Third Edition

Safe Handling of Hazardous Drugs

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Contents

Abbreviations

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

Introduction

Key Points

- Hazardous drugs (HDs) are toxic to genes, reproductive organs, and other body systems.
- Healthcare workers (HCWs) often are not aware of all sources of exposure to HDs.
- Nurses need to identify risks in their work settings and change practices that put themselves and colleagues at risk.

Many oncology nurses have a daily responsibility for preparing and administering drugs used in the treatment of cancer. Many of these drugs are HDs because they alter DNA or affect other intracellular processes that interfere with cancer cell growth. HDs are toxic to genes, reproductive organs, and other body systems. For patients, the benefits of treatment generally outweigh the risks. For HCWs, though, there are no benefits, and HD exposure should be avoided.

Most oncology nurses acknowledge the adverse effects associated with occupational exposure to HDs (Polovich & Clark, 2012). However, they may not know that they are potentially exposed during routine handling. Numerous studies demonstrate that work areas where HDs are prepared and administered are commonly contaminated with the drugs, which then become a source of HCW exposure (Berruyer, Tanguay, Caron, Lefebvre, & Bussières, 2015; Chu, Hon, Danyluk, Chua, & Astrakianakis, 2012; Connor et al., 2010; Yoshida et al., 2011). The evidence for environmental contamination, the adverse health outcomes associated with occupational HD exposure, and the fact that eight million HCWs in the United States are potentially exposed (U.S. Bureau of Labor Statistics, 2015) reinforces the need for safe handling.

Guidelines for the safe handling of HDs have been available in the United States since 1986, but 30 years of attention to the issue have not yet solved the problem of occupational HD exposure. There is, however, a steadily increasing awareness of the need for safe handling of HDs among HCWs, professional organizations, regulatory bodies, and even some state legislators. Progress in the past five years is evidenced by publication of updated guidance from the Occupational Safety and Health Administration (OSHA, 2016), the National Institute for Occupational Safety and Health (NIOSH, 2016), and the Oncology Nursing Society (ONS; Polovich, Olsen, & LeFebvre, 2014). At the time of this writing, legislation that provides for HD safety currently exists in three states (California Legislative Information, 2013; North Carolina General Assembly, 2014; Washington State Department of Labor and Industries, n.d.) and is pending in others. Acceptance and implementation of HD safe handling precautions is increasing (Boiano, Steege, & Sweeney, 2014, 2015). The implementation of the U.S. Pharmacopeial Convention (USP) General Chapter 800 standards for HD safe handling (USP, 2016a) will represent an important step forward for nurses and other potentially exposed HCWs.

This manual is based on the recommendations of NIOSH, OSHA, ONS, the American Society of Health-System Pharmacists (ASHP), and USP. Its intent is to help to translate safe handling recommendations into practice for nurses who handle HDs in the delivery of care to patients. Nurse managers, nurse administrators, and nurses responsible for employee health and wellness also may find this content useful. Nurses are encouraged to critically examine their workplaces and work practices to identify activities that might result in HD exposure and to change practices that put themselves and their colleagues at risk.

In preparing the update to these guidelines, the authors searched the National Library of Medicine's PubMed database using the following search terms:

- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("pharmacists"[MeSH] OR "nurses"[MeSH] OR "healthcare workers"[All Fields]) AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("DNA damage" OR "chromosome aberration" OR "genotoxic" OR "cancer") AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("gloves" OR "gowns" OR "personal protective equipment" OR "PPE" OR "safe handling precautions" OR "closed system" OR "nurses" OR "pharmacist") AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND ("guidelines" OR "standards" OR "recommendations") AND ("humans"[MeSH Terms] AND English[lang])
- "Occupational exposure"[MeSH] AND ("antineoplastic agents"[MeSH] OR "chemotherapy"[All Fields] OR "hazardous drugs"[All Fields]) AND

"administration" AND ("intravenous" OR "oral" OR "intraperitoneal" OR "intrathecal" OR "intracavitary" OR "intraperitoneal" OR "intraocular" OR "topical") AND ("humans"[MeSH Terms] AND English[lang])

- ("Risk"[MeSH] OR "risk" OR "safety") AND ("antineoplastic protocols"[MeSH] OR "immunotherapy"[MeSH] OR "chemotherapy" OR "immunotherapy" OR "antineoplastic" OR "antineoplastic" OR "antibodies, monoclonal"[mh] OR "monoclonal antibody" OR "monoclonal antibodies" OR "adalimumab" OR "bevacizumab" OR "certolizumab" OR "cetuximab" OR "denosumab" OR "natalizumab" OR "omalizumab" OR "palivizumab" OR "ranibizumab" OR "trastuzumab" OR "ustekinumab" OR "muromonab" OR "rituximab" OR "infliximab" OR "single-chain antibodies") AND ("breast feeding"[MeSH] OR "breast feeding" OR "breastfeeding" OR "breast milk")
- ("Occupational exposure"[MeSH] OR "exposure" OR "personal protective equipment"[mh] OR "personal protective equipment" OR "PPE") AND ("health personnel"[MeSH] OR "healthcare workers" OR "health personnel" OR "nurses" OR "nurse"[tw] OR "pharmacist" OR "pharmacists") AND ("antineoplastic agents"[MeSH] OR "antineoplastic" OR "chemotherapy" OR "anticancer" OR "anti-cancer") AND ("epidemiologic studies"[MeSH] OR "case-control" OR "retrospective" OR "cohort" OR "follow-up study" OR "follow-up studies" OR "prospective" OR "controlled study" OR "controlled trial" OR "descriptive study" OR "descriptive studies" OR "urinary" OR "urine" OR "buccal mucosa" OR "DNA damage" OR "chromosomal abnormalities") AND "last 5 years"[PDat]

Articles were limited to those published in the English language in peer-reviewed journals from 2005 through 2015. Older publications considered classic references also were included.

Further searches of the medical literature also were conducted (based on initial findings, group feedback, and authors' experience) to identify other relevant materials. In addition to searching peer-reviewed publications, the authors searched websites of known domestic or international regulatory agencies and professional societies involved in generating relevant materials (e.g., reports, white papers, official announcements) related to HD topics. The authors sought to identify literature leading to evidence-based practices and quality measures developed by healthcare organizations or specialty societies. Websites of the following organizations were searched:

- ASHP: www.ashp.org
- NIOSH: www.cdc.gov/niosh
- ONS: www.ons.org
- OSHA: www.osha.gov

Findings derived from these searches were used to generate additional searches for guidelines published in the United States and abroad.

Definition of Hazardous Drugs

Key Points

- All drugs are assessed for hazardous characteristics.
- Investigational agents and those with inadequate information should be considered hazardous.
- Organizations are required to develop a list of HDs used in the facility.

HDs require careful handling by healthcare personnel and others who come into contact with them to minimize exposure and the associated adverse health effects and to reduce contamination of the workplace with drug residue. A universally accepted definition of HDs is essential so that clinicians recognize the drugs for which safe handling recommendations apply. Drugs are classified as hazardous when they possess any one of the following six characteristics (ASHP, 2006; NIOSH, 2004a):

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

The sixth characteristic in the definition of HDs was first published by NIOSH in 2004 and serves as a reminder that new drugs should be critically evaluated using existing information and extrapolating data from similar agents. Organizations should evaluate the hazardous potential of all drugs, approved and investigational, when they are first introduced into a facility (ASHP, 2006; NIOSH, 2016).

The determination that a drug is hazardous is based on the characteristics in the aforementioned definition and not the chemical class to which the drug belongs. NIOSH evaluates newly approved agents and compares known characteristics of the drugs to the criteria in the definition. Older drugs with new warnings also are reviewed in this manner. Reviewers use information from the official U.S. Food and Drug Administration (FDA)-approved prescribing information (www.accessdata.fda.gov/scripts/cder/daf/index.cfm), DailyMed (https://dailymed.nlm.nih.gov/dailymed/index.cfm), DrugBank (www.drugbank.ca), and drug-specific safety data sheets (SDSs) to determine if any drug should be classified as hazardous and added to the NIOSH list. The NIOSH review is hazard identification, not risk assessment. A full risk assessment requires a dose-response assessment of harm to human health, which is not available for most drugs, as it is for other chemicals. About half of the drugs listed as hazardous are antineoplastic agents, and the rest are non–antineoplastic agents. Rather than suggesting a different level of risk based on drug category, NIOSH recommends that if a drug "meets one or more of the criteria for hazardous drugs in the NIOSH definition, handle it as hazardous" (NIOSH, 2016, p. 5).

All investigational agents should be regarded as potentially hazardous until information establishing their safety becomes available. In the event that data provided to the principal investigator about an investigational agent are insufficient to make a decision, it is prudent to handle the agent as though it is hazardous (ASHP, 2006; NIOSH, 2016). ASHP (2006) specifies that all drugs should be considered hazardous if the information obtained about the drug is insufficient to make an informed decision as to whether it is hazardous. Certainly, healthcare providers must recognize that erring on the side of caution is essential to protecting workers' health and safety and the safety of the work environment.

The International Agency for Research on Cancer (IARC) is part of the World Health Organization (WHO). IARC classifies agents as carcinogens (see Table 1). This agency has evaluated more than 900 substances for their cancer-causing potential. The 2012 IARC publication *Review of Human Carcinogens* includes six volumes developed by separate work groups: Pharmaceuticals; Biological Agents; Arsenic, Metals, Fibres, and Dust; Radiation; Personal Habits and Household Exposures; and Chemical Agents and Related Occupations (IARC, 2012).

In 2015, IARC convened a separate work group to conduct a systematic review of the literature. The group agreed on 10 key characteristics exhibited by human carcinogens to determine cancer hazard risk (Smith et al., 2015). The intent of this approach was to establish a more objective method to assess whether an agent is a potential human carcinogen by reviewing mechanistic data, which was not previously available. The 10 characteristics include the ability of an agent to

1. Act as an electrophile either directly or after metabolic activation.
2. Be genotoxic.

3. Alter DNA repair or cause genomic instability.
4. Induce epigenetic alterations.
5. Induce oxidative stress.
6. Induce chronic inflammation.
7. Be immunosuppressive.
8. Modulate receptor-mediated effects.
9. Cause immortalization.
10. Alter cell proliferation, cell death, or nutrient supply.

A comprehensive list of all drugs currently considered hazardous does not exist in the literature. NIOSH reviews new drugs approximately every two years and lists drugs identified as hazardous (NIOSH, 2017). Given the large number of new drug approvals each year, the NIOSH list will never be complete; therefore, organizations must have a process for evaluating the drugs they use to determine whether they are hazardous. Table 1 provides resources that will aid

Table 1. Resources for Developing a List of Hazardous Drugs

Resource	Description
American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System	The AHFS Pharmacologic-Therapeutic Classification System is a widely accepted system for classification of drugs into categories based on mechanism of action. The system designates all antineoplastic agents as category 10; all category 10 drugs are hazardous.
International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans	This resource includes six volumes (A–F): Pharmaceuticals; Biological Agents; Arsenic, Metals, Fibres, and Dust; Radiation; Personal Habits and Household Exposures; and Chemical Agents and Related Occupations. • Group 1: The agent is carcinogenic to humans. • Group 2A: The agent is probably carcinogenic to humans. • Group 2B: The agent is possibly carcinogenic to humans. • Group 3: The agent is not classifiable as to its carcinogenicity to humans. • Group 4: The agent is probably not carcinogenic to humans.
Safety data sheets (SDSs)	SDSs are developed by manufacturers to describe the chemical properties of a product and communicate the hazards, including the following: • Identification and labeling • Composition • First aid measures • Fire-fighting measures • Accidental release measures • Handling and storage • Exposure controls/personal protection • Physical and chemical properties • Stability and reactivity • Toxicologic information • Ecologic information • Disposal considerations • Transport information • Regulatory information
U.S. Department of Health and Human Services National Toxicology Program Report on Carcinogens, 14th edition	Carcinogens listed in this report are classified as either known human carcinogens or reasonably anticipated to be human carcinogens. The report can be obtained at https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html.
National Institute for Occupational Safety and Health List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings	This publication lists drugs that should be handled as hazardous. The hazardous drug list was updated in 2016 and can be found at www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf.
Package inserts for specific pharmaceutical agents	Package inserts for all U.S. Food and Drug Administration–approved medications contain information to assist clinicians in determining whether a drug should be classified as hazardous, including the following: • Drug classification • Pregnancy category and reproductive toxicity • Organ toxicities • Secondary cancers that may develop with exposure • Drug warnings

Note. Based on information from American Society of Health-System Pharmacists, 2016; International Agency for Research on Cancer, 2012; National Institute for Occupational Safety and Health, 2016; U.S. Department of Health and Human Services National Toxicology Program, 2016.

clinicians in evaluating whether a drug should be handled as hazardous.

In 2014, NIOSH divided its list of HDs into three groups:

- **Group 1: Antineoplastic drugs.** All drugs in this group belong to the American Hospital Formulary Service (2016) classification 10:00 antineoplastic agents, except for one drug, bacillus Calmette-Guérin (BCG), which belongs to the vaccine class. At the time of this publication, group 1 includes the monoclonal antibodies brentuximab vedotin, gemtuzumab ozogamicin, and pertuzumab, as well as 19 small molecules, such as afatinib and axitinib.
- **Group 2: Nonantineoplastic drugs.** This group includes drugs from multiple classes, such as immunosuppressants and antivirals. Examples of nonantineoplastic HDs are mycophenolate mofetil, tacrolimus, conjugated estrogens, and ganciclovir (NIOSH, 2016).
- **Group 3: Drugs that primarily pose a reproductive risk to men and women.** This group includes alitretinoin, fluconazole, oxytocin, and others.

This grouping is not meant to suggest that a different level of risk exists based on the group but rather to assist in the development of a facility-specific list in organizations where antineoplastic agents are not used. NIOSH asserts that drugs meeting one or more of the criteria in the HD definition should be handled as hazardous (NIOSH, 2016).

USP General Chapter 800, which must be fully implemented by December 1, 2019, requires organizations to develop a list of HDs present in the facility (USP, 2016a). The organization-specific HD list should be comprehensive and must contain any drugs that are on the current NIOSH list. A list is an essential first step because it determines the drugs to which all other containment standards apply (e.g., receipt, storage, disposal). Once the organization creates a list of HDs, labeling must be applied to each drug dispensed to ensure proper identification and safe handling.

Because HDs are administered in multiple clinical settings, it is imperative that safe handling policies and training extend throughout the organization in both inpatient and ambulatory areas. HD safe handling should be a top priority in any organization. The handling of HDs and HD waste affects all employees who work in the healthcare setting.

Adverse Effects of Hazardous Drug Exposure

Key Points

- Workplace exposure to HDs can cause acute and chronic health effects.
- HD exposure can cause both adverse health outcomes (acute symptoms and reproductive effects) and biologic effects (genetic damage).
- Use of safe handling precautions reduces occupational exposure and risk of adverse effects.

Serious adverse effects of HDs are well known, yet many of these drugs are essential for the treatment of cancer. Adverse health effects from occupational exposure to HDs are based on the inherent toxicities of the drug(s), and similar effects have occurred in both patients and HCWs with exposure. Workplace exposure to HDs can cause acute and chronic health effects, such as ocular irritation, headache, cough, dizziness, nausea and vomiting, skin rashes, adverse reproductive outcomes such as infertility and miscarriages, genetic changes such as DNA damage, and increased occurrence of cancer (Centers for Disease Control and Prevention [CDC], 2016). Adverse effects of occupational HD exposure are listed in Table 2. Most studies of occupational HD exposure have involved antineoplastic drugs.

Numerous studies have found widespread environmental contamination with HDs that places HCWs at risk for uptake, primarily via dermal exposure (Connor et al., 2010; Connor, Zock, & Snow, 2016; Ramphal, Bains, Goulet, & Vaillancourt, 2015). Studies consistently demonstrate a higher rate of genotoxicity in exposed workers compared to unexposed workers (Villarini et al., 2016). Despite the existence of published research studies, guidelines, and recommendations, HCWs do not always follow measures to reduce HD exposure. This lack of action places HCWs at risk for myriad adverse effects.

The consequences of antineoplastic HD exposure have been reported for more than 30 years. Adverse effects of HD exposure can be categorized as either biologic or health effects. Although biologic effects have not always been linked to changes in health at the time of the studies, those identified have been associated with adverse health outcomes. For example, chemotherapy-related malignancies (myelodysplastic syndrome and acute myeloid leukemia) are known to be associated with specific alterations in chromosomes 5, 7, and 11. These chromosomal changes have occurred in patients receiving alkylating agents for the treatment of cancer and have now been demonstrated in HCWs who handle antineoplastic HDs (McDiarmid, Oliver, Roth, Rogers, & Escalante, 2010; McDiarmid, Rogers, & Oliver, 2014).

The following section describes the biologic effects of HDs and is followed by evidence of adverse health outcomes of exposure. Table 3 summarizes studies since 2011 reporting the biologic effects of occupational HD exposure.

Table 2. Adverse Health Effects of Occupational Exposure to Hazardous Drugs

System Affected	Adverse Health Effect
Overall—malignancies	Bladder cancer Leukemia Liver cancer Non-Hodgkin lymphoma
Allergic	Allergic asthma Ocular irritation
Gastrointestinal	Abdominal pain Diarrhea Nausea Vomiting
Integumentary and mucosal	Hair thinning, partial alopecia Mouth and nasal sores Skin irritation/contact dermatitis
Neurologic	Dizziness Headaches
Reproductive	Congenital abnormalities Ectopic pregnancy Infertility Learning disabilities in offspring Low birth weight Premature delivery Spontaneous abortions, miscarriages Stillbirths
Respiratory	Dyspnea

Note. Based on information from Dranitsaris et al., 2005; Fransman, Roeleveld, et al., 2007; Lawson et al., 2012; Martin, 2005b; Petralia et al., 1999; Saurel-Cubizolles et al., 1993; Skov et al., 1990, 1992; Valanis et al., 1993, 1999; Walusiak et al., 2002.

Adverse Health Outcomes of Occupational Hazardous Drug Exposure

The most frequently reported adverse health outcomes of work-related HD exposure are the occurrence of acute symptoms and reproductive effects. In

Table 3. Genotoxic Outcomes Associated With Hazardous Drug Exposure

Author(s)/ Date	Purpose	Design	Sample	Measurement	Results
Bouraoui et al., 2011	Evaluate cellular DNA damage in nurses exposed to HDs	Laboratory studies; survey of precaution use	20 oncology nurses and 20 controls from a hospital in Tunisia; mean age 36 years	MN assay and CA test conducted on peripheral lymphocytes	MN frequency was significantly higher (9.4% vs. 1.85%) in exposed nurses. Mean number CA was significantly higher (1.85 vs. 0.32) in exposed nurses: 5.7 times that of controls. 70% reported wearing gloves, 10% wore gowns, and 5% used no PPE.
Buschini et al., 2013	Evaluate DNA damage associated with exposure to HDs	Laboratory studies	63 exposed nurses and 74 controls from 5 hospitals in Italy	Peripheral blood lymphocytes analyzed for DNA damage using 3 versions of comet assay	Significantly lower mean percentage of DNA in comet tail observed in exposed compared to controls, suggesting chronic exposure to cross-linking HDs
Ladeira et al., 2014	Examine surface contamination by 5-FU and assess the associated genotoxic risk	Laboratory studies	27 exposed nurses and 111 unexposed controls from 2 hospitals in Portugal	Peripheral blood lymphocytes analyzed for MN	Frequency of MN significantly higher in exposed workers compared to controls
McDiarmid et al., 2010	Determine the frequency of specific chromosomal abnormalities in HCWs handling alkylating agents	Laboratory studies; 6-week diary of HD handling frequency	46 oncology nurses, 9 pharmacists, and 8 pharmacy technicians; 46 unexposed controls	Peripheral blood analyzed for abnormalities in chromosomes 5, 7, and 11 using FISH	Excess structural and total abnormalities of chromosome 5 in high-exposure group; increased relative risk for abnormalities of chromosome 5 and either chromosome 5 or 7 obtained at 100 handling events for alkylating agents
McDiarmid et al., 2014	Determine the frequency of specific chromosomal abnormalities in HCWs handling non–alkylating agents	Laboratory studies; 6-week diary of HD handling frequency	46 oncology nurses, 9 pharmacists, and 8 pharmacy technicians; 46 unexposed controls	Peripheral blood analyzed for abnormalities in chromosomes 5, 7, and 11 using FISH	Dose-related increase in chromosome 5 damage related to handling non–alkylating agents
Moretti et al., 2015	Assess cytogenetic damage from occupational exposure to HDs	Laboratory studies; survey	71 exposed nurses and 77 controls from 5 hospitals in Italy	Peripheral blood lymphocytes analyzed for MN and CA	Significant increase in MN frequency and CA in exposed nurses versus controls
Santovito et al., 2014	Evaluate genetic damage associated with exposure to HDs, sterilizing gases, and anesthetics	Laboratory studies	20 exposed nurses and 20 matched controls from 2 hospitals in Italy	Peripheral blood lymphocytes analyzed for SCE and CA	Significant increase in SCE frequency in exposed nurses versus controls
Villarini et al., 2011	Evaluate genotoxic risks of HD handling	Laboratory studies; frequency of HD handling	52 exposed and 52 control HCWs in a hospital in Italy	Peripheral blood leukocytes assessed for DNA damage using comet assay	Primary DNA damage was significantly increased in leukocytes of exposed nurses. Use of PPE was inversely related to DNA damage.

