rule took effect federally on May 30, 2017.¹⁴⁸ States had until July 1, 2018, to adopt it, or until July 1, 2019, if legislation is required.¹⁴⁸ The rule changes the name of Conditionally Exempt Small Quantity Generators (CESQGs) to Very Small Quantity Generators (VSQGs). Waste management requirements are more stringent for large quantity generators (LQGs) than for small quantity generators (SQGs) and VSQGs.¹⁴⁹ The removal of epinephrine salts and medicinal nitroglycerin from the P-list is a tremendous benefit to healthcare facilities, since only 1 kg (2.2 lb) of P-listed waste per calendar month causes the organization to become an LQG.

In the past, healthcare facilities had to count the weight of the containers that held P-listed waste toward their generator status. In a 2011 memo, EPA provided additional options, including counting only the residue of the waste.¹⁴⁹ Since most of the P-listed waste containers are warfarin stock bottles, warfarin unit-dose blister packs, or nicotine wrappers, hospitals can use the residue calculation in the memo to document that their P-listed waste does not exceed 1 kg in a calendar month or 1 kg of stored P-listed waste. This practice may enable the facility to remain a VSQG or SQG, depending on the volume of other hazardous waste generated. If an organization is documenting P-listed residues only and total hazardous waste generation per month (not just pharmacy waste) is below 100 kg, it is a VSQG; if the total is 100-1000 kg, it is an SQG. Again, some states have not accepted this option, so state regulations must be consulted.

On September 25, 2015, EPA published its Proposed Rule: Management Standards for Hazardous Waste Pharmaceuticals.¹⁵⁰ When the final version of the rule is published, it will be important for organizations to review and modify their programs accordingly, as the proposed

rule contained very significant hazardous pharmaceutical waste management changes, many of them beneficial to healthcare facilities.

Medical Screening and Surveillance; Alternative Duty

Many drugs described in this document as hazardous are acutely toxic or are known or suspected human carcinogens; many more cause adverse reproductive outcomes.⁵⁵ Decades of literature show that HD contamination in the healthcare work environment is absorbed into healthcare workers.^{6,9,10-12,15,19} Marker HDs have been measured in the urine of workers who routinely handle HDs during the course of patient care,^{10,21, 46, 48, 49} and HD levels have also been found in the urine of workers not directly responsible for HD compounding or administration.²¹ This continued worker exposure has prompted many groups to advocate that healthcare workers tasked with handling HDs be identified and enrolled in medical screening programs before job placement and periodically during employment, and that they be maintained in a systematic medical surveillance program.^{6,13,14,27,110,120}

Medical screening and surveillance should be part of the comprehensive safety program for controlling workplace exposure to HDs, which must include engineering controls, training, work practices, and PPE. Such safety programs must be able to identify potentially exposed workers and those who might be at higher risk of adverse health effects due to this exposure. Guidance on medical surveillance programs is available from USP,⁸ OSHA,¹⁴ and NIOSH.¹⁵¹

Because reproductive risks have been associated with exposure to HDs, alternative duty (work assignments that do not involve handling HDs) should be offered to individuals who are pregnant, breast-feeding, or attempting to conceive or father a child.^{14,28} Employees' physicians

should be involved in making these determinations. Guidance on alternative duty is available from NIOSH.²⁸

All workers who handle HDs should be routinely monitored in a medical surveillance program.^{6,8,14,28,110} Medical surveillance involves the collection and interpretation of data for the purpose of detecting changes in the health status of working populations. Medical surveillance programs involve assessment and documentation of symptom complaints, physical findings, and laboratory values (such as a blood count) to determine whether there is a deviation from the expected norms. NIOSH encourages employees who handle HDs to participate in medical surveillance programs that are provided in the workplace.⁶ Limited resources may preclude the implementation of a comprehensive medical surveillance program for healthcare workers who are exposed to HDs. Workers handling HDs are encouraged to inform their personal healthcare providers of their occupation and possible HD exposure when obtaining routine medical care.⁶

Robotics

Robotics may be defined as mechanical devices that perform programmed, complex, and repetitive manipulations which mimic human behavior without continuous input from an operator. Robotic i.v. automation presents an opportunity for improving safety and efficiency in the compounding process by increasing accuracy and consistency for patients and reducing HD direct exposure for compounding staff.¹⁵² There are currently a number of robots and automated devices that are marketed for sterile HDs, and manufacturers should provide evidence-based data to support the use of any of these devices in compounding sterile HD

doses to provide patient safety and worker safety. There may also be legal requirements when using these devices in a pharmacy licensed through a state board of pharmacy, and these devices must also meet provisions of USP Chapter 797 when used for sterile compounding.^{7,153}

Studies have examined the accuracy of robotic devices compounding HDs for patient safety but did not include environmental contamination or worker safety considerations.^{154,155} Limited studies have been published examining the ability for robotics to reduce HD surface contamination during sterile compounding or to impact the safety of healthcare workers interacting with the robot during HD compounding. One study reported on observed work practices where the robot was found to produce a significant reduction in the number of potentially harmful staff safety events during compounding; however, no marker of exposure of staff was used during the study and neither robot cleaning nor waste disposal tasks were addressed.¹⁵⁶

Environmental contamination has been evaluated by wipe sampling for cyclophosphamide during robotic compounding by different manufacturer's robots. In the first study, cyclophosphamide was measured on work surfaces, in air samples, and in urine samples of workers.¹⁵⁷ Wipe samples of the subjects' hands was also done. Cyclophosphamide was detected on most surfaces inside the robot in small amounts, and the outer glove had the most contamination. The vials and ports of the i.v. bags where cyclophosphamide was injected had higher and more consistent contamination. No cyclophosphamide was detected on the personal air samplers or in the 14 urine samples of the two technicians. Although the contamination detected in the robot was low, the study identified work practices that needed

improvement, such as cleaning HD vials before placing into the robot, which may have resulted in cyclophosphamide transfer to gloves and final products.