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Table 3. Genotoxic Outcomes Associated With Hazardous Drug Exposure *(Continued)*

Author(s)/ Date	Purpose	Design	Sample	Measurement	Results
Villarini et al., 2016	Assess the degree of genotoxic damage in occupationally exposed HCWs	Systematic review of the literature	24 studies published from 1988–2015	Meta-analysis	15 of 24 (62.5%) studies demonstrated increased MN frequencies in exposed versus unexposed HCWs. Meta-analysis confirmed an overall effect of 1.67 (95% CI [1.41, 1.98]).

CA—chromosomal aberration; CI—confidence interval; FISH—fluorescence in situ hybridization; 5-FU—5-fluorouracil; HCW—healthcare worker; HD—hazardous drug; MN—micronuclei; PPE—personal protective equipment; SCE—sister chromatid exchange

addition, an increase in cancer occurrence in occupationally exposed workers has been shown (Martin, 2005b; Skov et al., 1992). Several historic studies have documented the adverse reproductive outcomes of occupational exposure. Fransman, Roeleveld, et al. (2007) compared outcomes in 4,393 exposed and unexposed (control) nurses in the Netherlands. Exposure to antineoplastic drugs was estimated using dermal measurements based on handling tasks. Nurses who were highly exposed, defined as 0.74 mcg/week exposure, took longer to conceive, had infants with lower birth weight, and had a higher incidence of preterm labor. A bibliography of publications reporting adverse health outcomes from HD exposure can be found online (CDC, 2016).

In a more recent study, Lawson et al. (2012) retrospectively collected information related to pregnancy outcomes and occupational exposures of nurses. Of 7,482 participants, 6,707 live births and 775 spontaneous abortions were reported. The authors concluded that occupational exposure to chemotherapy resulted in a 2-fold increase in risk for spontaneous abortion overall, with a 3.5-fold increase in nulliparous women. Compliance with safe handling guidelines and the types of HDs handled were not reported in this study (Lawson et al., 2012).

The consequences of low-dose, chronic HD exposure remain under investigation. While overall exposure is lower than in years past, more sensitive assays demonstrate that exposure continues to occur. Adverse outcomes from nonantineoplastic HDs have not been well studied. Based on the inherent toxicities for which they are classified as hazardous, all guidelines recommend the use of safe handling precautions for antineoplastic and nonantineoplastic HDs. Use of HD safe handling precautions reduces occupational exposure, yet publications from around the world indicate that adherence to HD safe handling guidelines, although improved, is lower than what is recommended.

Biologic Effects of Hazardous Drug Exposure

The most frequently reported biologic effects of occupational antineoplastic HD exposure are genetic damage, chromosomal aberrations, DNA damage, and urinary mutagenicity. Research studies indicate that nurses who were occupationally exposed to HDs sustained measurable genetic damage, which may be related to long-term health effects such as increased occurrence of cancer (Moretti et al., 2015). For example, studies of DNA of exposed workers showed a statistically significant increased frequency of damage to chromosome 5 or 7 and an increased frequency of damage to chromosome 5 alone using fluorescence in situ hybridization (McDiarmid et al., 2010, 2014). Another study, which evaluated the genotoxicity induced by HD exposure in nurses and pharmacists, demonstrated an increase in aberrant lymphocytes, chromosomal aberrations (CAs), and micronuclei (MN) frequencies when compared to the matched controls (El-Ebiary, Abuelfadl, & Sarhan, 2013). A recent systematic review confirmed the relationship between MN frequencies and occupational exposure to antineoplastic agents (Villarini et al., 2016). Nurses must receive education about the risks of handling HDs and integrate safe handling activities into their practice at all times to avoid the adverse biologic and health effects of HD exposure.

Evidence for Occupational Hazardous Drug Exposure

Key Points

- HCWs are exposed to HDs by absorption through skin or mucous membranes or inadvertent ingestion, inhalation, or injection.
- Although studies have shown the presence of HDs in urine and other body fluids, no recommendations for biologic monitoring currently exist. Methods for biologic monitoring include identifying biomarkers of exposure and biomarkers of effect.
- Environmental contamination monitoring is recommended in areas where HDs are handled. Environmental contamination can be measured by sampling of surface wipes, pads, and air.

Evidence of HD exposure in HCWs has existed since the late 1970s. Occupational HD exposure cannot be measured directly like radiation exposure, for which there are monitoring devices to detect the presence of radiation. In clinical settings, workers who have the potential for radiation exposure wear a film badge or dosimeter that records both the occurrence and extent of exposure. The measuring devices are evaluated on a regular basis, and the HCW is notified when a predetermined level of exposure is exceeded. Individuals are counseled to avoid exposure for a period of time.

Because HD exposure cannot be directly measured, efforts have focused on both biologic and environmental monitoring for indicators of exposure. Currently, no reliable method exists for biologic monitoring of occupational exposure to HDs. This type of monitoring is confined to research related to HD exposure. At this time, assays that measure HD exposure are only available in a small number of research laboratories. The laboratories are not clinical laboratories and thus are not Clinical Laboratory Improvement Amendments–certified. There is no good way to evaluate the implications of a "positive" result. In addition, there are no known interventions to offer, other than routine medical care. For these reasons, no guidelines or recommendations exist for routine biologic monitoring for occupational HD exposure in clinical practice.

Standards from USP (2016a) state that periodic monitoring for environmental contamination should be done as a means of evaluating the potential for HCW exposure.

Biologic Monitoring

HD exposure in HCWs occurs through various routes, including absorption through skin or mucous membranes and inadvertent ingestion, inhalation, or injection. When HD exposure occurs, the drugs are absorbed, metabolized, and excreted. Biologic monitoring methods include those for identifying biomarkers of exposure (evidence of drug uptake) and biomarkers of effect (evidence of physiologic or biochemical changes) as a result of exposure.

Biomarkers of Exposure

One of the most common methods of biologic monitoring for HD exposure is to analyze urine for the presence of drugs and their metabolites. Cyclophosphamide and ifosfamide are the most studied drugs because analytic methods for detecting these agents have been available for many years. Assays for detecting small amounts of these and other antineoplastic agents are available from a few specialty laboratories in the United States and Europe. Subjects are instructed to collect urine following handling of HDs or known exposure to HDs. The urine samples are frozen and shipped to the laboratory for analysis. Gas chromatography/mass spectrometry or tandem mass spectrometry (GC-MS or GC-MS/MS) or similar techniques are used.

In the analysis of urine or other body fluids for the presence of drugs, several factors influence the ability to detect the drug residue. First is the sensitivity of the assay. *Sensitivity* refers to the ability of the assay to detect very low levels of the drugs. GC-MS, a conventional method of analysis, has been used for many years to detect HDs in biologic and environmental samples. Newer technology such as high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) is a much more sensitive method that can detect measurable levels of HDs in samples that test negative using GC-MS (Ndaw, Denis, Marsan, d'Almeida, & Robert, 2010). This method can determine drug residue with a limit of detection (LOD) as low as 0.01–1 mcl/L. Some methods report the limit of quantification (LOQ), the lowest concentration for which a positive result can be measured.

A second consideration is the timing of sample collection relative to exposure. The route of exposure (e.g., inhalation, dermal absorption) and pharmacokinetics of the HD affect the time to excretion in urine. Drug metabolism also influences drug excretion. Metabolism may be so rapid that detection in urine is problematic (Turci et al., 2011). For example, 5-fluorouracil (5-FU) has a plasma half-life of 8–20 minutes when administered by short IV infusion.

Within the first hour, 7%–20% of the parent drug is excreted unchanged in the urine. Metabolites, primarily α-fluoro-β-alanine (FBAL), are excreted in the urine over three to four hours (Sandoz, 2010). If the urine is not collected at the right time, the results may be negative despite the occurrence of exposure.

Recovery of drug from urine is also limited by dilution of the sample. To increase the accuracy of findings, a sample from each voided urine over 24 hours should be collected, stored, and analyzed separately for the presence of HDs. Results from random urine samples or those collected for only a few hours may not accurately reflect exposure. This makes urine analysis for HD exposure impractical to use for routine monitoring.

More than 100 studies have evaluated the presence of HDs in the urine of exposed people since the early 1990s (CDC, 2016), with at least 20 published since 2010 (see Table 4). HDs have been detected in the urine of nurses, pharmacists, and pharmacy technicians, including workers not directly involved in handling the specific drugs (Friese, McArdle, et al., 2015; Ramphal, Bains, Vaillancourt, Osmond, & Barrowman, 2014). The authors concluded that routine handling of HDs results in contamination of the work environment and that dermal exposure is an important route for uptake of HDs.

In 20 studies published since 2010, all but five detected HDs in the urine of those tested. Suspiro and Prista (2011) suggested that negative studies using GC-MS may not reflect the absence of exposure but rather the use of a less-sensitive test. Two of the studies measured cyclophosphamide in the urine of family members of treated patients who likely were exposed from contaminated excreta in the home (Yuki, Ishida, & Sekine, 2015; Yuki, Sekine, Takase, Ishida, & Sessink, 2013).

Most studies measuring biomarkers of HD exposure include nurses and pharmacists. Several indicate exposure, uptake, metabolism, and excretion of HDs as a result of routine work activities even when no obvious source of exposure (e.g., drug preparation or administration) is identified. For example, Ndaw et al. (2010) found that positive urine samples were more common in auxiliary nurses involved in patient care but not in direct HD handling (37% vs. 15%). They concluded that exposure most likely occurred when workers were unaware of the potential for exposure and therefore did not use personal protective equipment (PPE).

Biomarkers of Effect

Most of the studies evaluating biomarkers for effect of HD exposure have measured genotoxic outcomes in HCWs. The first was a study by Falck et al. (1979) in which the Ames test (a test of mutagenic properties of chemicals) was positive for mutagenicity in the urine of exposed nurses. In a summary of biomarker studies conducted between 1984 and 2010, Suspiro and Prista (2011) reported that 27 of 29 were positive for genotoxic outcomes. Most genotoxicity biomarkers are nonspecific, meaning there are other potential causes besides HD exposure, but positive results occur with more frequency in HD-exposed compared to unexposed workers. Table 3 summarizes recent studies of genotoxic outcomes related to HD exposure.

Low levels of DNA damage can be detected in peripheral blood lymphocytes collected from exposed workers. CAs include changes in numbers and structure of chromosomes. These changes reflect DNA damage that is potentially related to low-level occupational exposure to HDs. CAs in HD-exposed workers were reported in seven studies published between 1984 and 2010 (Suspiro & Prista, 2011), and four additional studies since 2010 had similar findings (see Table 3). CAs are significant because they are associated with carcinogenesis. Two recent studies identified chromosome 5 damage related to the frequency of HD handling of both alkylating (McDiarmid et al., 2010) and nonalkylating (McDiarmid et al., 2014) cytotoxic agents in nurses and pharmacists. This specific type of CA is associated with acute myeloid leukemia and is similar to the damage caused by benzene (Escobar, Smith, Vasishta, Hubbard, & Zhang, 2007).

MN tests identify groups of nuclear material in the cytoplasm of cells following cell division (Suspiro & Prista, 2011). These are present as a result of chromosome breaks or other abnormal conditions occurring during mitosis. The number of MN is increased following exposure to agents associated with chromosomal damage. Five studies between 1991 and 2009 (reviewed in Suspiro & Prista, 2011) and three studies since 2010 (Bouraoui et al., 2011; Ladeira et al., 2014; Moretti et al., 2015) demonstrated increased frequency of MN in workers exposed to HDs. A recent systematic review and meta-analysis confirmed a relationship between MN frequencies and occupational exposure to antineoplastic agents (Villarini et al., 2016). Elevated MN frequency is associated with an increase in cancer occurrence (Bonassi et al., 2007).

Comet assay is a test for DNA strand breaks and incomplete DNA repair. This test is simple to perform when compared to other tests for DNA damage and therefore has been considered a reasonable screening tool for various occupational chemical exposures (Moller, Knudsen, Loft, & Wallin, 2000). Two recent studies reported increased DNA damage using comet assay in HD-exposed workers versus controls (Buschini et al., 2013; Villarini et al., 2011).

Sister chromatid exchanges (SCEs), or the exchange of products of DNA replication, are another indicator

Table 4. Biologic Monitoring for Hazardous Drug Exposure

Author(s)/Date	Purpose	Design	Sample	Measurement	Results
Andréasson et al., 2010	Measure exposure of operating room staff during HIPEC	Laboratory studies	1 surgeon and 1 perfusionist in an operating room in Sweden	Analysis of urine and blood samples for Pt	All samples below LOD; PPE and respiratory protection used
Connor et al., 2010	Evaluate HCWs' chemotherapy exposure over 6 weeks of handling	Laboratory studies	68 exposed workers and 53 unexposed workers from pharmacy and nursing areas in 3 university-based U.S. cancer centers	Diaries of HD handling events; 8-hour urine collection analyzed for HDs and TAX using HPLC-MS/MS	2 of 67 urine samples from exposed workers > LOD for CP; 1 of 67 urine samples from exposed workers > LOD for TAX
Friese, McArdle, et al., 2015	Evaluate HD exposure from spills via urinary excretion	Laboratory studies; survey	40 nursing and pharmacy staff in an academic infusion center	Urine samples from 9 staff reporting a spill and 8 staff not reporting a spill analyzed for HDs using LC-MS/MS	4 spill events in 6 months involving 9 staff 4 urine samples > LOD after spills; 4 urine samples > LOD in staff not reporting spills
Hama et al., 2012	Evaluate exposure from vial contamination via urinary excretion	Laboratory studies	63 CP vials; 1 dispensing pharmacist in hospital in Japan	Surface wipe samples from the exterior of CP vials; each voided urine in 29 hours from pharmacist analyzed for CP using LC-MS/MS	30%–60% of vials > LOD for CP 1 urine sample from day 2 > LOD for CP
Hon et al., 2015	Evaluate urinary excretion of HDs	Laboratory studies; survey	103 HCWs from 5 hospitals and 1 cancer treatment center in Canada; 8 job categories: pharmacists, pharmacy receivers, pharmacy technicians, porters, nurses, transport staff, unit clerks, others	All voided urine for 24 hours collected, pooled, and analyzed for CP using HPLC-MS/MS	111 of 201 (55%) of urine samples > LOD for CP. Staff from all 8 job categories had CP in urine. Higher CP levels seen in workers directly handling CP and those without safe handling training. Unit clerks had the highest average level.
Kopp et al., 2013	Measure Pt in urine of pharmacy workers	Laboratory studies	12 pharmacy workers using positive air pressure isolators to prepare HDs and 5 controls in 2 hospitals in France	Urine samples from the beginning and end of week analyzed for Pt using voltammetry	Pt present in 37 of 37 urine samples but did not differ between exposed and controls
Maeda et al., 2010	Assess urinary excretion of HDs in pharmacists and nurses	Laboratory studies	6 pharmacists and 2 nurses handling HDs in a Japanese hospital	1 24-hour urine sample from a pharmacist and spot samples from 6 pharmacists and 2 nurses analyzed for CP and IF using LC-MS/MS	No CP or IF detected in urine samples; IF not prepared on sampling days
Miyake et al., 2013	Compare urinary excretion of HDs before and after implementing a CSTD	Laboratory studies	4 pharmacists compounding HDs in a community hospital in Japan	24-hour urine samples from 4 pharmacists analyzed for CP using GC-MS/MS prior to and 7 months after initiating CSTD	26 of 34 preimplementation urine samples > LOD for CP 2 of 31 postimplementation urine samples > LOD for CP Urinary concentration decreased by 93%

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Table 4. Biologic Monitoring for Hazardous Drug Exposure *(Continued)*

Author(s)/Date	Purpose	Design	Sample	Measurement	Results
Ndaw et al., 2010	Measure HCWs' exposure to 5-FU using urinary excretion	Laboratory studies	19 HCWs in a pharmacy and oncology ward in a hospital in France	Pre- and post-shift urine samples from 6 pharmacy technicians and 13 nurses collected over 5 days and analyzed for 5-FU metabolite FBAL using HILIC-MS/MS	35 of 121 urine samples > LOQ for FBAL 5 of 6 pharmacists and 9 of 13 nurses had ≥ 1 positive sample using a very sensitive analytical method.
Pieri et al., 2010	Measure nurses' exposure to HDs using urinary excretion	Laboratory studies; survey	56 nurses performing drug preparation in oncology departments in 2 hospitals in Italy	End-shift urine samples from nurses analyzed for DOX and EPI using HPLC-FL	5 of 56 urine samples > LOQ: 3 for EPI, 1 for DOX, and 1 for EPI and DOX
Ramphal et al., 2014	Measure nurses' exposure to HDs using urinary excretion	Laboratory studies; survey	41 oncology nurses from a pediatric hospital, 39 nurse controls, and 10 community controls in Canada	24-hour urine samples collected. Collection of urine from nurses began halfway through work shift. Urine analyzed for CP using GC-MS.	CP detected in at least one urine sample in 14 of 41 (34%) oncology nurses and 13 of 39 (33%) of non-oncology nurses; no CP in community controls
Sabatini et al., 2012	Assess exposure to HDs using urinary excretion	Laboratory studies	3 studies in a large hospital in Italy: • 2001: 50 nurses preparing HDs and 50 controls • 2005: 81 nurses and pharmacy technicians preparing HDs • 2010: 54 staff handling HDs	End-of-shift urine samples analyzed for CP and MTX using LC-MS/MS	2001: 18 of 50 urine samples > LOD 2005: 9 of 81 urine samples > LOD 2010: 0 of 54 urine samples > LOD Drug preparation was centralized prior to 2010 monitoring.
Sottani et al., 2012	Measure exposure to HDs using urinary excretion	Laboratory studies	Nurses and pharmacists from 8 pharmacies and 9 treatment areas in Italy	Pre- and post-shift urine samples analyzed for 5 HDs using HPLC-MS/MS	0 of 100 urine samples > LOD for any HD
Sugiura et al., 2011	Measure exposure to HDs using urinary excretion	Laboratory studies	3 medical doctors, 3 pharmacists, and 4 nurses involved in HD preparation and administration in a university hospital in Japan	All urine collected over 24 hours and analyzed per sample for CP using GC-MS/MS	11 of 62 urine samples > LOD for CP Excretion occurred in 2 nurses and 1 doctor who administered HDs.
Sugiura et al., 2010	Measure exposure to HDs using urinary excretion	Laboratory studies	1 physician, 27 pharmacists, and 13 nurses from 6 hospitals in Japan	All urine collected over 24 hours and analyzed for CP using GC-MS	90 of 276 urine samples > LOD for CP Excretion occurred in 23 of 41 subjects.
Turci et al., 2011	Assess adherence to safe handling standards using a monitoring program of biologic measurement over 5 years	Laboratory studies; periodic surveys	7 hospitals in Italy	Beginning and end-of-shift urine samples analyzed for HDs using HPLC-MS/MS	No urine samples > LOD for HDs Authors credit CSTDs, adherence to SOPs, and decontamination procedures.

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Table 4. Biologic Monitoring for Hazardous Drug Exposure *(Continued)*

Author(s)/Date	Purpose	Design	Sample	Measurement	Results
Villarini et al., 2011	Evaluate HD exposure using urinary excretion	Laboratory studies; frequency of HD handling	52 exposed and 52 control HCWs in a hospital in Italy	End-of-shift urine samples analyzed for CP using GC-MS	7 of 40 urine samples > LOD for CP
Yoshida et al., 2011	Evaluate the relationship between HD exposure and handling	Laboratory studies; observation and interviews	17 pharmacists from 5 hospitals in Japan	24-hour urine samples analyzed for CP using GC-MS and for Pt-containing drugs using plasma MS	3 of 17 urine samples > LOD for CP
Yuki et al., 2015	Measure urinary HD excretion by patients and family members at home	Laboratory studies	8 patients treated with CP, 10 cohabiting family members, and 10 controls	Samples from all voided urine over 7 days from patients and family members analyzed for CP using GC-MS/MS	112 of 276 urine samples from patients > LOD for CP; CP detected up to 5 days post-treatment 52 of 243 urine samples from family members > LOD for CP; CP detected in urine from 6 family members
Yuki et al., 2013	Measure urinary HD excretion by patients and family members at home	Laboratory studies; questionnaire	2 patients treated with CP, 1 patient treated with 5-FU, and their cohabiting family members	Urine samples from patients and family members analyzed for CP using GC-MS/MS and for 5-FU using HPLC-UV	HDs detected in 35 of 35 samples from patients and 16 of 16 samples from family members

BSC—biosafety cabinet; CP—cyclophosphamide; CSTD—closed-system drug-transfer device; CYT—cytarabine; DOX—doxorubicin; EPI—epirubicin; FBAL—α-fluoro-β-alanine; 5-FU—5-fluorouracil; GC-MS—gas chromatography with mass spectrometry; GC-MS/MS—gas chromatography with tandem mass spectrometry; HCW—healthcare worker; HD—hazardous drug; HILIC—hydrophilic interaction chromatography; HIPEC—hyperthermic intraperitoneal chemotherapy; HPLC-FL—high-performance liquid chromatography with fluorescence; HPLC-MS/MS—high-performance liquid chromatography with tandem mass spectrometry; HPLC-UV—high-performance liquid chromatography–ultraviolet; IF—ifosfamide; LC-MS/MS—liquid chromatography with tandem mass spectrometry; LOD—limit of detection; LOQ—limit of quantification; MS—mass spectrometry; MTX—methotrexate; PPE—personal protective equipment; Pt—platinum; SOP—standard operating procedure; TAX—paclitaxel

of genetic damage. These DNA changes do not result in altered chromosome number or structure (Suspiro & Prista, 2011). The significance of SCEs is less clear than other measures of chromosomal damage.

Environmental Monitoring

Early support for precautions while handling HDs focused on the biologic effects in exposed individuals. Following the implementation of HD safe handling guidelines in most settings, pharmacists and nurses continued to demonstrate evidence of exposure despite the use of precautions such as biosafety cabinets (BSCs), gloves, and gowns. The most plausible source of exposure is an environment that is contaminated with HDs. As noted by Turci et al. (2011), "While biological monitoring can tell if contamination occurred, environmental monitoring can tell how, where, and even when it occurred" (p. 331). This is the primary reason that the USP General Chapter 800 standard recommends environmental monitoring for HD contamination. To reduce HCW exposure, the sources of exposure must be identified and addressed.

Exposure From Contaminated Surfaces

One method of measuring environmental contamination with HDs is surface wipe sampling. Surfaces in work areas where HDs are present (e.g., working areas of BSCs, tables, floors) are evaluated for the presence of HD residue. The sample areas are measured, moistened with a solvent, and wiped until dry. The wipes are placed in containers, frozen, and analyzed for the presence of several drugs (Connor et al., 2010). The ability of the assay to detect drug residue from wipe samples is related to the sensitivity of the assay, the recovery efficiency, and the thoroughness of the sampling procedure. A standard pattern of wiping (i.e., back and forth and up and down) and double sampling of each site is recommended for accuracy (Larson, Khazaeli, & Dillon, 2002). Assays are available for individual and groups of HDs. Results are reported as

above or below the LOD. Some assays report the exact quantity of drug residue in micrograms per square centimeter (mcg/cm^2). In addition to work surfaces, HD contamination has been measured on gloves and pads placed on the protective garb of HCWs. Table 5 summarizes the findings from 22 published studies between 2010 and 2015.

Several studies have detected drug contamination on the outside of drug vials when delivered by the manufacturers (Fleury-Souverain, Nussbaumer, Mattiuzzo, & Bonnabry, 2014; Hama, Fukushima, Hirabatake, Hashida, & Kataoka, 2012; Schierl, Herwig, Pfaller, Groebmair, & Fischer, 2010; Turci et al., 2011). Cyclophosphamide, 5-FU, ifosfamide, and platinum drugs all have been detected on vial exteriors using various wipe sampling and washing techniques. These findings indicate that nurses, pharmacists, and pharmacy technicians are at risk for skin exposure if they do not wear PPE while handling unopened drug vials. In addition, HD contamination from a vial can be transferred to other items or surfaces with which it comes into contact (Power, Sessink, Gesy, & Charbonneau, 2014).

Results from the many environmental monitoring studies demonstrate that the work areas where HDs are prepared and administered are commonly contaminated with the drugs. Workers who normally wear PPE for direct drug handling activities can be exposed when touching unknowingly contaminated surfaces with unprotected hands. Every study measuring environmental contamination using surface wipe sampling found evidence of surface contamination.

Inhalation Exposure

The inhalation exposure route is less likely for workers who use a BSC, but the risk is high for drug preparation outside of a containment primary engineering control (C-PEC). This includes inhalation of aerosols during the manipulation of tablets and HD spills (Fent, Durgam, & Mueller, 2014). Workers should consider inhalation as a possible route of HD exposure and avoid performing any HD handling activities that generate aerosols outside of a C-PEC.

To summarize, ongoing evidence shows that occupational HD exposure can and does occur. Few laboratories in the United States perform the assays described in this section, which makes routine monitoring impractical. In the absence of measured contamination in the workplace, nurses should consider the possibility of environmental contamination. Because a safe level of HD exposure does not exist, HCWs must take steps to minimize their exposure. Additional studies are needed that evaluate the magnitude of HD exposure of HCWs who consistently use safe handling precautions.

Table 5. Environmental Monitoring for Hazardous Drug Exposure

Author(s)/Date	Purpose	Design	Sample	Measurement	Results
Berruyer et al., 2015	Describe environmental contamination with HDs in pharmacy and patient care areas	Laboratory studies	6 standardized sites in pharmacy and patient care areas in 36 hospitals in Canada	Surface wipe samples analyzed for CP, IF, and MTX	198 of 422 samples > LOD for CP 75 of 422 > LOD for IF 11 of 422 > LOD for MTX Reduced level of contamination but similar proportion of positive samples compared to earlier studies
Bussières et al., 2012	Describe environmental contamination with HDs in pharmacy and patient care areas	Laboratory studies	6 standardized sites in pharmacy and patient care areas in 25 hospitals in Quebec	Surface wipe samples analyzed for CP, IF, and MTX using ultra-performance LC-MS/MS	135 of 259 samples > LOD for CP 53 of 259 > LOD for IF 7 of 259 > LOD for MTX
Chu et al., 2012	Determine environmental contamination with HDs in pharmacy and measure residual drug after cleaning	Laboratory studies	23 surfaces in pharmacies in 6 British Columbian hospitals	Surface wipe samples collected pre-cleaning and post-cleaning and analyzed for CP and MTX using LC-MS/MS	6 of 23 pre- and post-cleaning samples > LOD for MTX 14 of 23 pre- and 13 of 23 post-cleaning samples > LOD for CP 4 samples had higher concentration post-cleaning.

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Table 5. Environmental Monitoring for Hazardous Drug Exposure *(Continued)*

Author(s)/Date	Purpose	Design	Sample	Measurement	Results
Connor et al., 2010	Evaluate HCW chemotherapy exposure by environmental contamination	Laboratory studies	Work surfaces from pharmacy and nursing areas in 3 university-based U.S. cancer centers	Surface wipe samples analyzed for CP, IF, TAX, 5-FU, and CYT	60% of 143 wipe samples > LOD for at least one drug; 32% > LOD for more than one drug
Fent et al., 2014	Evaluate exposure to dust generated by automatic dispensing machines	Laboratory studies	43 employees at 3 pharmacies using automatic dispensing machines	Air samples collected near breathing zones analyzed for pharmaceutical dust	10 active pharmaceutical ingredients detected, including MTX
Fleury-Souverain et al., 2014	Evaluate outside and septum of vials for HD contamination	Laboratory studies	Vials containing HDs from Swiss manufacturers	Wipe samples from external vial surfaces analyzed for HDs using LC-MS/MS	63% of 133 vials > LOQ 20% of vials had contamination > 10 ng. 35% of vials had traces of other HDs. Low or no contamination detected on shrink-wrapped vials
Hama et al., 2012	Evaluate vial contamination with CP	Laboratory studies	63 CP vials from a hospital in Japan	Surface wipe samples from exterior of CP vials analyzed using LC-MS/MS	30%–60% of vials > LOD for CP
Kopp et al., 2013	Measure Pt on environmental surfaces	Laboratory studies	Pharmacies using positive air pressure isolators for HD preparation in 2 hospitals in France	Sampling of surfaces, gloves, and outer surface of HD vials analyzed using voltammetry	Pt detected on 70 of 70 wipe samples from preparation area 6 of 33 glove samples > LOD for Pt Highest contamination on gloves used to handle drug vials 17 of 51 vials > LOD for Pt
Ladeira et al., 2014	Assess environmental contamination with HDs	Laboratory studies	Environmental surfaces from 2 hospitals in Portugal	Surface wipe samples analyzed for 5-FU using HPLC-DAD	14 of 28 samples > LOQ site A 9 of 105 samples > LOQ site B Level of contamination similar in both
Maeda et al., 2010	Assess environmental contamination with HDs	Laboratory studies	2 drug preparation areas in a Japanese hospital	Surface wipe samples from 2 BSCs analyzed for CP and IF using LC-MS/MS	13 of 96 wipe samples > LOD for CP; no IF detected; IF not prepared on sampling days
Miyake et al., 2013	Compare environmental contamination by HDs before and after implementing a CSTD	Laboratory studies	6 sites from HD compounding areas in a community hospital in Japan	Surface wipe samples from drug preparation room analyzed for CP using GC-MS/MS prior to and 7 months after initiating a CSTD	Preimplementation: 4 of 6 wipe samples > LOD for CP Postimplementation: 1 of 6 wipe samples > LOD for CP Contamination decreased by 93%.
Moretti et al., 2015	Assess environmental contamination with HDs	Laboratory studies; survey	Surfaces from 5 hospitals in Italy	Surface wipe samples and personal pad samples analyzed for CP	100% of surface wipe samples and 100% of personal pad samples > LOD for CP

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Table 5. Environmental Monitoring for Hazardous Drug Exposure *(Continued)*

Author(s)/Date	Purpose	Design	Sample	Measurement	Results
Ramphal et al., 2014	Measure environmental HD contamination	Laboratory studies; survey	Medication rooms and patient care rooms in a pediatric hospital in Canada	Surface wipe samples from medication rooms and patient rooms analyzed for CP using GC-MS	3 of 6 wipe samples in the oncology unit > LOD for CP; all other wipe samples < LOD
Sabatini et al., 2012	Assess exposure to HDs using environmental monitoring	Laboratory studies	Preparation and patient care areas from 2 studies in a large hospital in Italy	Surface wipe samples analyzed for CP and MTX using LC-MS/MS	2001: 100% of wipe samples > LOD for CP and 46% > LOD for MTX 2010: 75% of wipe samples > LOD for CP and 14% > LOD for MTX Drug preparation was centralized prior to 2010 monitoring.
Sottani et al., 2012	Measure exposure to HDs using environmental monitoring and pad samples	Laboratory studies	Nurses and pharmacists from 8 pharmacies and 9 treatment areas in Italy	Personal pads placed on forearms and torso of pharmacy technicians and nurses and surface wipe samples analyzed for 3 HDs using HPLC-MS/MS	26% of 101 personal pad samples > LOD for 1 or more HDs 54% of 142 wipe samples > LOD for 1 or more HDs
Sugiura et al., 2011	Measure HD exposure using environmental monitoring	Laboratory studies	HD preparation and patient care areas in a university hospital in Japan	Surface wipe samples analyzed for CP using GC-MS/MS	15 of 15 surface wipe samples > LOD for CP
Sugiura et al., 2010	Measure HD exposure using environmental monitoring	Laboratory studies	12 sites each in 6 hospitals in Japan	Surface wipe samples from multiple locations analyzed for CP using GC-MS	35 of 72 wipe samples > LOD for CP
Turci et al., 2011	Assess adherence to safe handling standards using a monitoring program of environmental monitoring over a 5-year period	Laboratory studies; periodic surveys	7 hospitals in Italy	Air samples, wipe samples, personal pads, and gloves analyzed for HDs using HPLC-MS/MS	Surface contamination decreased over time to near the LOQ. Contamination of personal pads decreased over time. Authors credited CSTDs, adherence to SOPs, and decontamination procedures for these decreases. External vial contamination persisted.
Villarini et al., 2011	Evaluate environmental contamination with HDs	Laboratory studies; frequency of HD handling	52 exposed and 52 control HCWs in a hospital in Italy	Wipe samples and personal pads analyzed for 5-FU and CYT using HPLC-UV	22 of 75 wipe samples > LOD for 5-FU or CYT 6 of 46 personal pads > LOD for 5-FU; 2 of 12 pads > LOD for CYT
Yoshida et al., 2011	Evaluate the relationship between HD contamination and conditions of handling	Laboratory studies; observation and interviews	Preparation rooms from 5 hospitals in Japan	Wipe samples analyzed for CP using GC-MS, for 5-FU and GEM using HPLC-UV, and for Pt using plasma MS	57 of 109 wipe samples > LOD for HDs Contamination related to the number of drugs handled, methods of cleaning equipment, and skill of HCW in negative-pressure technique

(Continued on next page)

Table 5. Environmental Monitoring for Hazardous Drug Exposure *(Continued)*

Author(s)/Date	Purpose	Design	Sample	Measurement	Results
Yuki et al., 2013	Measure environmental contamination with HDs in patients' homes via excreta	Laboratory studies; questionnaire	Surfaces in the homes of 2 patients treated with CP and 1 patient treated with 5-FU	Wipe samples from home environment analyzed for CP using GC-MS/MS and for 5-FU using HPLC-UV	8 of 12 wipe samples > LOD for CP 0 of 5 wipe samples > LOD for 5-FU
Yuki et al., 2014	Measure environmental contamination with HDs in patients' homes via excreta	Laboratory studies	Surfaces in the homes of 5 female patients with breast cancer treated with CP	Wipe samples from home environment analyzed for CP using GC-MS/MS	17 of 28 wipe samples from homes of all 5 patients > LOD for CP Contamination found on toilet seats and toilet floors

BSC—biosafety cabinet; CP—cyclophosphamide; CSTD—closed-system drug-transfer device; CYT—cytarabine; 5-FU—5-fluorouracil; GC-MS—gas chromatography with mass spectrometry; GC-MS/MS—gas chromatography with tandem mass spectrometry; GEM—gemcitabine; HCW—healthcare worker; HD—hazardous drug; HPLC-DAD—high-performance liquid chromatography with diode array detection; HPLC-MS/MS—high-performance liquid chromatography with tandem mass spectrometry; HPLC-UV—high-performance liquid chromatography–ultraviolet; IF—ifosfamide; LC-MS/MS—liquid chromatography with tandem mass spectrometry; LOD—limit of detection; LOQ—limit of quantification; MS—mass spectrometry; MTX—methotrexate; Pt—platinum; SOP—standard operating procedure; TAX—paclitaxel

Interventions to Reduce Worker Exposure

Key Points

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

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

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

Hierarchy of Controls

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

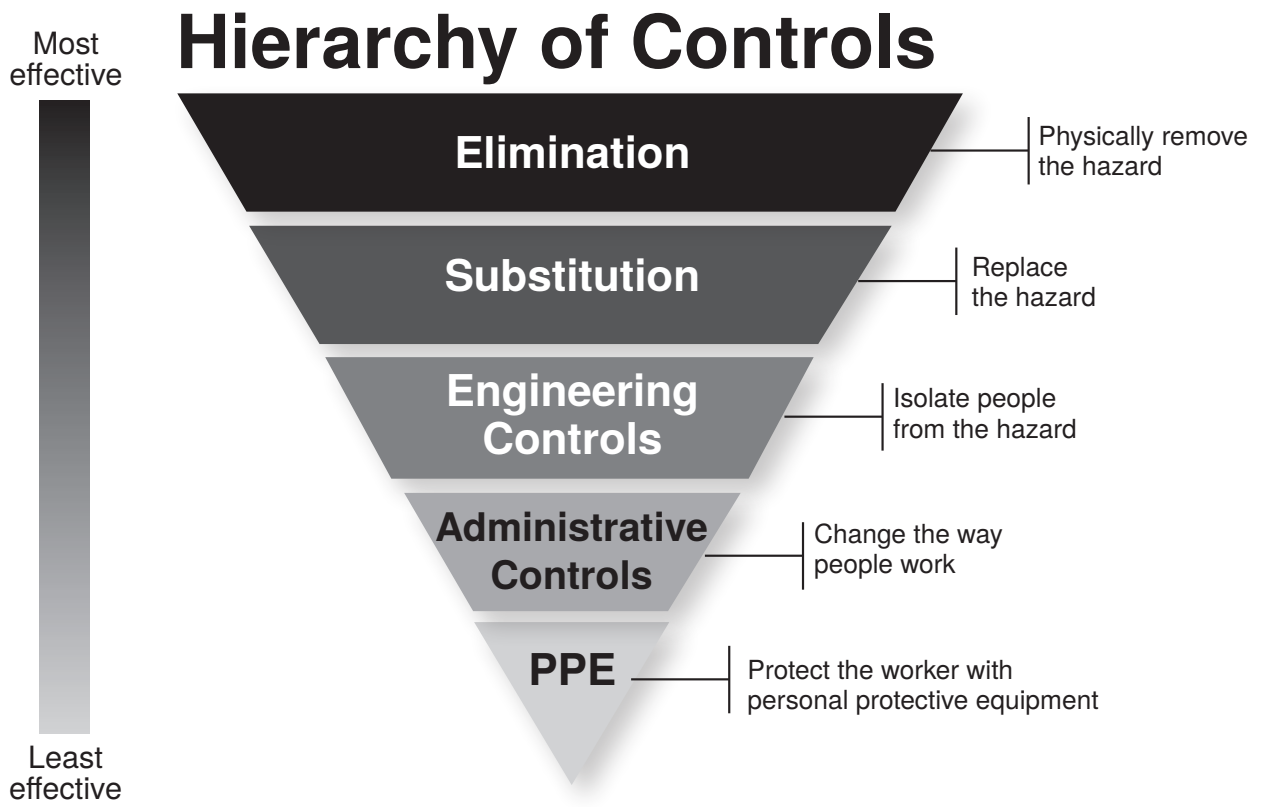
These steps involve elimination or substitution, engineering controls, administrative controls including work practices, and PPE. As elimination of HDs or substitution of non-HDs for HDs is not an option, the recognized methods of decreasing employee exposure to HDs are by implementing engineering controls,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

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

Engineering Controls

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

Figure 1. Hierarchy of Controls



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

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

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

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

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

Biosafety Cabinets

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

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

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

* Not inclusive of other HD requirements

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

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

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

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

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

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

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

Compounding Aseptic Containment Isolators

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

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

Containment Secondary Engineering Controls

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

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

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

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

Supplemental Engineering Controls

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

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

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

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

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

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

Administrative Controls

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

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

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

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

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

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

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

Work Practice Controls

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

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

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

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

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

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

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

Personal Protective Equipment

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

Gloves

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

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

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

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

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

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

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

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

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

Figure 3. Recommendations for Glove Use in Hazardous Drug Handling

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

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

Gowns

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

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

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

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

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

Eye and Face Protection

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

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

Respiratory Protection

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

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

Removal of Personal Protective Equipment

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

Drug Compounding

Key Points

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

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

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

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

General Information

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

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

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

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

Containment Primary Engineering Control Work Practices

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

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

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

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

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

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

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

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

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

(Continued on next page)

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

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

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

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

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

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

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

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

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

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

Limitations Specific to the Class II Biosafety Cabinet

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

Personal Protective Equipment in a Containment Primary Engineering Control

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

Compounding of Sterile Hazardous Drug Doses

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

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

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

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

Negative Pressure Technique

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

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

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

Closed-System Drug-Transfer Devices

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

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

Spiking IV Bags and Priming Lines

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

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

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

Nonsterile Hazardous Drugs

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

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

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

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

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

Safety Measures: Drug Labeling

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

Disposal of Compounding Supplies

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

Drug Administration

Key Points

- Administration of HDs by any route carries a risk for exposure.
- Safe handling precautions should be employed regardless of the route of administration.
- Recommendations for safe handling include handwashing with soap and water, use of appropriate PPE, and use of CSTDs when the dosage form allows.