In a second study, wipe samples were used to compare measured cyclophosphamide surface contamination in a BSC and robot after similar compounding over a 4-day period.¹⁵⁸ The detection rate for cyclophosphamide contamination was 70% of surface samples in the BSC versus 15% in the robot. Overall, cyclophosphamide contamination was quite low for both settings compared to that found in the literature.

These studies demonstrate that robotic HD compounders are dependent on work practices surrounding the actual compounding to achieve the lowest levels of contamination and the best protection for workers and the environment. Additional research is needed to evaluate the place of robotic HD compounders in patient and worker safety. Information about robotics in sterile compounding is available from ASHP.¹⁵⁹

Environment Sampling for HDs

Surface wipe sampling of healthcare settings for HD contamination is advocated as a means of environmental quality and control.^{6,8} Surface wipe sampling should be done routinely, first to determine a benchmark of contamination and then to monitor the effectiveness of safe handling programs. As no acceptable levels of HD surface contamination have been determined by any regulatory agency, surface wipe sampling should determine an operational baseline of at least several marker HDs from which a facility action level may be determined. Surface wipe sampling provides a way to determine the efficacy of HD handling equipment, ancillary devices, work practices, cleaning methods, and disposal, and is currently the method of choice to

determine surface contamination of the workplace with these drugs.¹⁶⁰ Wipe sampling should also be done if a lapse in the safe handling program occurs which may result in an excursion beyond a predetermined action level of HD surface contamination.^{6,8,161, 162}

Since it has been postulated that dermal uptake is the most likely route of occupational exposure to most HDs in healthcare settings, especially low-molecular-weight antineoplastic drugs, surface wipe sampling is a useful tool to evaluate contamination of the healthcare facility with HDs.^{48, 79} Wipe sampling methodology can be used for most classes of drugs. Published studies have focused on several sentinel antineoplastic drugs, most commonly cyclophosphamide, ifosfamide, 5-fluorouracil, methotrexate, and doxorubicin, although others are reported in the literature.⁹ As analytical methods become more sophisticated, more drugs can be analyzed simultaneously.

No standards exist for acceptable or allowable surface concentrations for HDs in the healthcare setting. Surface contamination levels for cyclophosphamide in early studies led USP to describe a 1ng/cm² action level for cyclophosphamide, above which drug uptake was believed to occur. More recent studies looking at a large number of samples done with standardized sampling and assay techniques have proposed hygienic guidance values (HGVs) for surface wipe sampling that are based on reporting 50th and 75th percentiles¹⁶¹ or 90th percentiles^{108,162} of samples. HGVs are not based on endpoints of either HD uptake by workers or on any measurable health effect. The Monitoring-Effect Study of Wipe Sampling in Pharmacies (MEWIP) method conducted in 130 German pharmacies looked at surface contamination with cyclophosphamide, docetaxel, etoposide, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate, and paclitaxel.¹⁰⁸ Based on the 90th percentile of the contamination

values, they recommend a substance-independent performance-based guidance value of 0.1 ng/cm² as the action level.¹⁰⁸ This is significantly more stringent than USP's observation.⁸ A review of studies with concurrent surface wipe sampling and urine monitoring for sentinel HDs noted that no statistically significant correlation was found between the two types of studies.¹⁶³ In the author's synthesis of results, he notes that none of the reviewed studies found detectable HDs in the urine for median surface levels below 0.01 ng/cm².¹⁶³ This value, as the others, is not based on endpoints of any measurable health effect.

Guidance values and action levels are all dependent on the methods used for wipe sampling and analytical assays, which have varied greatly in studies.⁹ The basic methodology that should be common to all protocols for wipe sampling was reviewed by Connor et al.¹⁶⁰ They stressed that proper validation of the sampling method is critical to obtaining reproducible results and being able to compare results across studies. USP notes there are currently no certifying agencies for vendors of wipe sample kits.⁸ Therefore, those purchasing or specifying the selection of a kit must be responsible for verifying its effectiveness. Factors to consider when selecting a wipe sampling kit or a laboratory to perform the analysis include validated sampling and analytical methods, extraction efficiency of drug from surface material, recovery of drug from sampling material, LOD, limit of quantification, and the qualifications and certifications of the laboratory.¹⁶⁰

No regulations or standards exist for allowable or acceptable HD surface concentrations in healthcare settings and many questions remain about the potential health risks associated with exposure to existing levels of environmental surface contamination. However, prudent

practice dictates that levels of HD surface contamination should be reduced to as low as reasonably achievable.^{15,110}

Conclusion

These guidelines represent the recommendations of many groups and individuals who have worked diligently over decades to reduce the potential of harmful effects on healthcare workers exposed to HDs. No set of guidelines on this topic, however comprehensive, can address all the needs of every healthcare facility. Healthcare professionals are encouraged to rely on their professional judgment, experience, and common sense in applying these recommendations to their unique circumstances and to take into account evolving federal, state, and local regulations, as well as the requirements of appropriate accrediting institutions. As additional research is needed in this area, healthcare workers must act as their own advocates and encourage studies that look at adverse health outcomes as well as practice standards that improve worker safety.

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Glossary

Appendix A—Recommendations for Use of Class II Biological Safety Cabinets (BSCs)

1. Use of a Class II BSC must be accompanied by a stringent program of work practices, including training, demonstrated competence, contamination reduction, and decontamination when used for compounding sterile and nonsterile HDs.
2. The Class II BSC has an 8-10 inch opening in the front where drugs and supplies are placed into the cabinet and whereby the compounder accesses the cabinet. Studies show that this opening is a source of HD contamination transfer to the environment. Care must be taken to restrict unnecessary movements in and out of the cabinet.
3. A Class II BSC used for sterile HD compounding must provide ISO Class 5 or better air quality and unidirectional airflow and be externally vented.
4. A Class II BSC used for nonsterile compounding must meet the USP Chapter 800 requirements for all containment primary engineering controls (C-PECs).⁸ It must be externally vented (preferred) or have redundant HEPA filters in series as an exhaust. Class I BSCs and containment ventilated enclosures (CVEs) are also acceptable C-PECs for nonsterile compounding.
5. The Class II BSC (as for all C-PECs) must be located in an externally vented, physically separate, negative pressure containment secondary engineering control (C-SEC) with appropriate air changes per hour (ACPH) to be used for compounding sterile and nonsterile HDs.
6. The C-SEC may be either an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified containment segregated compounding area (C-SCA).
7. Class II BSCs (as for all C-PECs) used in a facility that compounds both sterile and nonsterile HDs must be placed in separate rooms unless all the USP Chapter 800

- requirements for placement in the same room are met.
8. The Class II BSC (as for all C-PECs) must run continuously if it supplies some or all of the negative pressure in the C-SEC or if it is used to compound sterile HDs.
 9. A plastic-backed preparation mat that does not interfere with airflow to the front or back air grilles should be placed on the work surface of the Class II BSC. The mat must be changed routinely in batch compounding and immediately if a spill occurs.
 10. Appropriate chemotherapy personal protective equipment (PPE) must be worn when compounding or cleaning a Class II BSC. For sterile compounding, PPE must be donned per USP Chapter 797 instructions.⁷
 11. The Class II BSC must be decontaminated and disinfected prior to sterile compounding of HDs and routinely during batch compounding.
 12. For sterile compounding, reduce the bio-burden in the Class II BSC by wiping down supplies with an appropriate disinfectant before placing them in the cabinet.
 13. Reduce the HD contamination burden in the Class II BSC by wiping down HD vials with a decontaminant such as 0.5% sodium hypochlorite wipers⁷⁶ then with a disinfectant such as sterile 70% isopropyl alcohol before placing them in the cabinet.
 14. Consider using an FDA ONB-cleared closed system drug-transfer device (CSTD) while compounding HDs in a Class II BSC. Studies document a decrease in drug contaminants inside a Class II BSC when some such devices are used.^{6,8}
 15. Contain supply and drug waste in the Class II BSC in an appropriate waste bag or hard plastic container. Do not discard waste during operations in the Class II BSC, as entering and exiting the cabinet is a significant source of HD contamination transfer.
 16. Once HD compounding is complete, wipe down the dose(s), then label and transfer to clean transport bags, wearing noncontaminated gloves.
 17. Decontaminate the Class II BSC after completing HD compounding.
 18. Remove PPE according to SOPs and P&Ps and discard in an appropriate waste container.
 19. Wash hands thoroughly with soap and water.

Appendix B – Recommendations for Use of Class III BSCs and Compounding Aseptic Containment Isolators (CACIs)

1. Use of a Class III BSC or CACI must be accompanied by a stringent program of work practices, including training, demonstrated competence, contamination reduction, and decontamination when used for compounding sterile and nonsterile HDs.
2. A Class III BSC or CACI used for sterile HD compounding must provide ISO Class 5 or better air quality and unidirectional airflow in the main work chamber and be externally vented.
3. A Class III BSC or CACI must achieve containment at all times during the operation of the cabinet and during the transfer process from the antechamber (compounding isolator pass-through) to the main work chamber and in reverse.
4. A Class III BSC or CACI used for nonsterile compounding must meet the USP Chapter 800 requirements for all C-PECs.⁸ It must be externally vented (preferred) or have redundant HEPA filters in series as an exhaust.

5. The Class III BSC or CACI (as for all C-PECs) must be located in an externally vented, physically separate, negative-pressure C-SEC with appropriate ACPH to be used for compounding sterile and nonsterile HDs.
6. The C-SEC may be either an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified containment segregated compounding area (C-SCA).
7. Class III BSCs or CACIs (as for all C-PECs) used in a facility that compounds both sterile and nonsterile HDs must be placed in separate rooms unless all the USP Chapter 800 requirements for placement in the same room are met.
8. The Class III BSC or CACI (as for all C-PECs) must run continuously if it supplies some or all of the negative pressure in the C-SEC or if it is used to compound sterile HDs.
9. A plastic-backed preparation mat that does not interfere with airflow through the cabinet may be placed on the work surface of the Class III BSC or CACI. The mat must be changed routinely during compounding and immediately if a spill occurs.
10. A Class III BSC and CACI have sleeves and a fixed glove assembly or a gauntlet to access the main work chamber in the cabinet. Always inspect the condition of the sleeves and gauntlet as well as disposable gloves to ensure they are intact and not damaged. The sleeves and/or gauntlet must be decontaminated before and after HD compounding and disinfected prior to sterile compounding.
11. The decontamination and disinfecting process must be done in such a manner that surface contamination is contained in both the main chamber and antechamber (compounding isolator pass-through).
12. Gloves or gauntlets must not be replaced before completing appropriate decontamination and disinfecting of the cabinet. Use the device manufacturer's recommendations for changing gloves without breaking the HD containment.
13. Sterile gloves must be donned over the gauntlet or fixed glove before compounding sterile HDs (see glove section for additional details). In a negative pressure cabinet, the additional glove may require being taped to the fixed glove to avoid risking its being dislodged.
14. Appropriate chemotherapy PPE must be worn when compounding or cleaning a Class III BSC or CACI. There is no exemption from the requirement for wearing a chemotherapy gown when compounding in a Class III BSC or CACI. For sterile compounding, don PPE per USP Chapter 797 instructions.⁷ Sterile gloves tested to ASTM Standard D-6978 for chemotherapy gloves must be available near the cabinet to allow placement of the gloves into the antechamber to affix to the fixed glove assembly.
15. The Class III BSC or CACI must be decontaminated and disinfected prior to sterile compounding of HDs and routinely during batch compounding.
16. For sterile compounding, reduce the bio-burden in the Class III BSC or CACI by wiping down supplies with an appropriate disinfectant before placing them in the cabinet antechamber.
17. Reduce the HD contamination burden in the Class III BSC or CACI by wiping down HD vials with a decontaminant such as 0.5% sodium hypochlorite wipers⁷⁶ then with a