HDs can be administered by a variety of delivery systems and routes in which drugs are directed systemically, regionally, or locally. Although most HDs are given intravenously and orally, alternative routes of administration sometimes are used. Some drugs are administered intra-arterially, by subcutaneous (SC) or intramuscular (IM) injection, or topically, by inhalation, and into body cavities. As new treatments become available, alternative routes and delivery systems are likely to be more common. Several drug delivery systems are being studied for their future application in HD administration. These delivery systems include intraosseous access, convection-enhanced delivery, and intravitreal and nanoparticle-polymer drug delivery systems (Grossniklaus, 2014; Orsi & Varano, 2015; Tewari et al., 2015).

HDs are administered in nontraditional settings, such as surgical and procedural suites and interventional and radiology procedural rooms. HDs are used in many individuals for nonmalignant indications (see Figure 5).

Precautions for the safe administration of HDs by all routes are necessary because any HD handling involves an inherent opportunity for exposure. Recommendations for preventing exposure have evolved over the years as new information and new technologies have become available. Guidelines established by the American Society of Hospital Pharmacists (1990) and OSHA (1999) were based on studies of exposure during preparation and administration. Updated versions of these pioneering guidelines have since been published (ASHP, 2006; NIOSH, 2004). USP has released new standards for the safe handling of HDs in General Chapter 800 (USP, 2016a). Unlike guidelines from NIOSH and professional organizations, the USP standards are enforceable by FDA and state boards of pharmacy (in states that have adopted USP). The Centers for Medicare and Medicaid Services also includes USP standards in their Conditions of Participation (www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings).

Figure 5. Nonmalignant Conditions Treated With Hazardous Drugs

- Actinic keratosis
- Autoimmune inner ear disease
- Autoimmune neurologic disorders
  - Multiple sclerosis
  - Neuromyelitis optica
- Chronic autoimmune neuropathies
  - Anti-myelin–associated glycoprotein neuropathies
  - Chronic inflammatory demyelinating neuropathy
- Crohn disease
- Cytomegalovirus
- Idiopathic nephrotic syndrome
- Idiopathic pulmonary fibrosis
- Inflammatory bowel disease
- Inflammatory myopathies
  - Dermatomyositis, inclusion body myositis
  - Polymyositis
- Iron overload
- Juvenile dermatomyositis
- Juvenile idiopathic arthritis
- Mixed connective tissue disease
- Neuromuscular disease
- Paraneoplastic neurologic disorders
- Psoriasis, psoriatic arthritis
- Sarcoidosis
- Scleroderma
- Sickle-cell disease
- Sjögren syndrome
- Status post–organ transplantation
- Systemic lupus erythematosus
- Thalassemia
- Trophoblastic disease
- Vasculitis
  - Behçet disease
  - Granulomatosis with polyangiitis (Wegener granulomatosis)
  - Microscopic polyangiopathy
  - Primary angiitis of the central nervous system

Note. Based on information from Lloyd, 2017; Meneshian et al., 2017; Miller, 2017; Oncology Nursing Society, 2016.

HD safe handling precautions are consistent no matter what the route of administration or the location in which HDs are administered. Those precautions that apply in all situations are listed in Figure 6 (ASHP, 2006; NIOSH, 2004; Polovich et al., 2014). Most recommended precautions are not new; one exception is the requirement for using a CSTD for the administration of antineoplastic HDs whenever the dosage form allows (USP, 2016a). The following sections detail safe handling recommendations for specific routes of HD administration.

Intravenous Infusions

PPE including a gown tested for use with HDs and two pairs of ASTM D6978-05 standard gloves must be

worn when administering IV infusions of HDs (NIOSH, 2016). CSTDs can be used in a number of different configurations. Manufacturers offer bag spike adapters that fit between the IV bag and the IV tubing spike if spiking must occur at the bedside. These bag spike adapters can prevent HCWs from inadvertently spiking through the side of the IV bag, prevent splashing or spillage of HDs, and also allow for backflushing of nondrug solution using closed-system components. Direct spikes are also available from most manufacturers. These allow for connecting the chemotherapy bag directly to a tubing that contains the corresponding CSTD. When neither of these adapters are used, IV bags containing HDs should only be spiked in a C-PEC to prevent exposure. Spiking into the CSTD bag spike adapter at the bedside should be performed below eye level after the tubing has first been primed with a nondrug solution. If tubing is not preprimed with a nondrug solution, then after spiking into the CSTD bag spike adapter, a backpriming technique should be used. A nondrug solution from the primary IV bag is used for backpriming. Under no circumstances should tubing be primed in such a way as to allow the escape of HDs into the environment (e.g., priming into gauze pads, sinks, or trash containers). Such practices frequently result in drug leakage (Rioufol et al., 2014). Glass IV bottles should not be used because of the need to vent during infusion and the potential for breakage.

Depending on how the HD was compounded, drug residue can exist on the exterior of IV bags and syringes (ASHP, 2006). Therefore, nurses should avoid touching IV bags or syringes without proper PPE. Drug residue can easily be spread to different areas within the healthcare setting. Contamination has been detected on the hands of HCWs involved in patient care and supportive staff who are not providing direct patient contact (Hon, Teschke, et al., 2014; Hon, Teschke, Shen, Demers, & Venners, 2015).

Luer-lock connections should be used to securely attach all IV tubing. A CSTD attached to the distal end of IV tubing can prevent leakage caused by inadvertent disconnection or failure to secure the tubing clamp (ASHP, 2006; Eisenberg, 2017).

Unspiking HD bags should not be performed outside of a C-PEC (ASHP, 2006; NIOSH, 2016). Changing the bag and tubing together helps to prevent potential exposure and contamination associated with unspiking. After administration of the HD is complete, the tubing should be thoroughly flushed with a nondrug solution prior to disconnect (NIOSH, 2004a). Residual HD drug in the IV tubing should be flushed using a CSTD or by using a backflush method with secondary tubing as described in the following section.

Unless using a CSTD at the connection site, a new IV tubing is recommended for sequential administration. A nondrug solution should be used to flush tubing prior to disconnecting. This can be accomplished by infusing HDs through a secondary IV tubing, which allows flushing of the primary tubing using the primary solution. Should there be residual HD in the secondary tubing, this can be infused by backpriming additional compatible solution from the primary IV bag.

At the conclusion of the infusion, wash hands and don appropriate PPE for disposal of used equipment. Remove the bag containing the HD with the tubing attached. Use of a CSTD on IV tubing may prevent leakage when the tubing is disconnected. Depending on the CSTD design, a cap should not be placed on the end of tubing as this can "open" the connection and allow HD to escape the tubing. Do not remove the spike from the bag, and do not respike (Polovich et al., 2014). Dispose of PPE, other potentially contaminated items, and the IV bag and tubing in the appropriate HD waste container, and wash hands with soap and water.

Figure 6. General Recommendations for Administration of Hazardous Drugs (HDs)

- Ensure appropriate supplies for administration are available.
- Have access to a spill kit.
- Wash hands thoroughly before donning personal protective equipment (PPE).
- Inspect the drug delivery bag and its contents prior to handling.
- Don PPE before reaching into the delivery bag to remove the drug container.
- Wear two pairs of gloves tested for use with HDs (National Institute for Occupational Safety and Health, 2004).
- Wear a mask with face protection if there is a chance of the HD splashing.
- Perform all work below eye level.
- Use a closed-system drug-transfer device when the dosage form allows.
- Remove gloves and gown in such a way as to prevent transfer of HD contamination to the skin or clothes.
- Remove outer gloves before touching equipment.
- Do not hang up gowns and reuse them.
- Wash hands with soap and water (as opposed to using alcohol-based hand gels) because friction and rinsing are necessary to assist in removing HD contamination.

Intravenous Injections

PPE including a gown tested for use with HDs and double gloves should be worn when administering IV injections of HDs. Syringes should not be transported with needles attached. Although needleless systems reduce the chance of injury, they do not prevent leaks at connection points. Because USP General Chapter 800 requires a CSTD for administration, dispens-

ing the HD with the CSTD already attached has the added benefit of preventing leakage during transport (ASHP, 2006; USP, 2016a). Syringes with HDs should not be filled more than three-fourths full. Air should not be expelled from the syringe to prevent release of drug aerosols (ASHP, 2006). After administration of the IV injection, flush the tubing thoroughly. Dispose of all used PPE and contaminated materials in the appropriate HD waste container and wash hands with soap and water.

Subcutaneous and Intramuscular Injections

For safety of IM and SC HD administration, basic consideration of injection depth, volume, and technique is necessary. The following muscle groups are recommended for IM injections: deltoid, dorsogluteal, rectus femoris, ventro-gluteal, and vastus laterals. For SC administration, the needle should puncture the epidermis and dermal layers of the SC tissues (Clinical Oncological Society of Australia, 2008). Hopkins (2013) defined large-volume IM injections as 3–5 ml or greater. Large-volume IM injections are considered a safer method of administration of oncologic medications than SC injections (Hopkins, 2013). The "Z" track method or technique should be used to administer irritating injectable medications (Hopkins, 2013).

Don a chemotherapy gown and double gloves for IM or SC injections of HDs. Syringes should not be transported with needles for injection attached. Use syringes that are less than three-fourths full and fitted with a CSTD (USP, 2016a). Nurses administering HDs via an SC or IM route should remember that if the drug arrives with a CSTD, the system will be "open" and unprotected once a needle has been attached. Therefore, precautions such as using a plastic-backed absorbent pad and gauze pads should be taken to protect the immediate area where the needle is being attached. Do not expel air from the syringe or prime the needle (ASHP, 2006). Sterile gauze can be used to absorb drug leakage at the injection site. After administering the drug, DO NOT recap, clip, or crush the needle. Place the syringe with the attached needle directly into a puncture-proof container specifically designed for HD waste (ASHP, 2006; NIOSH, 2004a). Remove and dispose of PPE.

Oral Agents

The use of oral antineoplastic agents for the treatment of cancer has grown tremendously in the past decade. Benefits to patients with cancer include increased patient convenience, decreased travel time, potential for increased quality of life, and increased autonomy. It is estimated that approximately 25% of patients with cancer receive an oral antineoplastic agent as part of their treatment. Patients self-administering these medications, caregivers, and HCWs should be instructed on the proper handling and disposal of oral antineoplastic agents to prevent accidental exposure and ensure drug integrity. These agents may be air, moisture, or light sensitive.

NIOSH recommends a "universal precautions" approach to PPE use for handling HDs, with one exception: for unit-dose packages of intact oral doses, it is acceptable to don a single pair of chemotherapy gloves (NIOSH, 2016). Open the package carefully. Because even intact HD tablets or capsules may be coated with residual HD dust (ASHP, 2006), while wearing a single pair of gloves, place the oral HD tablet or capsule directly into a medicine cup for administration. Because of the chance of inhalation exposure, manipulation of oral forms, such as breaking, crushing, or mixing tablets with food or fluids, should not be performed outside of a C-PEC. For non-intact, non–unit-dose forms, wear double gloves and a gown. A face shield should be worn if there is a potential for sprays, aerosols, or splattering of the agent, such as with liquid HDs. Protect the work area with a plastic-backed absorbent pad if necessary.

Crushing tablets or opening capsules for administration (e.g., to mix in food or to administer through a feeding tube) increases the risk of exposure. Liquid formulations dispensed in an oral or enteral syringe are preferred. Pharmacy should prepare any oral HD agents that require manipulation. They should be provided in single unit doses, in the final form, in an appropriate oral syringe ready for administration (Goodin et al., 2011). When this is not feasible, a safer alternative is to have pharmacy dispense the powdered drug in a bottle with a cap that is compatible with an oral or enteral syringe. If crushing of HDs must be done outside of pharmacy, don full PPE, including face protection; use a plastic-backed pad to protect the work environment; and use a single-use plastic pouch to contain the powder. Multi-use pill crushers or mortar and pestle should not be used. For nonsterile HD compounding, a gown tested to protect from HD permeation and double gloves tested to ASTM Standard D6978-05 (2013) are required. Dispose of the plastic-backed pad and PPE according to guidelines. Decontaminate and disinfect the surfaces in the work area. Oral HD agents should not be placed in automatic counting machines (Goodin et al., 2011) because even intact HD tablets or capsules may be coated with residual HD dust (ASHP, 2006).

Dispose of all used PPE and contaminated packaging in the appropriate HD waste container and wash hands with soap and water.

Nasal Enteral Tube and Enterostomy Tube Delivery

A nasogastric/nasoenteric tube is used when patients require short-term enteral nutrition. The tip of the tube is located in the fundus of the stomach. For patients who are at high risk for aspiration, the tip may be advanced into the jejunum. An enterostomy tube is used for long-term enteral nutrition or decompression, with the tip placed in the stomach or jejunum. Placement of the tube may affect absorption of medications. See Figure 7 for HD preparation and administration via nasogastric or enterostomy tubes.

Because of an increase in the number of FDA-approved oral HDs (Weingart et al., 2008), enteral tubes have become more common for the delivery of HDs. Research is limited on the use of nasoenteric and enterostomy tubes for HD administration and professional education and role responsibilities (e.g., RN and pharmacist) related to this procedure (Cantarini, McFarquhar, Smith, Bailey, & Marshall, 2004). However, a plethora of literature exists related to oral and nonhazardous medication administration by that method. This administration modality represents an opportunity for HD exposure (Bankhead et al., 2009; Connor & Eisenberg, 2010; Williams, 2008).

Solid oral formulations must be crushed to allow administration by tube. Current HD safe handling recommendations do not recommend crushing oral HDs outside of an engineering control. Not all medications are suitable for crushing. Dosage forms that should not be crushed include sustained-release/extended-release/slow-release tablets, enteric-coated tablets, film-coated tablets, and buccal/sublingual forms (Kaufman, 2009; Williams, 2008) (see Table 6). See Mitchell (2016) for a list of medications that should not be crushed, including many HDs. Nurses and pharmacists should consult the manufacturer's prescribing information for recommendations for specific drugs and newly released medications not on this chart, which is maintained by the Institute for Safe Medication Practices (ISMP).

HD solutions and suspensions should be prepared within a designated C-PEC and provided in a syringe and delivery devices described by ISMP (2015) with a CSTD when the dosage form allows. To facilitate a closed system, modify the Washburn (2007) instillation setup, using a closed-system connector with an adapter. Attach the syringe or bag to the connector-adapter setup. Then, attach to the female opening of the nasogastric tube/enterostomy tube system (see Figure 8). Beaver and Magnan (2015) described another closed-system option using solutions placed in an IV bag and attached to a CSTD. To ensure safety, confirm that the drug delivery container is labeled as an HD, that the route of administration is clearly identified, and that enteral-specific fitments are used to prevent inadvertent IV administration of a drug meant for enteral administration (Guenter & Hancock, 2014; ISMP, 2015).

HDs in an enteral feeding syringe should have a leakproof end cap when dispensed. Some drug references

Figure 7. Hazardous Drug Preparation and Administration via Nasogastric or Enterostomy Tubes

1. Identify the type of tube, number of lumens, the lumen identified for medication administration, and tip placement location.
2. Identify the type of enteral feeding (if applicable) to avoid drug–drug and drug–nutrient interactions.
3. Discuss the above considerations with the pharmacist, nutrition service, and medical team, as they may affect drug dosing, dilution, and reconstitution.
4. Determine the need to hold feedings, resume feedings, or both to prevent alteration of drug bioavailability. Continuous feedings may need to be stopped for 1–2 hours before and after medication administration. The orders must include specified time frames for holding feedings prior to and after hazardous drug administration.
5. The American Society for Parenteral and Enteral Nutrition does not recommend adding medication directly to enteral feedings. Refer to the drug package insert for information about mixing the medication with food.
6. If the enteral tubing system has more than one lumen, administer the medication separately through the non-enteral lumen.
7. Equipment preparation: EnFit system lacks evidence supporting its use as a closed-system drug-transfer device. Adapt the Washburn setup.
   a. Absorbent pad to place under tube–syringe connection
   b. Closed-system drug-transfer device whenever possible
   c. Personal protective equipment (PPE) and face shield
   d. Syringe and sterile saline for flushing before, between medications, and after
   e. Hazardous drug disposal container
8. Mix contents of capsules and crushed tablets in a closed system and/or, with use of PPE, with sterile water.
9. Stop the feeding and flush the tube with at least 15 ml of sterile water.
10. Administer reconstituted suspensions or solutions with a 30 ml syringe.
11. Flush the tube lumen between medications. CAUTION: Consider the patient's volume status and the ability to have free water.
12. Following completion of all medication, administer a final flush of 15 ml of sterile water before capping the tube lumen or resuming enteral feeding as directed.

Table 6. Oral Hazardous Drug Formulation Categories and Avenues of Exposure During Preparation and Administration

Preparation	Comments	Safety Measures	Avenues of HD Exposure	Considerations
Liquids	Preferred formulation for gastrostomy tube administration because the drug is readily absorbed and less likely to cause tube clogging	Oral HD-filled syringes must be labeled as NG or ORAL-HD to prevent inadvertent IV administration. Do not administer suspension macrogranules or mineral oil in NG tubes.	**Preparation:** Leakage during transfer of liquids from bottle to administration syringe **Administration:** Leakage from administration syringe or medicine cup during oral administration; leakage at the tube–syringe connection or tube insertion site during enteral administration	High concentration of sorbitol in drug formulation; check with pharmacist or package insert. Consult with pharmacy to determine if there is a specific time frame in which liquids must be administered due to stability. Manufacturer challenges exist to creation or adaption of closed-system drug-transfer devices. Pediatric bottle–syringe transfer systems can be adapted. Use of Luer-lock syringe may require adapters to accommodate Luer-lock connections.
Suspension	Lower sorbitol concentration compared to liquids	High osmolality, requiring dilution with water to decrease tonicity	**Preparation:** Leakage during transfer of suspension from bottle to administration syringe **Administration:** Leakage from administration syringe or medicine cup during oral administration; leakage at the tube–syringe connection or tube insertion site during enteral administration	Few HDs come in suspension formulation (i.e., megestrol, mycophenolate mofetil, valganciclovir). Manufacturer challenges exist to creation or adaptation of closed-system drug-transfer devices. Pediatric bottle–syringe transfer systems can be adapted. Use of Luer-lock syringe may require adapters to accommodate Luer-lock connections.
Immediate release (i.e., compressed tablets, sugar- or film-coated)	Crushing minimizes pharmacokinetic changes and considered more beneficial than some of the liquid formulations	Minimal pharmacokinetic changes	**Preparation:** Manipulation with mortar and pestle may generate powder, resulting in inhalation exposure and surface contamination; after reconstitution, leakage during transfer of solution to administration syringe. Some techniques exist for dissolving tablets within a syringe. **Administration:** Inhalation exposure from powder particulates and dermal exposure from surface contamination; if dissolved, leakage at the tube–syringe connection or tube insertion site during enteral administration	Perform preparation in C-PEC designated for nonsterile HDs. If unavailable, wear PPE including respirator. Consult with pharmacy to determine if there is a specific time frame in which drug must be administered due to stability (e.g., cyclophosphamide, gefitinib). Manufacturer challenges exist to creation or adaptation of closed-system drug-transfer devices. Pediatric bottle–syringe transfer systems can be adapted. Use of Luer-lock syringe may require adapters to accommodate Luer-lock connections.
Enteric-coated tablet	DO NOT CRUSH; Not appropriate for delivery through a feeding tube	Medication is released in the small intestine instead of the stomach. Crushing may result in increased toxicity. Crushing will cause tube clogging.	**Administration:** Exposure not likely with intact, unit-dose formulations administered orally	N/A

(Continued on next page)

Table 6. Oral Hazardous Drug Formulation Categories and Avenues of Exposure During Preparation and Administration *(Continued)*

Preparation	Comments	Safety Measures	Avenues of HD Exposure	Considerations
Powder-filled capsule	DO NOT CRUSH	N/A	**Preparation:** Opening capsules may aerosolize powder, resulting in inhalation exposure and surface contamination; after reconstitution, leakage during transfer of solution to administration syringe **Administration:** Exposure not likely with intact, unit-dose formulations administered orally; leakage possible at the tube–syringe connection or tube insertion site for enteral administration	Perform preparation in C-PEC designated for nonsterile HDs. If unavailable, wear PPE including respirator.
Gel-filled capsule	DO NOT CRUSH	Soft gelatin capsule generally contains a pharmaceutical dissolved or dispersed in a carrier that is compatible with the capsule wall. In addition to liquids, the fill material may take the form of a semisolid, solid, or gel.	**Preparation:** Opening capsules may result in dermal exposure or surface contamination; if gel is diluted, leakage during transfer into administration syringe **Administration:** Exposure not likely with intact, unit-dose formulations administered orally; leakage at the tube–syringe connection or tube insertion site for enteral administration	Perform preparation in C-PEC designated for nonsterile HDs. If unavailable, wear PPE.
Buccal or sublingual	DO NOT CRUSH	Not designed for gastrointestinal absorption, thereby reducing efficacy.	N/A	N/A

C-PEC—containment primary engineering control; HD—hazardous drug; N/A—not applicable; NG—nasogastric; PPE—personal protective equipment

Note. Based on information from Institute for Safe Medication Practices; 2015; Mitchell, 2016; Occupational Safety and Health Administration, 2015; Williams, 2008.

suggest that tablets may be dispersed in water or apple juice, stirred until dissolved, and then administered by tube (Turkoski, Lance, & Tomsik, 2009). This represents an increased risk of exposure and requires the use of a gown, double gloves, and a mask with face protection and a CSTD whenever possible. The tablet can be dispensed in a glass bottle with an oral syringe–compatible cap, and the liquid can be added to the bottle via a syringe and withdrawn, after dissolving, for administration.