- disinfectant such as sterile 70% isopropyl alcohol before placing them in the cabinet antechamber.
18. Consider using an FDA ONB-cleared CSTD while compounding HDs in a Class III BSC or CACI. Studies document a decrease in drug contaminants inside a C-PEC when some such devices are used.^{6,8}
 19. Once HD compounding is complete, wipe down the outer glove and the dose(s), then label and transfer to the antechamber. Final doses should be placed in clean transport bags in the antechamber by someone wearing clean, tested chemotherapy gloves.
 20. Contain supply and drug waste in the Class III BSC or CACI in an appropriate waste bag or hard plastic container. Remove and contain the outer glove with other HD waste. Transfer the contained waste into the antechamber for removal and disposal. Alternatively, use the waste containers attached to the cabinet, if available.
 21. Decontaminate the Class III BSC or CACI after completing HD compounding.
 22. Remove PPE according to SOPs and P&Ps and discard in appropriate waste container.
 23. Wash hands thoroughly with soap and water.

Appendix C—Recommendations for Use of Gloves

1. Two pairs of ASTM D6978-tested gloves are required for compounding sterile and nonsterile HDs, for the administration of HDs, and for cleanup of HD spills.
2. Chemotherapy gloves should be worn for handling all HDs, including non-antineoplastics, and for reproductive-risk-only HDs.
3. Double gloves should be worn during any handling of HD shipping cartons or drug vials and handling of HD waste or waste from patients recently treated with HDs.
4. Select powder-free, high-quality gloves made of latex, nitrile, polyurethane, neoprene, or other materials that meet ASTM D6978 for chemotherapy gloves.
5. Inspect gloves for visible defects.
6. For sterile HD compounding, the outer glove must be sterile.
7. Sanitize gloves with sterile 70% isopropyl alcohol or other appropriate disinfectant before performing any aseptic compounding activity. Wipe gloves using a saturated wipe, never spray.
8. Change gloves every 30 minutes during compounding or immediately when damaged or contaminated, unless otherwise recommended by the manufacturer's documentation.
9. Remove outer gloves after wiping down final preparation but before labeling or removing the preparation from the C-PEC.
10. Outer gloves must be placed in a containment bag while in the C-PEC.
11. In a C-PEC with fixed gloves and sleeves, these must be surface cleaned after compounding is completed to avoid spreading HD contamination to other surfaces.
12. Clean gloves (e.g., the clean inner gloves) should be used to surface decontaminate the final preparation, place the label onto the final preparation, and place the preparation into the antechamber and transport bag.
13. Wear fresh gloves to complete the final check, place preparation into a clean transport bag, and remove the bag from the antechamber.

14. Remove gloves with care to avoid contamination. Specific procedures for removal must be established and followed.
15. Outer gloves should be removed and contained inside the C-PEC.
16. Change gloves after administering an HD dose or when leaving the immediate administration area.
17. Dispose of contaminated gloves as contaminated waste.
18. Wash hands with soap and water after removing gloves.

Appendix D—Recommendations for Use of Gowns

1. Gowns should be worn during compounding, during administration, when handling waste from patients recently treated with HDs, and when cleaning up spills of HDs.
2. Select disposable gowns of material tested to be protective against the HDs to be used.
3. 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 them every 2–3 hours or immediately after a spill or splash.
4. Remove gowns with care to avoid spreading contamination. Specific procedures for removal must be established and followed.^{7,8}
5. To avoid spreading HD contamination and exposing other healthcare workers, gowns worn in HD handling areas must not be worn to other areas.
6. Dispose of gowns immediately upon removal.
7. Contain and dispose of contaminated gowns as trace chemotherapy waste.
8. Wash hands after removing and disposing of gowns.

Appendix E—Recommendations for Working in Any Containment Primary Engineering

Controls (C-PECs)

1. The C-PEC must be appropriately vented to the outside. Check all gauges and alarms prior to using a C-PEC for compounding HDs.
2. Select the appropriate C-PEC for the type of HD compounding (sterile or nonsterile).
3. PPE appropriate to the C-PEC must be worn when compounding HDs in a C-PEC.
4. The use of a C-PEC must be accompanied by a stringent program of work practices, including operator training and demonstrated competence, contamination reduction, and decontamination.
5. Decontaminate the C-PEC prior to beginning HD compounding at the beginning of the day and per the established decontamination schedule. If rinsing is required, use sterile water for irrigation to remove the cleaning agent.
6. Disinfect the C-PEC with sterile 70% isopropyl alcohol before beginning sterile HD compounding and routinely during batch compounding. Use sterile wipers to apply the disinfectant. Do not spray anything into a C-PEC used for HD compounding to avoid aerosolizing or transferring HD residue.

7. Do not place unnecessary items in the work area of the C-PEC, where HD contamination from compounding may settle on them.
8. Do not crowd the C-PEC.
9. Gather all needed supplies before beginning compounding. Avoid exiting and re-entering the work area of the C-PEC.
10. A plastic-backed preparation mat that does not interfere with airflow through the C-PEC may be placed on the work surface of the direct compounding area (DCA). The mat must be changed routinely during compounding and immediately if a spill occurs.
11. Appropriate handling of the preparation in the C-PEC, including wiping with sterile 70% isopropyl alcohol or another appropriate disinfectant, is necessary for sterile compounding.
12. Reduce the HD contamination burden in the C-PEC by wiping down HD vials before placing them in the C-PEC.
13. To avoid inadvertent contamination of the outside surface, transport bags must never be placed in the C-PEC work area during compounding.
14. Final preparations should be surface decontaminated within the C-PEC and placed into the transport bags, wearing clean gloves, taking care not to contaminate the outside of the transport bag.
15. Decontaminate the work surface of the C-PEC before and after compounding per the manufacturer's recommendations or with detergent, sodium hypochlorite solution, and neutralizer, or another tested decontaminating cleaner.
16. Decontaminate all surfaces of the C-PEC at the end of the batch, day, or shift, as appropriate to the workflow according to facility policy. Typically, a C-PEC in use 24 hours a day would require decontamination two or three times daily. Disinfect the C-PEC before compounding a dose or batch of sterile HDs with sterile 70% isopropyl alcohol.
17. Wipe down the outside of the Class II BSC front opening and the floor in front of the BSC with detergent, sodium hypochlorite solution, and neutralizer, or another tested decontaminating cleaner, at least daily.
18. Wipe down the inside and outside of the antechamber door of the Class III BSC or CACI at least daily and the handle of the antechamber frequently with detergent, sodium hypochlorite solution, and neutralizer, or another tested decontaminating cleaner.
19. Seal and then decontaminate surfaces of waste and sharps containers before removing from the C-PEC.

Appendix F—Recommendations for Compounding and Handling Nonsterile HD Dosage Forms

1. HDs should be labeled or otherwise identified as such to prevent improper handling.
2. Tablet and capsule forms of HDs should not be placed in automated counting machines, which subject them to stress and may introduce powdered contaminants into the work area.
3. During routine handling of nonsterile HDs and contaminated equipment, workers should wear two pairs of gloves that meet ASTM D6978 requirements.¹⁰⁰

4. Counting and pouring of HDs should be done carefully, and clean equipment should be dedicated for use with these drugs.
5. Contaminated equipment should be cleaned initially with gauze saturated with sterile water; further cleaned with detergent, sodium hypochlorite solution, and neutralizer; and then rinsed. The gauze and rinse should be contained and disposed of as contaminated waste.
6. Crushing tablets or opening capsules should be avoided; liquid formulations should be used whenever possible.
7. During the compounding of HDs (e.g., crushing, dissolving, or preparing a solution or an ointment), workers should wear nonpermeable gowns and double gloves. Compounding should take place in a ventilated cabinet.
8. Compounding nonsterile forms of HDs in equipment designated for sterile products must be undertaken with care. Appropriate containment, deactivation, and disinfection techniques must be utilized.
9. HDs should be dispensed in the final dose and form whenever possible. Unit-of-use containers for oral liquids have not been tested for containment properties. Most exhibit some spillage during preparation or use. Caution must be exercised when using these devices.
10. Bulk containers of liquid HDs, as well as specially packaged commercial HDs, must be handled carefully to avoid spills. These containers should be dispensed and maintained in sealable plastic bags to contain any inadvertent contamination.
11. Disposal of unused or unusable non-injectable dosage forms of HDs should be performed in the same manner as for hazardous injectable dosage forms and waste.

Appendix G—Recommendations for Reducing Exposure to HDs During Administration in All Practice Settings^{110, 120}

Intravenous administration

1. Only trained and certified staff may administer HDs.
2. Appropriate PPE must be worn when administering HDs.^{8,55}
3. The use of gloves, gown, and face shield (as needed for splashing) is required.
4. Gloves for handling HDs must be tested to and meet ASTM D6978 for chemotherapy gloves.^{8,100}
5. Two pairs of tested chemotherapy gloves are required for administering injectable antineoplastic HDs.⁸
6. Gather all necessary equipment and supplies, including PPE.
7. Closed system drug-transfer devices (CSTDs) are required when the dosage form allows.
8. Use needleless systems whenever possible.
9. Use Luer-Lok fittings for all needleless systems, syringes, needles, ancillary devices, infusion tubing, and pumps. If a CSTD cannot be used, position gauze pads to catch leaks from needleless and other devices that may leak at connection points.
10. Designate a workplace for handling HDs.
11. Have a spill kit and HD waste container readily available.

12. Procedure for gowning and gloving: Wash hands, don first pair of gloves, don gown and face shield, and then don second pair of gloves. Gloves should extend beyond the elastic or knit cuff of the gown. Double-gloving requires one glove to be worn under the cuff of the gown and the second glove over the cuff.
13. Always work below eye level.
14. Visually examine HD dose while it is still contained in the transport bag.
15. If HD dose appears intact, remove it from the transport bag while wearing gloves.
16. Place a plastic-backed absorbent pad under the administration site to absorb leaks and prevent drug contact with the patient's skin.
17. If priming occurs at the administration site, prime i.v. tubing with an i.v. solution that does not contain HDs or prime using the backflow method.
18. Use the transport bag as a containment bag for HD containers and i.v. sets and all materials contaminated with HDs.
19. Discard HD i.v. containers with the administration sets attached; do not remove the set.
20. Wash surfaces that come into contact with HDs with detergent, sodium hypochlorite solution, and neutralizer, if appropriate.
21. Wearing gloves, contain and dispose of materials contaminated with HDs.
22. To remove PPE, carefully begin with outer gloves. Still wearing the inner gloves, remove remaining PPE from least to most contaminated and discard as trace waste.
23. HD waste containers must be sufficiently large to hold all discarded material, including PPE.
24. Do not push or force materials contaminated with HDs into the waste container.
25. Carefully remove, contain, and discard gloves.
26. Wash hands thoroughly after removing gloves.