Topical Agents

Cream or gel formulations of HDs are applied directly to the skin and are absorbed into cancerous lesions. The indications for topical HDs include squamous cell carcinoma and basal cell carcinoma, cutaneous T-cell lymphoma, penile cancer (National Comprehensive Cancer Network® [NCCN®], 2016a, 2016b, 2017a, 2017b), and some non-oncology indications. Intraoperatively, HDs may be placed in solution and then be applied topically to the trachea or eye (Mellinger, Skinker, Sears, Gardner, & Shult, 2010). Although little information exists concerning safety practices for topical HDs, dermal absorption is a primary concern for HCWs (Hon, Teschke, et al., 2014). Therefore, double gloves and gowns should be used, with eye protection if splashing is possible and respiratory protection if inhalation is possible (NIOSH, 2016). Clothes and linens that come in contact with the topical HDs should be handled with PPE. For isolated lesions, cover with gauze to prevent linen and clothing contamination. Keep the HD container in a zipper-lock bag, separate from all other medications, and handle only with PPE. Store carefully away from children and pets.

Intracavitary Administration

Intracavitary administration includes the instillation of HDs into the bladder, peritoneal space, chest, or other body cavity. These procedures represent a significant opportunity for exposure because the drug delivery equipment used is not designed to protect

HCWs. Washburn (2007) described a closed administration system for use with a syringe and any type of catheter that has a female opening (e.g., Foley catheter, feeding tube, suprapubic catheter, chest tube) by combining several pieces of equipment. A food-dye test demonstrated that leakage did not occur during drug administration when using this system. Figure 8 shows the Washburn setup.

For intracavitary HD administration, use a CSTD. Full PPE including face protection is required. Place plastic-backed absorbent pads under connections. If a closed system is not available for the dosage form, wrap sterile gauze around the tubing connection to reduce the potential for spraying or leaking of drug into the environment when attaching or removing the tubing or syringe.

Intravesical Administration

Intravesical HD administration is performed using a Foley catheter placed in the bladder for direct instillation. This type of treatment is used for patients with transitional cell cancer or urothelial bladder cancer (NCCN, 2017a). The HD usually is delivered through a urinary catheter placed into the bladder. A suprapubic catheter inserted through the pubic wall into the bladder also may be used to deliver HDs into the bladder. The type of catheter used will determine the type of connection needed for safe administration. If the catheter adapter has a slip connection, leaking can occur if the connection is loose, when excessive pressure is used during drug delivery, or when the syringe is disconnected from the catheter, such as when attaching a drainage bag.

Begin by having the patient empty the bladder or empty the urinary drainage bag of all urine. Use the Washburn (2007) setup when administering the drug by syringe. Place a plastic-backed absorbent pad under connections. While wearing PPE, administer the HD into the bladder through the Foley catheter followed by a normal saline flush. Clamp the Foley catheter. If ordered, instruct the patient to rotate from side to side to increase distribution of the drug solution to the entire bladder cavity. After the ordered dwell time, unclamp the Foley catheter and let the HD-contaminated fluid drain into the closed gravity-dependent Foley bag system. Prior to Foley removal, place a plastic-backed absorbent pad under the patient. Don double chemotherapy gloves, a chemotherapy gown, and a mask with face protection. Contain the entire intact urinary drainage system in a sealable bag and discard it in the designated HD waste container.

Beaver and Magnan (2015) developed a safe method for gravity administration of HDs into the bladder using IV tubing connected to the specimen port of a Foley catheter. If this method is used, the tubing must be labeled "For Intravesical Use Only" to prevent inadvertent IV administration. The tubing remains attached to the port until the catheter is discontinued, maintaining a closed system. The authors reported no spills or exposure over an eight-year period.

Intraperitoneal Delivery

Intraperitoneal (IP) delivery is a type of intracavitary administration of HD into the peritoneal space. The indication for IP administration is cytoreduced epithelial ovarian or peritoneal cancer (Markman & Olawaiye, 2017; NCCN, 2017b). This type of HD delivery results in high drug concentrations and longer drug half-life in the peritoneal cavity, thus increasing local effects of the drugs without high systemic concentration (Almadrones, 2007; Anastasia, 2012).

IP HDs are delivered through an IP implanted port where the catheter tip is located directly in the peritoneal cavity. The port device is placed subcutaneously over the lower ribs. The attached catheter is

Figure 8. Washburn Setup

Note. Image courtesy of Becton, Dickinson and Company. Used with permission.

either fenestrated (multiple holes along the distal half of the catheter in addition to the distal opening) or standard (with only the distal end open). This device may be placed during cytoreductive surgery (NCCN, 2017b) or using fluoroscopy in interventional radiology. Use IV tubing with a CSTD. Anchor the noncoring right-angle Huber needle securely to the port septum. Check the patency of the port system by flushing with sterile normal saline. If there is no resistance, proceed with administration.

A fenestrated Tenckhoff peritoneal dialysis catheter also may be used for peritoneal HD delivery. It is an external catheter that is inserted through the abdominal wall into the peritoneal cavity. A Dacron® cuff reduces peritoneal leaking and bacterial tracking (Rippe, 2007). When using an external catheter for IP drug delivery, use an adapter and CSTD that will accommodate a locking connection.

During IP delivery of HDs, wear a gown, double gloves, and a mask with face protection, and place a plastic-backed absorbent pad under connections. The prefilled infusion bag and tubing must be labeled "For Intracavitary Use Only" to prevent inadvertent IV administration. Infuse the drug solution. Once the infusion is complete, follow the physician's order regarding patient positioning and dwell time. If the infused solution is to be drained, leave the administration set connected. After drug delivery and prescribed dwell time (if applicable), withdraw or drain the residual solution. Handle the residual solution as contaminated body fluid and HD waste.

Intrapleural Administration

HD administered through the chest wall into the pleural space is indicated for malignant pleural effusions caused by mesotheliomas, carcinoma of the lung, breast cancer, lymphomas, ovarian cancer, and gastrointestinal tract cancers. Treatment for malignant pleural effusion includes repeated thoracentesis, chemical sclerosing, talc pleurodesis, and HD administration. A long-term intrapleural catheter may be placed, such as a chest tube, pigtail catheter, or fenestrated catheter (Shoji, Tanaka, Yanagihara, Inui, & Wada, 2002) or a Tenckhoff catheter (Walker & Bryden, 2010). A temporary thoracentesis needle can be used for fluid removal and HD administration. These placement procedures may be performed at the bedside, intraoperatively, or in interventional radiology.

While wearing a gown, double gloves, and a mask with face protection, place a plastic-backed absorbent pad under connections. Infuse the drug solution. The tubing must be labeled "For Intrapleural Use Only" to prevent inadvertent IV administration. Once the infusion is complete, follow the physician's order regarding patient positioning and dwell time. If the infused solution is to be drained, leave the administration set connected. After drug delivery and prescribed dwell time (if applicable), withdraw or drain the residual solution. Handle the residual solution as contaminated body fluid.

When using a chest tube (with or without collection device), implanted port, or Tenckhoff catheter, use IV tubing with a CSTD. After drug delivery and prescribed dwell time, attach the drainage apparatus to the connection and lower it to collect the residual solution. If the catheter tubing has a female opening, consider adaptation of the Washburn setup as shown in Figure 8.

Handle the residual solution as contaminated body fluid, wearing a gown, double gloves, and a mask with face protection. Dispose of all materials used in the administration as HD waste. Remove PPE, seal in plastic bag, and dispose of in appropriate container. Wash hands thoroughly with soap and water. Don gloves and decontaminate equipment used during administration. Wash hands thoroughly.

Transpulmonary chemoembolization may be performed using mitomycin C, cisplatin, gemcitabine, or doxorubicin embedded into embolizing microspheres. A gown, double gloves, a mask with face protection, and CSTD are recommended for the preparation, administration, and aftercare (Vogl, Shafinaden, Sangos, Lindemayr, & Vatankhah, 2013).

Aerosolized or Inhaled Administration

Aerosol delivery is the administration of HDs via particles that are inhaled and absorbed through the lungs. Aerosol drug administration may be referred to as *inhalation* or *nebulized therapy*. Aerosols include metered dose inhaler systems, dry powder inhalers, and nebulizers for delivery of high concentrations of HDs locally while minimizing systemic toxicity. The target area for delivery is the pulmonary system (Kaparissides, Alexandridou, Kotti, & Chaitidou, 2006) and the central nervous system (CNS). When administering aerosolized HDs, the HCW must wear a NIOSH-certified respirator (ASHP, 2006; OSHA, 2016; USP, 2016a). Coordinate the procedure with the safety officer and respiratory therapist (Mooney, Melvin, & Douglas, 2014). Inhalation of HDs should take place in a negative pressure room using a closed inhalation system that isolates the patient in a vinyl enclosure similar to an oxygen tent. Air is drawn upward from the area inside the canopy and flows through a HEPA filter. Don PPE including a full-facepiece, chemical cartridge-type respirator or powered air-purifying respirator (PAPR), a gown, double gloves, a cap, and shoe covers when aerosolized HDs are present because aero-

sols may be deposited on skin and surfaces (Latchford & Shelton, 2003; Mooney et al., 2014).

A new method for treating peritoneal disease is with aerosolized drugs. This is referred to as pressurized intraperitoneal aerosol chemotherapy (PIPAC). Prior to doing the procedure, simulations must occur to ensure reduction of environmental contamination and to maintain therapeutic effect (Solass, Giger-Pabst, Zieren, & Reymond, 2013).

Implanted Time-Release Delivery

The chance of occupational exposure to nanoparticles has not been addressed but is possible because of the particle size (Stern & McNeil, 2008). A thin-film polymer sandwich of nanodiamonds clustered with HDs, RNA, or other targeting material is placed in a tumor bed following tumor removal or debulking. This delivery system allows drug release to a specific location (Ho, 2008; Kunwar et al., 2007; Mardor et al., 2005). An example of this is the use of polymer wafers in the treatment of brain tumors (polifeprosan 20 with carmustine implant). These HD-impregnated wafers are placed intraoperatively following tumor debulking. The surgical team wears gloves tested for use with HDs when handling the wafer during implantation and disposes of the wafer packaging in an HD waste container. Refer to the package insert to determine duration of drug release and length of time to use precautions after placement.

Intraventricular, Intrathecal, Intraspinal, and Intracerebral Administration

The blood-brain barrier significantly limits drug penetration into the CNS when drugs are administered by the parenteral or oral route (Batchelor & Supko, 2009; Neuwelt, 2004; Sampson et al., 2006). A number of delivery methods are designed to allow HDs to cross the blood-brain barrier. These systems include intraventricular, intrathecal, intra-arterial, intracerebral, convection-enhanced delivery procedure and device, and interstitial.

The intraventricular and intrathecal routes are methods used to deliver HDs into the cerebrospinal fluid (CSF). Indications for administration of HD via these routes include CNS carcinomatosis, leptomeningeal metastasis, and CNS leukemic infiltrates (Aiello-Laws & Rutledge, 2008; Batchelor, 2015; Batchelor & Supko, 2009; Becker & Baehring, 2015; Sampson et al., 2006).

Intrathecal HD administration is delivered through a lumbar puncture by a credentialed physician or advanced practitioner. The lumbar puncture is an invasive and sterile procedure. Sterile gloves tested for use with HDs should be worn. The provider dons a sterile gown, double gloves (outer sterile gloves), and a mask with face protection and places a plastic-backed absorbent pad under the site where the needle enters the spine and the syringe connection. To prevent increased CSF pressure, a small volume of CSF equal to the volume of drug is removed. The HD-filled syringe that is labeled "For Intrathecal Administration Only" is attached to a spinal needle, and the HD is slowly injected. The HD-filled syringe may not be sterile on the outside. The provider should access the CSF with sterile gloves and then administer intrathecal medication without touching the sterile access site. The lumbar needle and infusion syringe/tubing set should be discarded in an HD waste container.

If an epidural catheter is used for the intrathecal delivery system, the catheter can be accessed for intermittent bolus administration or can be attached to an infusion pump. Access and administration using these delivery systems may be performed by credentialed advanced practitioners or RNs who have demonstrated clinical competence for this procedure. Recommended safe handling precautions are the same as for IV HD administration.

An implanted reservoir (Ommaya reservoir) is a silicone reservoir placed subcutaneously under the scalp that can be used to deliver HDs into the ventricles. The reservoir may be placed surgically or in interventional radiology. HD administration using an implanted reservoir is performed by a physician, an advanced practitioner, or an RN with demonstrated clinical competence, depending on the state nurse practice act or local policy. When accessing the implanted reservoir, use a CSTD connected to the appropriate tubing and needle. Wear double gloves, a gown, and a mask with face protection. The HD-filled syringe labeled "For Intraventricular or Ommaya Use Only" may not be sterile on the outside. The provider should access the implanted reservoir with sterile gloves and then administer intrathecal medication without touching the sterile access site. Handle CSF fluid as contaminated, and dispose of all materials used in the administration as HD waste.

An interstitial CNS drug delivery system circumvents the blood-brain barrier, resulting in higher HD concentrations with minimal systemic exposure and toxicity. Three categories of interstitial CNS delivery systems exist based on the infusion mechanism of the pumps. The catheters can be placed in the epidural space or intracranially. These pumps may be implanted for external attachment and are as follows:

- The Infusaid™ Pump uses compressed pressure generated from Freon® gas vapor to deliver HDs at a constant rate.

- The MiniMed® Programmable Implantable Infusion System uses a solenoid pumping mechanism.
- The SynchroMed® drug delivery system uses a peristaltic mechanism.

These pumps may also be used for other HD delivery applications (i.e., intra-arterial). Accessing and refilling these delivery systems may be performed only by credentialed physicians, advanced practitioners, or RNs who have demonstrated clinical competence for this procedure.

Ocular Administration

HDs may be administered into the eye, by either subconjunctival or intravitreal administration. This type of procedure is performed by a credentialed practitioner or ophthalmologist for refractory or recurrent intraocular parenchymal or leptomeningeal lymphoma (de Smet, Vancs, Kohler, Solomon, & Chan, 1999), retinoblastoma (Hayden et al., 2004; Mulvihill et al., 2003), and ocular Behçet disease (Atmaca-Sonmez, Atmaca, & Aydintug, 2007).

The HD is prepared in a syringe with an attached CSTD for injection. Wear double chemotherapy gloves, a chemotherapy gown, and a mask with face protection. Drape the patient to contain leakage. Handle any drainage as contaminated body fluid, and dispose of all materials used in the administration as HD waste.

For subconjunctival HD administration, sterile sponges soaked in the HD are then applied. The current practice involves placement of the sponges in open surgical bowls with placement of the HD solution into the bowl. Manufacturers are now developing closed-system kits for HD infusion of sponges in closed containers. This system allows for removal of residual HD prior to extracting the presoaked sponges, thereby reducing the amount of HD handling, dripping, and aerosolization (Mobius Therapeutics, LLC, 2012).

Intra-Arterial Delivery

HDs may be administered into an artery that is the primary blood supply to a tumor. Angiography is performed to visualize the vessels that supply the tumor. A catheter is placed and advanced into the identified artery. The HD is administered, exposing the tumor to high drug concentrations with significant reduction in systemic toxicities. One of the goals of this procedure may also be to occlude the arteries feeding the tumor. This procedure is used for primary hepatocellular carcinoma, head and neck cancers, and solitary hepatic metastases from other primary tumors (Roth et al., 2000). HDs should be prepared by pharmacy and labeled "For Intra-Arterial or Hepatic Administration Only" and provided for administration with the use of CSTDs. A gown, double gloves, and a mask with face protection should be worn during intra-arterial delivery of HDs.

Percutaneous Intra-Arterial Administration

Femoral, brachial, or carotid vessels are the most common arteries accessed percutaneously for intra-arterial administration of chemotherapy. The hepatic arteries are the most common vessels entered. Percutaneous administration may represent a significant opportunity for exposure because of bleeding at the puncture site and because the drug delivery equipment used may not be designed to protect HCWs. Use a CSTD or locking connections whenever possible. Wear double sterile chemotherapy gloves, a sterile impermeable gown, and a face shield if indicated. Sterile gloves must be changed every 30 minutes for lengthy procedures (ASHP, 2006; Wallemacq et al., 2006). Place plastic-backed absorbent pads under the patient. Wrap sterile gauze around the connection to reduce the potential for spraying or leaking of the drug into the environment when attaching or removing the tubing or syringe. Dispose of all materials used in the administration as HD waste. If HDs are transferred from vials or other systems in the procedural suite, the transfer must be performed using a CSTD to prevent exposure of staff and environmental contamination. If closed systems are unavailable, then all staff must wear a respirator (ASHP, 2006; Matthews, Snell, & Coats, 2006; Muehlbauer et al., 2006; NIOSH, 2004a).

Continuous Infusion by Intra-Arterially Placed Pump

HDs may be delivered intra-arterially through an implanted pump by nurses with a demonstrated clinical competence for this procedure, advanced practitioners, or physicians. When accessing or using the intra-arterial infusion pump, use a closed or Luer-lock connection and a Huber needle-tubing system. Don double gloves, a gown, and a mask with face protection. Place plastic-backed absorbent pads under the connection. Wrap sterile gauze around the connection to reduce the potential for spraying or leaking of the drug into the environment when attaching or removing the tubing or syringe. Once the procedure is completed, dispose of the administration equipment as HD waste.

Chemoembolization

Chemoembolization is a cancer treatment that combines local delivery of chemotherapy and occlu-

sion of blood vessels supplying the tumor. It is most commonly used for liver tumors. In addition to cytotoxic agents, embolic agents are injected with the goal of trapping the chemotherapy in the tumor-feeding vessel(s). Transcatheter arterial chemoembolization allows for delivery of higher doses of chemotherapy and higher drug concentration over a longer period of time. Microspheres are loaded with either doxorubicin or cisplatin and then injected into the liver or tumor.

This procedure is performed in interventional radiology. HD PPE must be incorporated into the sterile procedure using CSTDs for drug preparation and administration. HD PPE is recommended for aftercare.

Nontraditional Settings for Hazardous Drug Delivery

HD handling can occur in many healthcare settings. The opportunities for HCW exposure to HDs in alternative settings are related to the type of procedures performed. Procedures may involve administration of HDs or may be performed for patients who have recently received HDs, and their body fluids are a source of exposure. HD PPE precautions are necessary to avoid exposure while handling patients' contaminated excreta, including blood, urine, feces, tissue specimens, effusions, and all body fluids. It is essential that nurses communicate with personnel in these settings where patients are cared for so that they will be aware of the potential for HD exposure. The staff in these settings may not be trained in the use of HD safe handling precautions. Non-nursing staff may be involved with the handling or processing of body fluids and tissue and need to be informed that the materials or substances require handling precautions.

To assist the personnel in these settings and determine what HD PPE should be used, consider the type of HD exposure potential. In addition to HD administration, personnel may be responsible for handling contaminated excreta (urine, feces, vomitus, respiratory secretions), tissue specimens (e.g., blood, urine, CSF, tissue). Patients may be diaphoretic, be unable to control their own saliva, or require assistance with bathing and showering. Consider the need for cleaning surfaces and disposing of waste. Understanding the situation will help in determining the selection of HD PPE and when HD PPE would be used.

Some examples of nontraditional settings for HD administration or management include the following:

- Radiology departments
- Pulmonary laboratories (e.g., during bronchoscopy)
- Nuclear medicine departments
- Computed tomography/magnetic resonance imaging locations (i.e., biopsies)
- Gastrointestinal laboratories (e.g., during endoscopy or sigmoid-colonoscopy)
- Cardiac catheterization laboratories/suites
- Radiation therapy departments
- Ultrasound/sonography departments (e.g., effusion removal, fluid pocket aspirations, biopsies)
- Skilled nursing facilities and long-term care facilities
- Rehabilitation facilities
- Homecare settings
- Hemodialysis departments
- Pheresis departments
- Operating room (OR) and postanesthesia care settings
- Veterinary clinics and hospitals
- Pharmacy mini-clinics
- Clinical laboratories
- Camps and schools
- Coroner's offices
- Mortuaries
- Dental offices
- Wound care clinics

Dialysis and Pheresis

When patients receiving HDs undergo hemodialysis, it is strongly recommended that the HD administration be coordinated with the nephrologist and hemodialysis RN. Any staff involved in patient care must wear chemotherapy (HD)-designated PPE when disposing of the dialysate solution and tubing. The hemodialysis equipment must be decontaminated prior to its next use or removal from the patient care setting.