Intramuscular or subcutaneous administration

1. The use of double gloves and gown is required.
2. Gather all necessary equipment and supplies, including PPE.
3. Use Luer-Lok safety needles or retracting needles or shields.
4. Syringes should have Luer-Lok connections and be less than three-fourths full.
5. Designate a workplace for handling HDs.
6. Have a spill kit and HD waste container readily available.
7. Procedure for gloving: wash hands, then don double gloves (one pair under gown, one over).
8. Always work below eye level.
9. Visually examine HD dose while still contained in transport bag.
10. If HD dose appears intact, remove it from the transport bag.
11. Remove the syringe cap and connect appropriate safety needle.
12. Do not expel air from syringe or prime the safety needle.
13. After administration, discard HD syringes (with the safety needle attached) directly into an HD waste container.
14. Wearing gloves, contain and dispose of materials contaminated with HDs.

15. Do not push or force materials contaminated with HDs into the HD waste container.
16. Carefully remove, contain, and discard gloves.
17. Wash hands thoroughly after removing gloves.

Oral administration

1. Double gloves are required, as is a face shield if there is a potential for spraying, aerosolization, or splashing.
2. Workers should be aware that tablets or capsules may be coated with a dust of residual HD that could be inhaled, absorbed through the skin, ingested, or spread to other locations, and that liquid formulations may be aerosolized or spilled.
3. No crushing or compounding of oral HDs may be done in an unprotected environment.
4. Gather all necessary equipment and supplies, including PPE.
5. Designate a workplace for handling HDs.
6. Have a spill kit and HD waste container readily available.
7. Procedure for gloving: wash hands and don double gloves.
8. Always work below eye level.
9. Visually examine HD dose while it is still contained in transport bag.
10. If HD dose appears intact, remove it from the transport bag.
11. Place a plastic-backed absorbent pad on the work area, if necessary, to contain any spills.
12. After administration, wearing double gloves, contain and dispose of materials contaminated with HDs into the HD waste container.
13. Do not push or force materials contaminated with HDs into the HD waste container.
14. Carefully remove, contain, and discard gloves.
15. Wash hands thoroughly after removing gloves.

Appendix H—Recommended Contents of HD Spill Kit

1. Sufficient supplies to absorb a spill of about 1000 mL (volume of one i.v. bag or bottle).
2. Appropriate PPE to protect the worker during cleanup, including two pairs of disposable gloves (one outer pair of heavy utility gloves and one pair of inner gloves tested to ASTM D6978).
3. Disposable HD-resistant gown or coverall tested against HD permeability.
4. Disposable HD-resistant shoe covers.
5. Chemical splash goggles.
6. Protective face shield to be used with goggles (for full range of splash protection).
7. NIOSH-approved disposable respirator.*
8. Absorbent, plastic-backed sheets or spill pads.
9. Disposable toweling.
10. At least two sealable, thick plastic hazardous waste disposal bags (prelabeled with an appropriate warning label).
11. One disposable scoop for collecting glass fragments.

12. One puncture-resistant container for glass fragments.
 13. An approved cartridge respirator must be available for use with contents of spill kit.*
- *Respirators may only be used by workers who have been trained and fit-tested to the appropriate respirator.

Appendix I—Recommendations for Spill Cleanup Procedure

General

1. Assess the size and scope of the spill. Call for trained help, if necessary.
2. Spills that cannot be contained by two spill kits may require outside assistance.
3. Post signs to limit access to spill area.
4. Obtain spill kit and respirator.
5. Don appropriate PPE, including inner and outer gloves and respirator.
6. Once fully garbed, contain spill using spill kit.
7. Carefully remove any broken glass fragments and place them in a puncture-resistant container.
8. Absorb liquids with spill pads.
9. Absorb powder with damp disposable pads or soft toweling.
10. Spill cleanup should proceed progressively from areas of lesser to greater contamination.
11. Completely remove and place all contaminated material in the disposal bags.
12. Rinse the area with water and then clean with detergent, sodium hypochlorite solution, and neutralizer or other validated decontamination solution.
13. Rinse the area several times and place all materials used for containment and cleanup in disposal bags. Seal bags and place them in the appropriate final container for disposal as RCRA hazardous waste.
14. Carefully remove all PPE using the inner gloves. Place all disposable PPE into disposal bags. Seal bags and place them into the hazardous waste container (not trace-contaminated waste).
15. Remove inner gloves; contain in a small, sealable bag; and then place into the appropriate final container for disposal as hazardous waste.
16. Wash hands thoroughly with soap and water.
17. Once a spill has been initially decontaminated, have the area cleaned by housekeeping, janitorial staff, or environmental services.

Spills in a C-PEC

1. Spills occurring in a C-PEC should be cleaned up immediately.
2. Obtain a spill kit if the volume of the spill exceeds 30 mL or the contents of one drug vial or ampul.
3. Utility gloves (from spill kit) should be worn to remove broken glass in the C-PEC. Take care not to damage the sleeve or fixed-glove assembly in the Class III BSC or CACI.
4. Place glass fragments in the puncture-resistant HD waste container located in the C-PEC.
5. Thoroughly clean and decontaminate the C-PEC.

6. Clean and decontaminate the drain spillage trough located under the Class II BSC or similarly equipped Class III BSC or CACI.
7. If the spill results in liquid being introduced onto the HEPA filter or if powdered aerosol contaminates the “clean side” of the HEPA filter, use of the C-PEC should be suspended until the equipment has been decontaminated and the HEPA filter replaced.

Appendix J—OSHA-Recommended Steps for Immediate Treatment of Workers with Direct Skin or Eye Contact with HDs¹³³

1. Call for help, if needed.
2. Immediately remove contaminated clothing.
3. Flood affected eye with water or isotonic eyewash for at least 15 minutes.
4. Clean affected skin with soap (not a disinfectant cleanser) and water; rinse thoroughly.
5. Obtain medical attention.
6. Document exposure in employee’s medical record and medical surveillance log.
7. Supplies for emergency treatment (e.g., soap, eyewash, sterile saline for irrigation) should be immediately located in any area where HDs are stored, compounded, or administered.