Apheresis is a procedure that involves removing whole blood and separating it into individual components so that a particular component can be removed. The remaining blood components are then reinfused into the bloodstream of the patient or donor. Apheresis is used for the collection of donor blood components as well as for the treatment of certain medical conditions. Screen the patient's or donor's medication list for use of HDs within the past 48 hours. Use HD safe handling precautions during the procedure. Consider all disposable equipment contaminated, and discard it in an HD waste container. Decontaminate all nondisposable equipment after use.

Operative and Interventional Settings

When HDs are administered intraoperatively, the rooms must be prepared prior to the patient's arrival. Take into consideration "open" versus "closed" surgical procedures when setting up the rooms. Place absorbent pads on the OR table to absorb HD-contaminated fluids that may leak during the procedure. Place absor-

bent pads on the floor between the setup table and the OR table. This is a high-traffic area for the medical, nursing, and technician team preparing medications, guidewires, and other instrumentation. Fluids that leak on the floor could potentially be tracked elsewhere on the shoe covers of the OR team (Connor & Eisenberg, 2010). Dispose of all fluid collection devices (e.g., nasogastric, Foley, suction drains and canisters) and surgical sponges as HD waste. Coordinate HD drug preparation with the pharmacy. Using a CSTD will minimize HD leakage and aerosolization (Foltz, Wavrin, & Sticca, 2004). HD PPE gloves and gowns are to be sterile. PAPRs are highly recommended (NIOSH, 2004) to prevent exposure to splashing, contact, and inhalation with HD-soaked tissues.

When feasible, use disposable equipment. Decontaminate reusable equipment (Muehlbauer et al., 2006). Ensure that instrument carts with contaminated/used instruments are labeled with a chemo/HD label. Handle tissue specimens as contaminated items. Make sure that recovery staff wear PPE when coming in contact with the patient and any excreta for at least 48 hours. If the patient is discharged home, inform the family and caretakers about the appropriate precautions for handling excreta. Examples of some types of intraoperative procedures involving HDs include the following:

- Isolated limb perfusion for extremity sarcomas or melanomas (Matthews et al., 2006; Singer, Tap, Crago, & O'Sullivan, 2015)
- Isolated hepatic perfusion (Fong, Dupuy, Feng, & Abou-Alfa, 2015; Muehlbauer et al., 2006)
- Intraoperative IP HD administration
- Intraoperative closed technique: Following cytoreduction, inflow and outflow catheters are placed. Following temporary closure of the abdomen, the chemotherapy solution is infused. The abdominal wall is manually agitated during the perfusion period to promote uniform infusate distribution. At the completion of the perfusion, the abdomen is reopened, and the solution is evacuated.
- Open abdomen technique (coliseum technique): Inflow and outflow catheters are placed as described. A Silastic® sheet is sutured over a retractor and to the patient's skin, over the abdominal opening. This creates a container for the instillation of the chemotherapy infusate.

Hyperthermic IP chemotherapy: Following cytoreductive surgery, a Tenckhoff catheter and closed suction drains are placed through the abdominal wall and made watertight with purse-string sutures at the skin. Temperature probes are secured into the skin. The skin edges are then sutured to the self-retaining retractor, and a plastic sheet is incorporated into these sutures to create an open space beneath using the coliseum technique. During a 1½-hour perfusion, all the peritoneal anatomic structures are uniformly exposed to heat and chemotherapy. The surgeon vigorously manipulates all viscera to minimize peritoneal adherence. A heat exchanger keeps the circulating fluid at 44°C–46°C. A smoke evacuator is used to pull air from beneath the plastic cover through activated charcoal, reducing aerosols in the OR suite. Following completion of the intraoperative perfusion, the abdomen is suctioned and surgically closed (Foltz et al., 2004; Yan, Stuart, Yoo, & Sugarbaker, 2006). Drapes and gloves used during the surgical procedure are likely to be contaminated with HDs (Villa et al., 2015).

PIPAC: PIPAC for peritoneal carcinomatosis is a new procedure that is showing promise. This is performed during a closed abdomen procedure that is remotely controlled. Safety conditions include laminar airflow, controlled aerosol waste, a protective curtain, and a toxicology workplace analysis before and after procedural implementation to ensure safety is attained (Solass et al., 2013). The air at the surgeon's and anesthesiologist's working positions is sampled for HDs. Strict adherence to safety procedures and use of a closed system for the nebulizer and infusion tubing are paramount in reducing environmental contamination and OR staff exposure. Sterile gloves tested for use with HDs and protective glasses should be worn. The OR team should follow HD precautions during the procedure and the suite cleaning. The staff caring for the postprocedural patient must use HD PPE for at least 48 hours after the procedure.

Post-Administration Issues

Key Points

- Most drugs are excreted in body fluids within 48 hours of administration.
- PPE, consisting of a gown and two pairs of HD-tested gloves, should be worn when handling body fluids of patients within 48 hours of drug administration. A face shield should be worn if splashing is likely.

Variable amounts of HDs and their metabolites are excreted in the urine, stool, sweat, and other body excreta of patients receiving HDs. As an example, cyclophosphamide has been detected in patients' urine for up to five days after an IV dose (Yuki et al. 2015). Not all references agree on elimination data, and variables such as infusion rate and renal and hepatic function can influence how long active drug or metabolites are present in stool and urine. Although information is not available for all drugs, two days (48 hours) has been recommended as a time frame for use of HD precautions when handling body fluids because the majority of drugs are excreted within this time (American Society of Hospital Pharmacists, 1990; OSHA, 2016). Drugs falling outside of that window are presented in Table 7. It should be noted that not all drug references are clear regarding whether the drug is excreted in an active form or as metabolites, and limited evidence exists to determine the potential hazard of those metabolites. Some practice settings may prefer to adapt drug-specific time frames for instituting protective precautions, whereas others may opt to simplify by using one time frame for all HDs. Organizations using computerized provider order entry may add information about the duration of precautions to orders for specific HDs.

Other exceptions to the duration of the precautions may occur. One of these is the presence of effusions. HDs have been measured in peritoneal and pleural effusions (Gotlieb et al., 2007; Pestieau, Schnake, Stuart, & Sugarbaker, 2001; Shoji et al., 2002; Van der Speeten, Stuart, Mahteme, & Sugarbaker, 2009; Yulan et al., 2003). This has implications for invasive procedures, such as paracentesis, thoracentesis, or pericardiocentesis. In addition, nanoformulations of drugs also extend or delay HD release or activation (Muehlbauer et al., 2006; Muthu & Singh, 2009). HD residue may be present longer, necessitating use of precautions for extended periods of time.

Some HDs are secreted in breast milk. Although information about drug secretion in breast milk is

Table 7. Hazardous Drugs Requiring Personal Protection for Longer Than Two Days

Hazardous Drug	Detected in Urine	Detected in Stool or Bile
Brentuximab vedotin	24% excretion for up to 7 days	72% excretion for up to 7 days
Carmustine	60% excretion for at least 4 days	–
Cisplatin	At least 5 days	–
Cyclophosphamide	Detected in urine up to 5 days	–
Docetaxel	9% excretion for up to 7 days	< 8% excretion for up to 7 days
Doxorubicin	5%–12% excretion for up to 5 days	40% excretion (biliary) for up to 7 days
Eribulin mesylate	7% excretion (> 40 hours)	72% excretion (> 40 hours)
Etoposide	25% excretion for at least 5 days	44% excretion for at least 5 days
Gemcitabine	< 10% excretion for at least 7 days	–
Imatinib mesylate	5%* excretion for up to 7 days	20% excretion for up to 7 days
Ixabepilone	5.6% excretion for up to 7 days	1.6% excretion for up to 7 days
Mitoxantrone	7% excretion for up to 5 days	Up to 5 days
Temsirolimus	4.6% excretion for up to 14 days	76% excretion for up to 14 days
Teniposide	40%* excretion for up to 5 days	–
Vincristine	10%–37% excretion for up to 3 days	80% excretion for up to 3 days
Vincristine liposomal	8% excretion for up to 4 days	–
Vinorelbine	8% excretion for at least 3 days	50% biliary excretion for at least 3 days

Note. All percentages are for active/unchanged drug unless denoted by an asterisk.

Based on information from American Society of Health-System Pharmacists, 2009; Bedikian et al., 2006; "Cyclophosphamide," 2015; Hospira Inc., 2013; Wolters Kluwer, 2015.

often unknown, it is available for some HDs (see Figure 9). Nursing infants may receive up to 10% of the maternal dose of imatinib. It is also possible for some drugs to be present in higher concentrations in breast milk than in serum. Breastfeeding nurses should avoid exposure to HDs because of the potential for drug in breast milk.

HDs may be present in emesis following oral administration. Methotrexate also has been measured in the emesis of patients who received it intravenously (Mader et al., 1996). HDs have been measured in the sweat of patients receiving high doses of methotrexate (Mader et al., 1996) and other HDs administered in myeloablative doses such as thiotepa (Horn, Beveridge, Egorin, Abeloff, & Hood, 1989). Cyclophosphamide has been found in the seminal fluid of rats (Hales, Smith, & Robaire, 1986). Hays et al. (2013) published a case study in which platinum levels were monitored in the breast milk of a patient with ovarian cancer. After a 70 mg dose of cisplatin on day 1, platinum levels were undetectable by 66 hours. The authors concluded that additional research is needed to determine the effect on levels after repeat dosing of cisplatin.

The American Academy of Pediatrics (2012) stated that breastfeeding is not recommended during therapy with chemotherapy agents; however, it does not specify when breastfeeding can be safely resumed. Patients who are breastfeeding should consult with their oncologist and obstetrician for guidance. The National Institutes of Health offers useful resources for breastfeeding women at www.toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. Medications and Mothers' Milk Online (www.medsmilk.com/pages/home) is another resource that provides information related to breastfeeding while taking medications.

Figure 9. Some Hazardous Drugs Known to Be Secreted in Breast Milk

- Arsenic trioxide
- Cisplatin
- Cyclophosphamide
- Cyclosporine
- Doxorubicin
- Etoposide
- Exemestane
- Goserelin
- Imatinib
- Interferon alfa-2b
- Lomustine
- Megestrol acetate
- Mercaptopurine
- Methotrexate
- Mitomycin
- Mitoxantrone
- Streptozocin
- Tacrolimus
- Tretinoin
- Vincristine
- Zidovudine

Note. Based on information from Turkoski et al., 2009.

HCWs must wear a gown and double gloves when handling the body fluids of patients who have received HDs for a minimum of two days after completion of therapy (Polovich et al., 2014). Some HDs are excreted for longer than two days (see Table 7). A mask with face protection should be worn whenever splashing is possible.

Published surveys have demonstrated poor compliance of HCWs for wearing PPE while handling excreta of patients being treated with HDs (Martin & Larson, 2003; Nieweg et al., 1994). When nurses do not follow safe handling precautions, they place themselves at risk for exposure (Connor & McDiarmid, 2006). Some hospitals and clinics post a sign in the patient's bathroom alerting nurses and ancillary staff to use PPE when emptying excreta. This may be particularly useful for staff who are not aware that the patient has received HD.

No published research has established the effectiveness of double flushing for reducing HD contamination. Some hospital toilets use powerful, high-pressure flushing mechanisms, and many do not have a lid, which can potentially result in aerosolization during flushing. The toilet should be covered with a plastic-backed absorbent pad while flushing. This can protect the HCW from splashing and minimize environmental contamination of HD. A bedpan washer (e.g., hopper) should not be used to clean containers that contain HD waste. Single-use bedpans or urinals should be used. It is not recommended to rinse or wash these items between uses. The HCW should wear PPE while handling the plastic-backed pad and dispose of it in the appropriate waste container.

Double flushing at home may be useful in situations where there is insufficient volume or pressure to clear the toilet after use (Polovich et al., 2014). Nurses should discuss the topic with patients prior to discharge and ultimately allow them to determine whether the additional flush is warranted. When family members handle patients' contaminated excreta, they should wear double gloves and avoid contact with the patient's urine or other body fluids, as absorption of HD can occur (Yuki et al., 2013).

In addition to donning PPE, nurses and supportive personnel should consider other ways to reduce exposure to HDs found in body fluids. Such measures may include the following:

- Use patients' weights rather than intake and output to monitor fluid status.
- Weigh urinary output collected in drainage bags rather than measuring volume to reduce the risk

of splashing when transferring urine into a second container before disposal.
- Encourage men to sit on toilet seats rather than standing to reduce the risk of droplet contamination.
- Encourage use of toilets rather than urinals and bedpans when feasible to decrease the possibility of spillage and the need for handling urine by HCWs.
- Collect drainage of pleural, peritoneal, and other body fluids in a closed system that can be disposed of intact.
- Use disposable ostomy pouches rather than rinsing and reusing them.
- Protect the skin of incontinent patients from their own excreta. The metabolites of drugs found in the urine or stool may be damaging to the skin. Cleanse the skin with soap and water and apply a moisture barrier to the perineal and perirectal areas following each incontinent episode of urination or stool. Apply a clean disposable diaper. Use a plastic-backed disposable pad under incontinent patients to provide a barrier to the linens and bed.
- A Foley catheter should be considered for incontinent patients who are within 48 hours of HD administration to protect staff from exposure to HD-contaminated urine.
- Use a Vacutainer® system when collecting blood samples to reduce the chance of blood exposure when transferring blood from a syringe to a specimen tube.

Linen Handling

Key Points

- Many drugs are excreted in the urine and other body fluids, creating a risk of exposure to anyone handling contaminated linens.
- In healthcare institutions, linens contaminated with body fluids should be double bagged with a specially marked linen bag inside and an impervious bag on the outside.
- In the home, linens contaminated with body fluids should be double washed separately from other laundry.

Linens contaminated with HDs pose a potential health risk for HCWs, family members, and other caregivers who come in contact with them. In a survey of four Dutch hospitals, Fransman, Huizer, Tuerk, and Kromhout (2007) found measurable concentrations of cyclophosphamide on approximately 75% of the bed linens of patients being treated with cyclophosphamide. Meijster, Fransman, Veldhof, and Kromhout (2006) found that workers sorting contaminated linens in an industrial laundry facility were exposed to low levels (approximately 4.5 ng/m^3) of airborne cyclophosphamide. While the HD exposure may be less when handling contaminated linens than when handling a drug during the preparation and administration phases, many drugs are excreted unchanged in the urine, and a safe level of HD exposure is unknown. When considering linen handling, there should be two primary areas of focus. First, implement practices to prevent linen contamination. Second, ensure safe handling of linens that are contaminated with HDs to reduce occupational exposure and workplace contamination.

Figure 10 identifies ways to reduce the contamination of linens with HDs. These methods focus on using disposable items and fabrics that are less permeable to fluids than traditional cloth linens. Particular attention should be paid to these practices when patients are incontinent. Disposable items that are contaminated with HDs should be disposed of in accordance with federal, state, and local laws (OSHA, 2016).

In the event that linens do become contaminated with HDs as a result of a spill or contact with body fluids that may contain residual HDs because of incontinence, vomiting, or diaphoresis, the linens require special handling. OSHA (2016) specifies that linens contaminated with blood, other potentially infectious materials, and excreta must be handled according to the Bloodborne Pathogens Standard (1992). It recommends that linens contaminated with HDs be double bagged, first in a specially marked bag and then in labeled impervious bags. At the laundry facility, OSHA recommends that the outer impervious bag should be removed and discarded after the inner bag containing the contaminated linens is placed directly into the washing machine. The laundry bag and contents should be prewashed alone before a second washing with other laundry (OSHA, 2016). There is evidence that prewashing alone is sufficient to remove HDs from contaminated laundry (Fransman, Huizer, et al., 2007), but a second washing is still recommended. Recommendations from NIOSH (2004a) specify that workers who handle contaminated linens should wear two pairs of gloves tested for use with HDs and a disposable impermeable gown.

Some hospitals and laundry services do not require HD-contaminated laundry to be double bagged because they treat all linens as potentially hazardous or biohazardous waste. To that end, they double wash and bleach all linens, and laundry personnel don full PPE for handling all linens. The OSHA Bloodborne Pathogens Standard (1992) requires employers to ensure that employees wear appropriate PPE, such as gloves, gowns, masks, and face protection, when handling linens contaminated with bloodborne pathogens. OSHA does not set specific standards for handling linens contaminated with HDs but refers to the Bloodborne Pathogens Standard (1992) for guidance. In organizations where all laundry is handled as contaminated, the laundry must be bagged in an impervious bag to prevent environmental contamination resulting from soak-through and leakage. Nurses working in settings where all linen waste is not double bagged should investigate to ensure that appropriate care is being taken in the laundry department to protect the employees and the environment.

Figure 10. Ways to Reduce Contamination of Linens With Hazardous Drugs

- For incontinent patients, both children and adults, disposable, plastic-backed, leak-resistant diapers are preferred to cloth diapers that are intended for washing and reuse.
- Use plastic- or vinyl-covered pillows rather than cloth-covered pillows to make cleaning easier in the case of hazardous drug contamination.
- Discourage the use of bedpans and bedside urinals, which are prone to spilling. Instead, encourage ambulatory patients to use the bathroom facilities.
- Use plastic- or vinyl-treated chairs that can be easily decontaminated rather than upholstered chairs that cannot be readily cleaned.

The current standard for handling HD-contaminated linens is to adhere to recommendations in the bloodborne pathogens standard as described previously. The Association for Linen Management (formerly the National Association of Institutional Linen Management), however, proposes strict double bagging of all hospital laundry of patients who have received HDs in the past 48 hours (up to seven days in specific instances). The association proposes a three-step process that includes recognition of potentially contaminated linens, education and training, and work practice recommendations. The proposal recommends that HD-contaminated linens be identified as such and suggests use of yellow bags, as yellow is typically used to identify trace chemotherapy wastes. They specifically state that red bags should not be used for HD-contaminated linens, as the red bag communicates to laundry personnel that the bag contains biohazardous waste that has been sent accidentally to the laundry (Association for Linen Management, 2009).

For patients receiving HDs, home linens can be handled the same as other household laundry. Special handling should be implemented if an HD spill occurs in the home or if laundry becomes contaminated with the excreta of the person receiving HDs. In the home, patients should handle their own contaminated linens when feasible. Family members or caregivers should don gowns and double gloves if they are handling contaminated linens. Contaminated linens in the home should be double washed with hot water and detergent separately from other household laundry. Bleach should be used when feasible, considering the fabric, for its role in deactivating HDs. Whenever possible, the contaminated items should be placed directly into the washing machine to avoid contamination of any intermediary storage container. If the contaminated laundry cannot be washed immediately, placing the items in a plastic bag prevents contamination of a laundry basket or storage container. The plastic bag should be disposed of immediately in the household trash after the linens are placed in the washing machine to prevent spreading contamination. A commonsense approach to handling HD-contaminated linens will prevent further environmental contamination in both the homecare and healthcare settings.

Environmental Decontamination

Key Points

- No one cleaner has been shown to effectively decontaminate and clean surfaces exposed to HDs.
- Sodium hypochlorite (bleach) has been shown to be the most efficient solution to clean and decontaminate HD surfaces but can cause damage to surfaces and requires deactivation.
- Thorough cleaning with a detergent solution is recommended in areas where HDs are administered.

A review of the literature on the decontamination and cleaning of HD-contaminated surfaces reveals that there is no "magic bullet" cleaning agent that exhibits 100% removal efficiency for all drugs on all surfaces. However, a number of studies have shown that sodium hypochlorite (bleach) has the highest average removal efficiency of all the agents tested (Gohma, Inoue, Asano, & Sugiura, 2015; Hon, Chua, Danyluk, & Astrakianakis, 2014; Lee, Ambados, Tkaczuk, & Jankewicz, 2009; Queruau Lamerie et al., 2012; Touzin, Bussières, Langlois, Lefebvre, & Métra, 2010). In at least one study, a combination of cleaning agents was shown to be more effective than use of a single agent. Hon, Chua, et al. (2014) reported that the application of IPA, after the use of an initial cleaning agent, resulted in a further reduction in the amount of HD residues.