Glossary

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a drug preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.⁸

Alternative duty: Performance of other tasks that do not include the direct handling of HDs.⁸

Antechamber: Chamber in a compounding isolator that leads to the main compounding chamber. The antechamber is used to load supplies and drugs into the isolator and unload final preparations and waste.

Ante-room: An ISO Class 7 or cleaner room where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The ante-room is the transition room between the unclassified area of the facility and the buffer room.⁸

Antineoplastic drug: A chemotherapeutic agent that controls or kills cancer cells. Drugs used in the treatment of cancer are cytotoxic but are generally more damaging to dividing cells than to resting cells.⁶

Aseptic: Free of living pathogenic organisms or infected materials.⁶

Assessment of risk: Evaluation of risk to determine alternative containment strategies and/or work practices.

Beyond-use date (BUD): The date or time beyond which a compounded preparation cannot be used and must be discarded (see USP Chapters 795 and 797).^{7,61} The date or time is determined from the date or time when the preparation was compounded.

Biological safety cabinet (BSC): Biological safety cabinets or biosafety cabinets are used as the primary means of containment for working safely with infectious microorganisms. Biosafety cabinets are designed to prevent biological exposure to personnel and the environment and may also protect experimental material from being contaminated when appropriate practices and procedures are followed. Class II BSCs have been adopted for use in compounding HDs as they protect the product, the worker, and the environment. Descriptions of the various classes and types of BSCs may be found in the Centers for Disease Control and Prevention Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th ed., Appendix A.⁸¹

Buffer room: A type of C-SEC under negative pressure that meets ISO Class 7 or better air quality where the C-PEC that generates and maintains an ISO Class 5 environment is physically located. Activities that occur in this area are limited to the preparation and staging of components and supplies used when compounding HDs.⁸

Chemotherapy drug: A chemical agent used to treat diseases. The term usually refers to a drug used to treat cancer.⁶

Chemotherapy glove: A medical glove that meets the ASTM Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs (D6978) or its successor.⁸

Chemotherapy waste: Discarded items such as gowns, gloves, masks, i.v. tubing, empty bags, empty drug vials, needles, and syringes used while preparing and administering antineoplastic agents.⁶

Classified space: An area that maintains an air cleanliness classification based on the International Organization for Standardization (ISO).⁸

Cleaning: The process of removing soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.⁸

Closed system: A device that does not exchange unfiltered air or contaminants with the adjacent environment.⁶

Closed-system drug-transfer device: 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.⁶

Compounded preparation: A nonsterile or sterile drug or nutrient preparation that is compounded in a licensed pharmacy or other healthcare-related facility in response to or anticipation of a prescription or a medication order from a licensed prescriber.⁸

Compounding aseptic containment isolator (CACI): A specific type of compounding aseptic isolator (CAI) that is designed for the compounding of sterile HDs. The CACI is designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment with unidirectional airflow for compounding sterile preparations.⁸

Compounding aseptic isolator (CAI): An isolator specifically designed for compounding sterile, non-hazardous pharmaceutical ingredients or preparations. The CAI is designed to maintain an aseptic compounding environment throughout the compounding and material transfer processes.⁸

Compounding personnel: Individuals who participate in the compounding process.⁸

Containment primary engineering control (C-PEC): A ventilated device designed and operated

to minimize worker and environmental exposures to HDs by controlling emissions of airborne contaminants through the following:

- The full or partial enclosure of a potential contaminant source.
- The use of airflow capture velocities to trap and remove airborne contaminants near their point of generation.
- The use of air pressure relationships that define the direction of airflow into the cabinet.
- The use of HEPA filtration on all potentially contaminated exhaust streams.⁸

Containment secondary engineering control (C-SEC): The room with fixed walls in which the C-PEC is placed. It incorporates specific design and operational parameters required to contain the potential hazard within the compounding room.⁸

Containment segregated compounding area (C-SCA): A type of C-SEC with nominal requirements for airflow and room pressurization as they pertain to HD compounding.⁸

Containment ventilated enclosure (CVE): A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through HEPA filtration and prevent their release into the work environment.⁸

Cytotoxic: A pharmacologic compound that is detrimental or destructive to cells within the body.⁶

Deactivation: Treating a chemical agent (such as an HD) with another chemical, heat, ultraviolet light, or another agent to create a less hazardous agent.⁶

Decontamination: Inactivation, neutralization, or removal of toxic agents, usually by chemical means.⁶ Surface decontamination may be accomplished by the transfer of HD contamination from the surface of a nondisposable item to disposable ones (e.g., wipes, gauze, towels).

Direct Compounding Area (DCA): A critical area within an ISO Class 5 primary engineering control (PEC) where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.⁷

Disinfecting: Removal of viable organism from surfaces using 70% isopropyl alcohol or other appropriate disinfectant prior to compounding of sterile HDs.