Gohma et al. (2015) looked at the degradation effects of three cleaning agents—sodium hypochlorite (5%), sodium thiosulfate (25%), and sodium hydroxide (32%)—individually and in mixtures on four antineoplastic compounds: cyclophosphamide, epirubicin, cisplatin, and carboplatin. They found that the bleach solution alone degraded 100% of all but the cyclophosphamide, which was degraded about 86%. The persistence of cyclophosphamide after decontamination with bleach was also seen by Hon, Chua, et al. (2014), whose study showed that a 5.25% bleach solution was approximately 97% effective. Touzin et al. (2010) found that use of Surface Safe, a commercial product that uses a 2% bleach and soap cleaning solution followed by a sodium thiosulfate and benzyl alcohol neutralizing solution (for the bleach), effectively removed more than 99.5% of cyclophosphamide residue from a hood surface. Lee et al. (2009) reported that a 0.5% bleach solution was extremely (more than 99%) effective in degrading a 1.2 mg/ml concentration of paclitaxel.

Perhaps the most ambitious evaluation of decontaminating solutions was undertaken by Queruau Lamerie et al. (2013). They evaluated the effectiveness of eight cleaning agents (water, IPA, acetone, bleach, dishwashing liquid, sodium dodecyl sulfate, Tween® 40, and Span® 80) for 10 antineoplastic agents (cytarabine, gemcitabine, methotrexate, etoposide phosphate, irinotecan, cyclophosphamide, ifosfamide, doxorubicin, epirubicin, and vincristine) on two surfaces (stainless steel and glass). Overall, the 0.5% bleach solution was the most effective cleaning agent. Queruau Lamerie et al. (2013) also noted that the surfactant sodium dodecyl sulfate was the next best performing cleaner and that its performance was enhanced by the addition of IPA to the mixture. However, the sodium dodecyl sulfate left a residual film on the cleaned surfaces, which could promote cross contamination.

Although bleach solutions may be the best single cleaning agent for HDs in general, the use of bleach poses several drawbacks. For stainless steel surfaces, such as those found in biosafety cabinets, bleach can cause pitting and corrosion of the steel. Thus, after cleaning, the bleach residue would have to be rinsed with a copious amount of water or neutralized with a solution such as sodium thiosulfate. Bleach has a strong odor, and some staff may experience mucous membrane and respiratory irritation when using it. Queruau Lamerie et al. (2013) also mentioned that degradation products of the bleach–HD reaction may themselves be mutagenic.

Although most studies have focused on the cleaning agent, cleaning protocol also has been investigated. In assessing the efficacy of several cleaning solutions in removing carboplatin residues, Lê et al. (2013) found that both using larger volumes of cleaning solution and spraying the solution onto a simulated spill rather than using a saturated wipe reduced residual contamination. Conversely, Hon, Chua, et al. (2014) did not report any significant differences in contaminant residues between direct application of the cleaning agent and applying the agent with a wipe in areas where HDs are handled.

Management of Spills

Key Points

- Spill kits must be readily available so that spills can be cleaned up quickly to decrease environmental contamination and staff exposure.
- All personnel involved with cleaning a spill are required to wear PPE, including a gown, double gloves, face protection, and respiratory protection (as appropriate).
- Healthcare personnel contaminated with HDs need to take steps to decontaminate and reduce dermal exposure.

HD spills continue to be a significant problem in oncology. In a survey of 1,954 nurses, Boiano et al. (2104) reported that 9% of the respondents experienced a spill within the week prior to the survey. In addition, the number of spills that go unreported has not been determined. Spills result in both environmental contamination and staff exposure. Friese, McArdle, et al. (2015) reported spills involving nine nursing staff over a six-month period in an outpatient oncology setting. Four of nine personnel involved with spill cleanup tested positive for HD in their urine, along with four nurses who were not involved with the events. The authors also noted that one spill exposed multiple workers. Therefore, appropriate equipment and safe handling should always be used to prevent HD spills (see Table 8).

Unfortunately, despite precautions, environmental contamination can still occur. ONS describes a spill as "any leak greater than a few drops" (Polovich et al., 2014, p. 112). Larger spills present a greater hazard potential and require more equipment for containment. However, because no acceptable exposure limits for HDs have been determined (NIOSH, 2004a), even a small-volume spill should be considered a source of exposure and handled appropriately, particularly because dermal exposure and subsequent absorption can easily occur (Fransman, Vermeulen, & Kromhout, 2004). In an unpublished study conducted at Johns Hopkins Bloomberg School of Public Health (C. Chen, personal communication, March 12, 2013), Chen found that the longer the delay in cleaning a spill, the lower the cleaning effectiveness, so the quicker a spill is cleaned up and the more frequently a drug preparation surface is cleaned, the more effective the decontamination process will be. For this reason, spill kits must be readily available wherever HDs are stored, prepared, or administered and where HD-contaminated excreta are handled.

Employees who are responsible for managing HD spills must be properly trained (OSHA, 2016; USP, 2016a). Organizations may use a Hazardous Material Response Team for large-volume HD spills. Policies must clearly designate who is responsible for handling HD spills, address the size of the spill, and outline the specific cleanup procedures. If a spill occurs, an incident report should be completed and should include the drug(s), volume, location, individuals potentially exposed, and cleanup procedure. A root cause analysis to investigate the etiology of the spill should be conducted to prevent future HD spills.

Access to the area around an HD spill should be limited to personnel directly involved with cleanup operations; ideally, patients should be moved away from the spill until it has been adequately cleaned. A sign should be posted to alert staff not involved in the cleanup, as well as patients and visitors.

Spill kits can be purchased commercially or assembled by the individual institution. At minimum, kits should contain the items listed in Figure 11. All personnel involved with cleaning a spill are required to wear PPE, which includes a gown, double gloves, face protection, and appropriate respiratory protection.

Respiratory Protection During Spill Cleanup

An appropriate NIOSH-approved respirator must be used for spill cleanup involving both powder and liquid spills (NIOSH, 2008; USP, 2016a). Paper surgical masks do not provide protection and should not be used during HD spill cleanup. Face protection including the eyes and a full-face chemical canister-type respirator or PAPR should be used for large spills (Eisenberg, 2017; USP, 2016a). N95 and N100 respirators are designed for protection against particles and aerosols (NIOSH, 2008). Particles may potentially be encountered while handling an HD that is in powder form, as could occur during compounding. Aerosols are generated when liquids are sprayed as a fine (visible) mist. When an HCW is dealing with a spill of liquid HDs, the primary respiratory danger is potential generation of vapors, rather than aerosols or particulates.

Vapor molecules are extremely small and are not visible to the naked eye. Very few studies have been conducted to determine which HDs vaporize at room temperature (Connor, Shults, & Fraser, 2000; Kiffmeyer et al., 2002), and the number of drugs tested is relatively small. Figure 12 lists HDs with the potential to vaporize. Several variables should be considered

Table 8. Interventions for Hazardous Drug Spill Prevention

Potential Spill Situations	Preventive Interventions	Rationale
Compounding HDs	Perform in C-PEC and use CSTDs, including CSTD bag spike adapter.	To prevent escape of HD
Spiking IV bags containing HDs	Perform in C-PEC. Use CSTD bag spike adapter.	To prevent escape of HD
Priming IV tubing	Prime tubing with nondrug solution	To prevent leakage of HD from end of tubing
Leaks at connection points	Use CSTDs. Use Luer-lock connections. Use bonded connections.	To prevent inadvertent disconnection and leakage or large spill
Unspiking IV bag containing HD	Do not unspike HD bags. Place HD on secondary set with CSTD. Discard tubing with IV bag attached.	Removing bag can spread drops or result in aerosolization of HD. Using a secondary tubing allows tubing to be backflushed with nondrug solution. Discarding tubing and bag intact maintains a closed system to the bag to prevent exposure.
Connecting/disconnecting IVP syringes	Use CSTD at end of syringe and at needleless connector administration site.	To prevent leakage from syringe before administration and during disconnect
Purging air from syringes containing HDs	Remove air bubbles inside C-PEC. Do not purge air from tubing or syringes containing HD.	Purging HD can spread drops or result in aerosolization of HD.
Transporting leaking syringes or IV bags	Use CSTDs. Place all HDs in leakproof bags.	To contain accidental leaks and prevent environmental contamination
Excreta containing HDs and metabolites	Use urinals with tight-fitting lids. Use CSTDs when handling urine or body fluids after IP or intravesicular HD administration. Educate support staff regarding safe handling of excreta. Post signs for 48 hours after patient receives HDs.	To prevent spilling of HD-containing urine or other body fluids All staff should be aware of the potential for contamination and the need for PPE.

C-PEC—containment primary engineering control; CSTD—closed-system drug-transfer device; HD—hazardous drug; IP—intraperitoneal; IV—intravenous; IVP—intravenous push; PPE—personal protective equipment

during cleanup, including the volume of the spilled drug, airflow in the immediate environment, and concentration of the drug itself, but in all cases, proper protection should be used.

There are no published studies regarding the optimal respiratory protection for HDs that vaporize. However, the Washington State Hazardous Drugs Advisory Committee has posted recommendations (Crickman, Eisenberg, Reyes, & Bowman, 2015) as part of the state's 2012 hazardous drug rule, which requires the adoption of the NIOSH guidelines. These recommendations are based on the chemical origins of HDs, in particular tracing the marker drug cyclophosphamide to its chemical parent compound nitrogen mustard (which originated from mustard gas) (Fleming, 1997), and on the 2008 NIOSH Workplace Solutions bulletin (NIOSH, 2008). Washington State has recommended that a combination canister respirator with an OV/CN/CS designation be used. These designations protect against organic vapors (OV) and riot control gases (CN/CS) (3M, 2015). The combination respirator also contains an N95/N100 component and therefore requires fit testing and annual HCW assessment. PAPRs that utilize the same cartridge are also recommended by the Washington State Hazardous Drugs Advisory Committee. No fit testing is required for wearing a PAPR, although training and HCW assessment are recommended.

Procedure for Cleanup of Hazardous Drug Spills

Information on decontamination and cleaning of HD-contaminated surfaces can be found in the Environmental Contamination section of this book. When

Figure 11. Contents of a Hazardous Drug Spill Kit

- Absorbent plastic-backed sheets or spill pads
- Disposable chemotherapy-resistant gowns (with back closure)
- Chemical-resistant shoe covers
- 2 pairs of chemotherapy gloves
- Chemical splash goggles
- Respirator masks approved by the National Institute for Occupational Safety and Health*
- Disposable scoop
- Plastic disposable brush
- Puncture-proof container if glass fragments are present
- Large heavy-duty hazardous drug waste sealable disposal bag
- Hazardous waste label (if bags are unlabeled)

*N95 or N100 suitable for aerosols and particulates only. Chemical cartridge respirator or powered air-purifying respirator designated OV/CN/CS required for drugs that potentially vaporize at room temperature and powder.

Note. Based on information from American Society of Health-System Pharmacists, 2006; Crickman et al., 2015.

Figure 12. Hazardous Drugs With Potential to Vaporize at Room Temperature

- Carmustine
- Cisplatin
- Cyclophosphamide
- Etoposide
- 5-Fluorouracil
- Ifosfamide
- Nitrogen mustard
- Thiotepa

Note. Based on information from Connor et al., 2000; Kiffmeyer et al., 2002.

a spill of an HD occurs, first assess the exposure of any individuals involved and isolate them from the spill.

If an individual's clothing or skin has made contact with the hazardous agent, immediately remove the contaminated clothing and wash the skin with soap and water (see the Acute Exposure section for additional information). Immediately evacuate patients and personnel from the area. All individuals involved with the spill cleanup must don HD-tested PPE, including double gloves, gown, and respiratory and face protection.

- Wear a NIOSH-approved respirator as discussed previously.
- Standard paper surgical masks are ineffective.
- Contain the spill using plastic-backed absorbent sheets or spill pads. If possible, obtain assistance from another trained person who can hold the spill waste disposal bag. This will prevent contamination of the bag when discarding absorbent pads and other materials inside. Individuals assisting with a spill cleanup must also wear appropriate PPE.
- Place pads or towels into the waste disposal bag, avoiding contamination of the opening of the bag.
- Spills originating from chest or waist height can cause droplets to spread several feet from the source. HCWs need to evaluate the extent of these droplets by moving away from the spill and checking under patient beds, carts, and tables while using a good light source to ensure the entire spill is cleaned.
- Avoid touching any other parts of the environment during spill cleanup because gloves will most likely be contaminated.
- Use a commercially available deactivation product for drugs that have been tested. If no information is available, consider a bleach solution, based on the surface, and a detergent solution to clean the spill. Begin with the least contaminated area and finish with the most contaminated area. This prevents spreading of the spilled drug to noncontaminated areas.
- Rinse area with plain water. Adequate dilution of HD residue is necessary to ensure that drug and any chemical residue has been removed and transferred to the wipes.
- Discard all material used in cleanup in an HD waste bag.
- Seal the waste bag and place it in a puncture-proof container designated for HD waste.

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

Broken Glass

Glass IV bottles should not be used because of the need to vent during infusion and the potential for breakage. If a glass vial breakage occurs, while wearing PPE, pick up glass fragments by using a small scoop and brush. Place glass in the puncture-proof container using the designated scoop. Dispose of PPE, other potentially contaminated spill cleanup items, and scoop and brush in an appropriate HD waste container and wash hands with soap and water.

Spills on Carpeting

Research is lacking regarding the procedure for managing HD spills on carpeting. Carpeting should be avoided in areas of direct patient care in the healthcare environment and other areas where spills are possible (CDC, 2013). To clean the spill, don PPE and appropriate respiratory protection. Use an absorbent powder to absorb the spill. Vacuum the area to remove the dried powder. Prudent practice suggests that a vacuum used in spill cleanup should be equipped with a HEPA filter to contain the HD-contaminated absorbent powder and limit further environmental contamination. Clean the carpet according to the institutional procedure.

Spills Within a Containment Primary Engineering Control

ASHP recommends the use of a spill kit if the volume of the spill within a BSC or other PEC exceeds 30 ml or the contents of one drug vial (ASHP, 2006). Use a scoop and brush to remove any broken glass and place in a puncture-resistant HD container inside of a PEC. Heavy utility gloves are recommended for removing saturated pads prior to decontamination (ASHP, 2006). Clean and decontaminate the C-PEC using an appropriate deactivating agent and detergent, followed by a sterile water rinse. If the spill contaminates the HEPA filter, the C-PEC should be shut down and decontaminated and the filter replaced (ASHP, 2006).

Regardless of geographic location, an incident report should be completed to document spill occurrence. Include events leading up to the spill, the drug involved, the estimated volume of the spill, the cleanup procedures used, any individuals exposed, and those directly involved with the cleanup. Exposed individuals should be referred for medical evaluation, as described later in the Medical Surveillance section.

Hazardous Drug Spills at Home

The growing use of home infusion chemotherapy also increases the likelihood of an HD spill occurring outside of the hospital or clinic setting. Nurses working in the homecare setting must be trained in proper safe handling techniques and be able to provide patient education. Patients should be given a prepackaged spill kit with easy-to-follow instructions on how to clean themselves and their environment, how to dispose of contaminated materials, and to whom they should report the spill (Polovich et al., 2014).

Acute Exposure

Even with the diligent use of PPE and meticulous attention to safe handling techniques, accidental exposures to HDs can occur. Exposure can involve contamination of clothing, protective equipment, skin, mucous membranes, or the respiratory tract. HCWs may also be unknowingly exposed (Ben-Ami, Shaham, Rabin, Melzer, & Ribak, 2001; Hon, Teschke, et al., 2014; Hon et al., 2015; Labuhn, Valanis, Schoeny, Loveday, & Vollmer, 1998). In clinical practice, many accidental exposures may go unnoticed or unreported. It is imperative that nurses be attentive to the possibility of exposure and understand that it may not be limited to the healthcare setting. Exposure has been documented outside of the healthcare setting in patients' homes. A recent study demonstrated that caregivers living with patients who were treated with cyclophosphamide tested positive for HD in their urine (Yuki et al., 2013). This underscores the challenges in containing HD exposure both in and outside of the healthcare environment. Patients and caregivers should be educated on the safe handling of HD in the home (see Patient and Family Education section).

The following steps should be taken in the event of a known exposure (ASHP, 2006):

- Immediately remove contaminated PPE and any clothing items that may have been contaminated, taking care not to spread the contamination.
- Wash affected areas immediately with soap and water. Although evidence shows that dermal absorption is a significant concern, no specific recommendations exist for how long the skin should be cleansed. Decontamination procedures may be suggested in the SDS for the agent of exposure.
- If eyes are affected, rinse for 15 minutes with water or an isotonic eyewash solution. If an eyewash station is not available, this can be accomplished by connecting IV tubing to a bag of 0.9% sodium chloride.
- Visit the employee health professional or the emergency department, as institutional policy directs, to document and ensure complete decontamination.
- Complete an incident report to document employee injury or exposure, according to policy.

Inhalation and Ingestion Exposure

As mentioned previously, certain HDs have been shown to vaporize between 27°C and 37°C (80.6°F–98.6°F) (Connor et al., 2000; Kiffmeyer et al., 2002). However, outside of the laboratory, little is known about the behavior of all HDs at various temperatures and concentrations. Neither ASHP nor OSHA provides specific guidelines on the management of accidental inhalation of HDs in powdered form or procedures for accidental ingestion. For these types of exposures, drug SDSs may contain information on steps to take in the event of accidental exposure. SDSs are provided by drug companies and also

are available through other sources online. Each SDS includes information on signs and symptoms of exposure, acute and chronic health hazards, and emergency or first-aid procedures.

In the event of accidental exposure, the exposed individual, or those treating the individual, should review any applicable SDSs. In some instances, the SDS provides limited information and refers to the drug's package insert. SDSs and package inserts are readily available online, and staff should be versed in how to quickly access these resources. Providing a quick link on the institutional website can be a helpful strategy for ensuring resources are accessible. Additional advice may be obtained from the medical affairs department of the specific manufacturer.

Follow-Up

All employees exposed during spill cleanup should receive monitoring and follow-up care (ASHP, 2006). The medical care should be based on the exposure and may be different for various routes of exposure and types of HDs. This may occur in an employee health department, occupational health clinic, emergency department, or elsewhere as designated in institutional policies. Also see the Medical Surveillance section in this text.

Accidental exposure can occur in any setting. Therefore, nurses working in inpatient areas, home care, outpatient clinics, and all other settings must know the appropriate protocols for dealing with accidental HD exposure (ASHP, 2006; NIOSH, 2004a).

Disposal of Hazardous Drugs and Hazardous Drug Waste

Key Points

- Facilities should have a comprehensive waste management program to track hazardous waste from disposal through incineration.
- Waste containers should be puncture proof, have a lid that seals securely, and be labeled with an appropriate warning.
- HD waste is separate from biohazard and other waste and should be disposed of in a designated container.