Don: To put on PPE.⁸

Engineering controls: Devices designed to eliminate or reduce worker exposures to chemical, biological, radiological, ergonomic, or physical hazards. Examples include laboratory fume hoods, glove bags, retracting syringe needles, sound-dampening materials to reduce noise levels, safety interlocks, and radiation shielding.⁶

EPA-registered disinfectant: Antimicrobial products registered with the Environmental

Protection Agency (EPA) for healthcare use against pathogens specified in the product labeling.⁸

Externally vented: Exhausted to the outside.⁸

Final dosage form: Any form of a medication that requires no further manipulation before administration.⁸

Genotoxic: Capable of damaging DNA and leading to mutations.⁶

Globally Harmonized System of Classification and Labeling of Chemicals (GHS): A system for standardizing and harmonizing the classification and labeling of chemicals.⁸

Goggles: Tight-fitting eye protection that completely covers the eyes, eye sockets, and facial area that immediately surrounds the eyes. Goggles provide protection from impact, dust, and splashes. Some goggles fit over corrective lenses.⁸

Hazardous drug (HD): Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or animals, genotoxicity, and new drugs that mimic existing HDs in structure or toxicity.⁶

Hazardous waste: Any waste that is an RCRA-listed hazardous waste [40 C.F.R. 261.30-.33] or that meets an RCRA characteristic of ignitability, corrosivity, reactivity, or toxicity as defined in 40 C.F.R. 261.21-.24.⁶

Healthcare settings: All hospitals, medical clinics, outpatient facilities, physicians' offices, retail pharmacies, and similar facilities dedicated to the care of patients.⁶

Healthcare workers: All workers who are involved in the care of patients. These include pharmacists, pharmacy technicians, nurses (registered nurses, licensed practical nurses, nurses' aides, etc.), physicians, home healthcare workers, and environmental services workers (housekeeping, laundry, and waste disposal).⁶

HEPA filter: Filter rated 99.97% efficient in capturing particles 0.3- μm in diameter.⁶

Horizontal-laminar-airflow hood (horizontal-laminar airflow clean bench): A device that protects the work product and the work area by supplying HEPA-filtered air to the rear of the cabinet and producing a horizontal flow across the work area and out toward the worker.⁶

Laboratory coat: A disposable or reusable open-front coat, usually made of cloth or other permeable material.⁶

Mutagenic: Capable of increasing the spontaneous mutation rate by causing changes in DNA.⁶

Negative-pressure room: A room that is maintained at a lower pressure than the adjacent areas; therefore the net flow of air is into the room.⁸

Pass-through: An enclosure with interlocking doors that is positioned between two spaces for the purpose of reducing particulate transfer while moving materials from one space to another. A pass-through serving negative-pressure rooms needs to be equipped with sealed doors.⁸ (Note: A pass-through located prior to the main chamber of a compounding isolator is an antechamber).

Personal protective equipment (PPE): Items such as gloves, gowns, respirators, goggles, and face shields that protect individual workers from hazardous physical or chemical exposures.⁶

Positive-pressure room: A room that is maintained at a higher pressure than the adjacent areas; therefore, the net flow of air is out of the room.⁸

Repackaging: The act of removing a product from its original primary container and placing it into another primary container, usually of smaller size.⁸

Respirator: A type of PPE that prevents harmful materials from entering the respiratory system, usually by filtering hazardous agents from workplace air. A surgical mask does not offer respiratory protection.⁶

Risk assessment: Characterization of potentially adverse health effects from human exposure to environmental or occupational hazards. Risk assessment can be divided into five major steps: hazard identification, dose–response assessment, exposure assessment, risk characterization, and risk communication.⁶

Safety data sheet (SDS): An informational document that provides written or printed material concerning a hazardous chemical (previously known as a Material Safety Data Sheet [MSDS]). The SDS is prepared in accordance with the HCS.⁸

Spill kit: A container of supplies, warning signage, and related materials used to contain the spill of an HD.⁸

Standard operating procedure (SOP): Written procedures describing operations, testing, sampling, interpretation of results, and corrective actions that relate to the operations that are taking place.⁸

Supplemental engineering control: An adjunct control (e.g., a CSTD) that may be used concurrently with primary and secondary engineering controls. Supplemental engineering controls offer additional levels of protection and may facilitate enhanced occupational protection, especially when handling HDs outside of primary and secondary engineering controls (e.g., during administration).⁸

Surface decontamination: Transfer of HD contamination from the surface of non-disposable items to disposable ones (e.g., wipes, gauze, towels). No procedures have been studied for surface decontamination of HD-contaminated surfaces. The use of gauze moistened with 70% isopropyl alcohol, sterile water, peroxide, or sodium hypochlorite solutions may be effective. The disposable item, once contaminated, must be contained and discarded as hazardous waste.

Unclassified space: A space not required to meet any air cleanliness classification based on the International Organization for Standardization (ISO).⁸

Ventilated cabinet: A type of engineering control designed for purposes of worker protection (as used in these guidelines). These devices are designed to minimize worker exposures by controlling emissions of airborne contaminants through (1) the full or partial enclosure of a potential contaminant source, (2) the use of airflow capture velocities to capture and remove airborne contaminants near their point of generation, and (3) the use of air pressure relationships that define the direction of airflow into the cabinet. Examples of ventilated cabinets include BSCs, containment isolators, and laboratory fume hoods.⁶

Table 1. Comparison of NIOSH and ASHP definitions of hazardous drugs.

NIOSH ⁶	ASHP ⁴
Carcinogenicity	Carcinogenicity in animal models, in the patient population, or both as reported by the International Agency for Research on Cancer
Teratogenicity or developmental toxicity ^a	Teratogenicity in animal studies or in treated patients
Reproductive toxicity ^a	Fertility impairment in animal studies or in treated patients
Organ toxicity at low doses ^a	Evidence of serious organ or other toxicity at low doses in animal models or treated patients
Genotoxicity ^b	Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems)
Structure and toxicity profile of new drugs that mimic existing drugs determined hazardous by the above criteria	

^aThe NIOSH definition contains the following explanation: "All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg/day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 micrograms/meter³ after applying appropriate uncertainty factors [Sargent and Kirk 1988; Nauman and Sargent 1997; Sargent et al. 2002]. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers."⁶

^bThe NIOSH definition contains the following explanation: "In evaluating mutagenicity for potentially hazardous drugs, responses from multiple test systems are needed before precautions can be required for handling such agents. The EPA evaluations include the type of cells affected and *in vitro* versus *in vivo* testing [51 Fed. Reg. 34006-34012 (1986)]."⁶

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