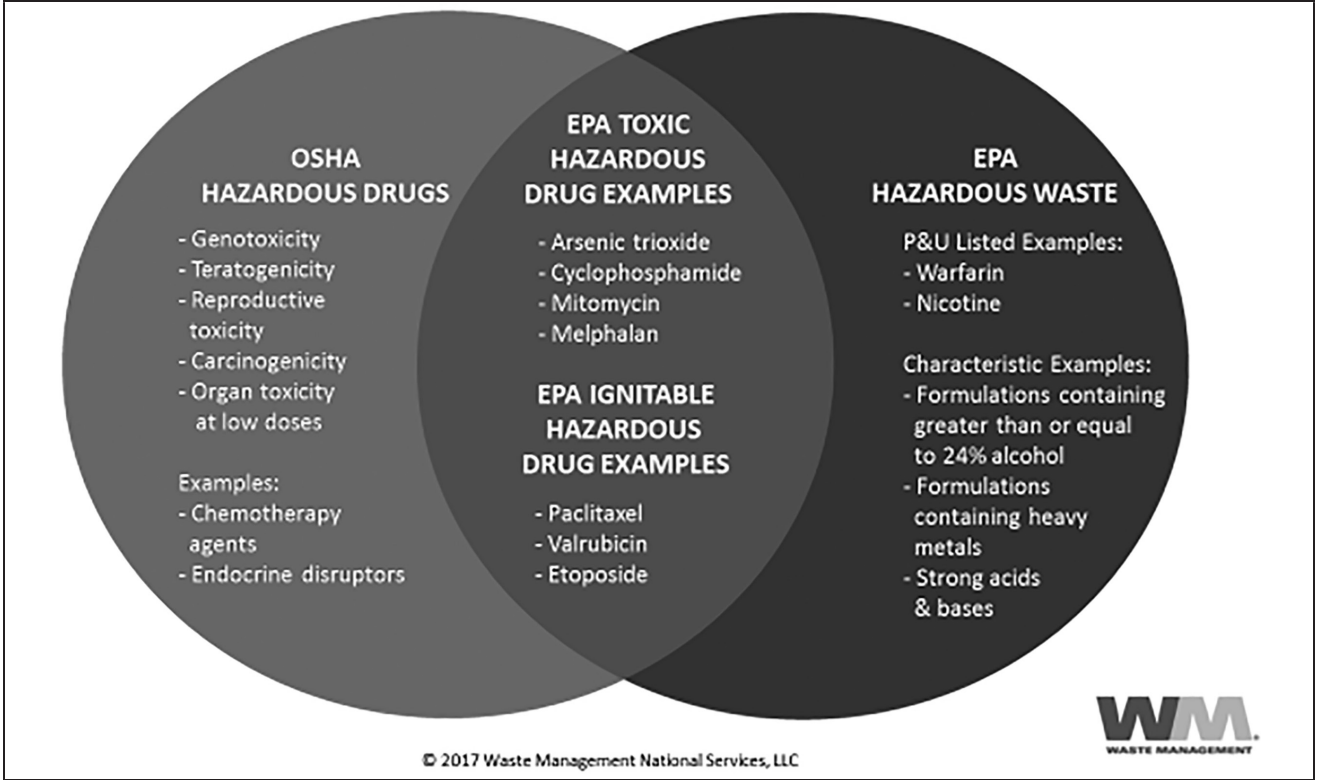
The term *hazardous drug* applies to a group of drugs of varying degree of hazard that have been identified as such by an expert committee, published by NIOSH, and updated approximately every two years (NIOSH, 2016). When discarded, HDs and items that come in contact with them become waste that must be handled separately from other waste. This ensures that individuals handling the waste are protected from exposure and helps to safeguard the environment. When discarded, some HDs also become hazardous waste, as defined by the U.S. Code of Federal Regulations (Identification and Listing of Hazardous Waste, 2017).

Hazardous waste is defined by the U.S. Environmental Protection Agency (EPA) in the Resource Conservation and Recovery Act (RCRA, 2017) as waste that may "cause, or significantly contribute to, an increase in mortality or an increase in serious irreversible illness, or incapacitating reversible, illness; or pose a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed" (para. 6). It is important to note that the term *hazardous drug* refers to risks to employees and is managed by OSHA, whereas *hazardous waste* refers to risks to the environment and is regulated by EPA. While some overlap exists, not all HDs are currently regulated as hazardous waste, although EPA (2012) recognizes that some HDs, particularly antineoplastics, should be. Likewise, a number of common drugs, such as nicotine, are hazardous to the environment but are not a risk to HCWs. These are regulated as hazardous waste but do not require safe handling precautions for administration. Figure 13 provides an example of the two sets of definitions.

EPA defines hazardous wastes in several ways and divides them into two categories: listed wastes and characteristic wastes. Listed wastes are given P codes (acutely hazardous) and U codes (toxic), among others. The only P-listed chemotherapy agent is arsenic trioxide. Several chemotherapy drugs are U-listed (chlorambucil, cyclophosphamide, daunorubicin, melphalan, mitomycin C, streptozocin) because of their toxicity. Several other chemotherapy drugs exhibit the characteristics of ignitability prior to dilution because of their alcohol content (paclitaxel, valrubicin, etoposide, teniposide). Managing hazardous wastes is a relatively complex process and requires "cradle-to-grave" tracking and incineration at a hazardous waste facility. Hospital safety officers or environmental services managers need to be actively involved in implementing a comprehensive waste management program that includes those drugs that are identified as hazardous to employees or the environment. Many other antineoplastic agents have characteristics similar to the original listed drugs. Although EPA has not updated the list in 40 years, these drugs should be managed as hazardous waste based on their toxicity.

Hazardous waste containers must be available in all areas where HDs that are also identified as hazardous waste are prepared and administered (OSHA, 2016). The waste containers should be puncture proof, have a lid that seals securely, and be labeled with an appropriate warning. The warning label identifies the contents as "Hazardous Waste" so that the individuals transporting the waste are alerted to the need for special handling. The container should be distinctly different from other types of waste containers (such as those used for infectious waste) and should be used only for hazardous waste (ASHP, 2006; NIOSH, 2004a, 2016; OSHA, 2016). Plastic bags may be used to contain hazardous waste, such as the sealable bag that is used for drug transport, but these should then be placed inside a rigid waste container. They must not, however, include the biohazard symbol, as this could cause the hazardous waste treatment facility to reject the shipment. Bags labeled only as "Hazardous Drugs" or "Chemotherapy" are suitable. The lid of the waste container should be kept closed except when placing waste into the containers. These practices reduce the risk of drug vapors being released into the environment, as has been described by Connor et al. (2000). This practice also meets hazardous waste regulation requirements for containment (U.S. EPA, 2011). Several manufacturers provide black hazardous waste containers designed for use in healthcare settings to differentiate them from containers used for other types of wastes.

Figure 13. Hazardous Drugs Versus Hazardous Waste



EPA—U.S. Environmental Protection Agency; OSHA—Occupational Safety and Health Administration; P&U—acutely hazardous (P) and toxic (U)

Note. Copyright 2017 by Waste Management National Services, LLC. Used with permission.

Disposal requirements for hazardous waste are less stringent when a container is considered "empty" under RCRA. Therefore, HCWs must be able to determine whether a container that held a listed waste is "RCRA-empty." For a P-listed drug, such as arsenic trioxide, the container is never empty because of an EPA requirement that all containers that have held a P-listed waste must be triple rinsed to be considered empty (Residues of Hazardous Waste in Empty Containers, 2017). Because that is not practical in health care, all ampoules or IVs that contained arsenic trioxide must be disposed as hazardous waste. The only exception is an exclusion EPA granted in April 2008 for a used syringe (U.S. EPA, 2008). For HDs that are U-listed or exhibit one of the characteristics of a hazardous waste, such as ignitability, a container is considered "RCRA-empty" if all the contents have been removed that can be removed by common means and no more than 3% remains (Residues of Hazardous Waste in Empty Containers, 2017). For example, if the contents of an IV bag have been fully administered but droplets of the regulated drug remain in the IV tubing, this would meet the definition of RCRA-empty, and the entire set could be disposed of as trace chemotherapy waste rather than hazardous waste, which is a less expensive option. Practically, then, if any HD remains in an IV bag, vial, or unused syringe, it is not RCRA-empty and must be discarded as hazardous waste if it is a P- or U-listed drug.

Trace Chemotherapy Waste

Any item that has come into contact with an HD during its preparation or administration is considered to be trace contaminated and is defined as *trace waste* or *chemotherapy waste*. Although it is not regulated in all states, the best management practice is to segregate these items into a separate waste stream, using a distinctively labeled sharps container (usually yellow), and have them incinerated as regulated medical waste. This ensures they are not autoclaved with red-bag waste and also enables needles and other sharps to be properly disposed. Combining needles and other sharps with hazardous waste creates a dual biohazardous/hazardous waste stream, which is very expensive to dispose of.

Items including used needles, syringes, empty drug vials, ampoules, IV tubing, IV bags or bottles, and connecting devices should be discarded in the

yellow trace chemotherapy waste container to protect HCWs, including environmental services personnel, from exposure. Such items should be discarded intact without separating components to reduce the possibility of dispersing drug droplets. To prevent HD exposure and needlestick injury, crushing or clipping needles is not recommended (OSHA, 2016). Needles and other sharps used to administer HDs must be disposed of in a puncture-proof container. Use of protected needle devices for intramuscular or SC injections of HDs is required by the Bloodborne Pathogens Standard (U.S. Department of Labor, 2012). A disposal container should be present at the site of drug administration to eliminate the need to transport an exposed needle and used IV bags and lines. This recommendation also applies when discontinuing an IV access device with an exposed needle. Trace contaminated items, such as gauze, wipes, and paper drapes, can be placed into either the yellow containers or plastic hamper bags labeled as "Chemotherapy Waste." All should be incinerated as regulated medical waste.

PPE, such as gowns, gloves, and face shields, worn during drug handling should be disposed of in either the yellow container or the yellow hamper bag. Reusable items (e.g., trays, goggles) that have been contaminated should be handled while wearing PPE and cleansed with soap and water before being returned to use. Disposable items contaminated by body fluids of patients who have received HDs in the previous 48 hours are considered contaminated. Discard disposable items such as pads, diapers, urinals, bedpans, measuring devices, Foley catheters, and drainage bags in the trace chemotherapy waste container. Drainage collected following an HD bladder instillation should be disposed of in a sealed plastic bag for initial containment and then into the trace chemotherapy waste container. Because the residual drug collected after the treatment is "used as intended," it does not fit the definition of hazardous waste and its disposal is not regulated under RCRA; however, it is hazardous to HCWs and therefore must be discarded as trace chemotherapy waste and incinerated at a regulated medical waste facility.

Managing Hazardous Waste Containers

HCWs should not reach into hazardous waste containers when discarding contact material. Disposal containers should not be overfilled. Seal waste containers when three-fourths full. Once the containers are sealed, notify the appropriate personnel to remove the waste containers from the preparation or administration area. Only individuals who wear appropriate PPE and who have been trained regarding the exposure risks should handle the hazardous waste containers.

Hazardous waste should be managed separately from other hospital trash. Hazardous waste must be stored in a secure storage accumulation area in covered, leakproof containers or drums with distinct labels including the words *hazardous waste* and the initial storage date. Additional labeling, manifesting, and other paperwork must be generated prior to shipping by a hazardous waste vendor who meets all EPA, Department of Transportation, and state requirements. Cradle-to-grave tracking is required, and the hospital retains full liability for ensuring proper disposal and documentation. The safety officer, facility manager, or environmental services manager is normally responsible for these activities. Hazardous waste must be incinerated at a federally permitted treatment, storage, and disposal facility. All those involved in hazardous waste disposal must maintain records related to its transport and disposal. Trace chemotherapy waste should be stored with other regulated medical waste and be incinerated at a regulated medical waste facility, not autoclaved.

Medical Surveillance of Healthcare Workers Handling Hazardous Drugs

Key Points

- Medical surveillance programs are designed to detect a health problem early and address it.
- Medical surveillance should be done on an ongoing basis and when an acute exposure occurs.
- HCWs who are trying to conceive, are pregnant, or are breastfeeding are accountable for notifying their employers about such situations.
- Employers should offer alternative duty that does not include preparation or administration of HDs.

The inherent toxicity and mode of action of many anticancer agents combined with reports of therapy-related secondary malignancies in treated patients drove early efforts to minimize HD exposure in HCWs out of concern about cancer risk (Connor & McDiarmid, 2006). Adverse reproductive health effects have surfaced as biologically plausible outcomes that add urgency to attempts at controlling workplace exposure. Historically, nurses and pharmacists who are exposed to HDs in their workplaces have reported an increased number of adverse reproductive events, including spontaneous abortions, stillbirths, and congenital malformations, compared to unexposed HCWs (Hemminki, Kyyronen, & Lindbohm, 1985; Selevan, Lindbohm, Hornung, & Hemminki, 1985; Stucker et al., 1990; Valanis, Vollmer, & Steele, 1999). Importantly, recent studies have reported increases in miscarriages, preterm births, and infertility (Connor, Lawson, Polovich, & McDiarmid, 2014; Lawson et al., 2012; Martin, 2005a); increased congenital defects (Walusiak, Wagrowska-Koski, & Palczynski, 2003); and increases in time to conception and low-birth-weight offspring as a function of exposure intensity (Fransman, Roeleveld, et al., 2007). A recent study of female veterinarians who handled cytotoxic drugs during pregnancy found an increased risk of birth defects (Shirangi, Bower, Holman, Preen, & Bruce, 2014). These reports and others highlight the health risks that HD handlers still face in the course of handling these agents (Eisenberg, 2009).

The classic occupational health approach to controlling exposure to workplace hazards by applying a combination of exposure control technologies also pertains to the healthcare setting. In addition to using engineering controls, such as a BSC, administrative controls, safer work practices, and PPE to control and prevent exposure to HDs, workers who handle these agents should be routinely monitored in a medical surveillance program (ASHP, 2006; NIOSH, 2013; OSHA, 2016; USP, 2016a). As seen in Figure 14, virtually every occupational public health agency and oncology professional organization has endorsed some form of medical surveillance for HD handlers. Although NIOSH and ASHP recently have renewed calls for adoption of surveillance activity in comprehensive programs of exposure control, the recommendation for such inclusion is 20 years old (OSHA, 2016). Historical compliance with a surveillance provision has been poor, and recent surveys still report only moderate compliance (Polovich & Clark, 2012). This gap in adoption of recommendations for a comprehensive approach to manage workplace exposure is particularly troubling because it occurs in the absence of both specific federal regulations to protect exposed workers and recommended exposure levels to guide compliance (Gambrell & Moore, 2006).

What Is Medical Surveillance?

Medical surveillance involves the collection and interpretation of data to detect changes in the health status of working populations. Surveying the health status of a group of workers is a component of a comprehensive approach to hazard control. If exposure to a hazardous therapeutic drug cannot be eliminated through substitution of a less dangerous agent or satisfactorily captured through engineering controls, then administrative controls, PPE (e.g., gloves, gowns, footwear), and equipment (e.g., respirators) are vital to minimize exposure (NIOSH, 2008; Niland, 1994). Medical surveillance is considered an administrative control in the hazard control hierarchy because it is a policy-oriented approach requiring an administrative decision by the employer to implement.

The general purpose of surveillance is to minimize adverse health effects in personnel exposed to potentially hazardous agents (Baker, Honchar, & Fine, 1989; McDiarmid & Emmett, 1987; NIOSH, 2013; OSHA, 2016; Wesdock & Sokas, 2000). Surveillance is longitudinal in scope and geared to follow employees over their working lifetime. Medical surveillance programs involve assessment and documentation of symptom complaints, physical findings, and laboratory values

Figure 14. Recommended Medical Surveillance for Hazardous Drug Handlers

	NIOSH (1)	(2)	ONS Oncology Nursing Society (3)	ISOPP (4)	ashp (5)	OSHA (6)	USP U.S. Pharmacopeial Convention (7)
Medical and exposure history	✓	✓	✓	✓	✓	✓	✓
Physical exam	✓	✓	✓	✓	✓	✓	✓
Routine labs	✓ *	✓	✓	✓	✓	✓	✓
Specialized tests	✓ **		✓ **	✓ ***		✓ ****	✓ ****

* NIOSH recommends baseline labs.

** Biological monitoring as needed for workers who have shown health changes suggesting toxicity or who have experienced acute exposure (spill).

*** Follow-up recommended for workers who have shown health changes and/or have been exposed to hazardous drugs.

**** Post-exposure evaluation is tailored to the type of exposure; treatment and laboratory studies follow as indicated.

Note. Based on information from American Society of Health-System Pharmacists, 2006; Department of the Army, 2014; International Society of Oncology Pharmacy Practitioners, 2007; National Institute for Occupational Safety and Health, 2013; Occupational Safety and Health Administration, 2016; Polovich, 2011; U.S. Pharmacopeial Convention, 2016a.

to determine whether there is a deviation from the expected norms.

Medical surveillance can be viewed as a secondary prevention tool providing a means of early detection of a health problem. Tracking employees through medical surveillance allows comparison of health variables over time in individual workers, which facilitates early detection of a change in a laboratory value or health condition. Medical surveillance programs look for trends in populations of workers. Examining grouped data and comparing it to data from unexposed workers may reveal a small alteration or increase in the frequency of an abnormal laboratory result or health event (such as a spontaneous abortion) that would be obscured if individual workers' results alone were considered.

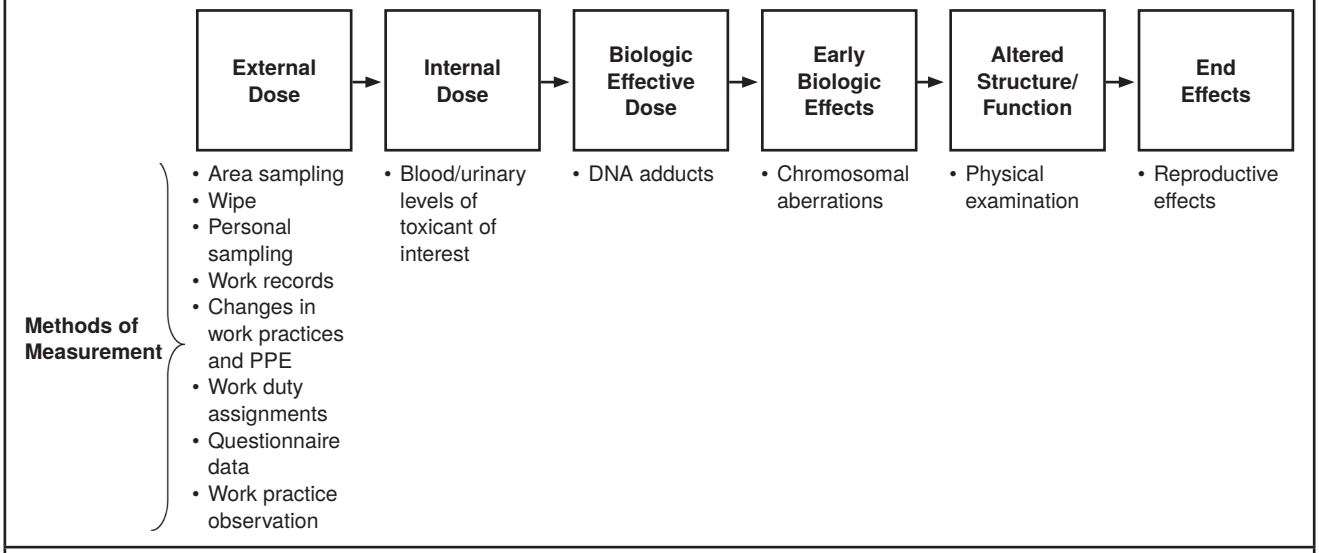
The work environment can undergo surveillance. This involves an inspection for hazards, as well as air or work surface monitoring for the presence of hazardous contaminants. Surveillance, both medical and environmental, complements the use of engineering controls and good work practices, providing feedback on their efficacy. This feedback can be an impetus for the implementation of alternative or additional measures to minimize exposures and prevent adverse health outcomes.

Data Elements in a Surveillance Protocol

A medical surveillance program contains four data elements: worker history (medical and occupational), physical examination, laboratory studies, and biologic monitoring (biologic monitoring typically is not included in routine surveillance but is included in special cases; see discussion later in this section). Taken together, these elements give a reasonably comprehensive view of the health status of a worker and of a population of workers. Each component of the surveillance protocol helps to track the progression of workplace exposure from initial contact with HDs through ultimate biologic effects (see Figure 15).

The exposure history elements of a surveillance program facilitate the identification of employees who are potentially at increased risk for adverse health events and provide a semi-quantitative estimate of external dose (e.g., duration or frequency

Figure 15. Hazardous Drug Exposure Assessment: Exposure–Effect Pathway



PPE—personal protective equipment

Note. Adapted from "Biological Markers in Environmental Health Research," by Committee on Biological Markers of the National Research Council, 1987, *Environmental Health Perspectives, 74,* p. 4. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474499.

of drug handling). Information on exposure levels (e.g., intensity) in work areas, employee duty assignments, and questionnaires that assess the frequency of drug handling can help to estimate the external dose to which an employee has been exposed. The physical examination may yield signs of early biologic effects from exposure to HDs (e.g., skin lesions, hair loss) (Krstev, Perunicic, & Vidakovic, 2003; Kusnetz & Condon, 2003; Rogers & Emmett, 1987; Valanis, Vollmer, Labuhn, & Glass, 1993). Results from laboratory studies assess early biologic effects from exposure. Biologic monitoring can help to quantify the internal dose of HDs. More specialized monitoring can potentially indicate specifically targeted effects (such as formation of DNA adducts), termed a *biologically effective dose*. Slightly farther in the exposure–effect pathway, measures of genotoxicity may be viewed as early biologic effects of drug binding with the DNA target. The results of these studies give both direct and indirect evidence of an employee's exposure and the adverse health outcomes that may result. Ideally, medical surveillance can determine whether HCWs who are exposed to HDs are at risk for adverse health outcomes before they occur (by picking up early signs of exposure), thereby providing the opportunity for early intervention.

Targeted medical surveillance for HD handlers can be incorporated into ongoing employee health evaluations. Preplacement histories and medical examinations are important components of medical surveillance to document each worker's baseline health status. It is important to perform periodic examinations that gather the same information about signs, symptoms, and laboratory measures over time so that workers are monitored throughout their employment and any changes in health status can be assessed.

History

A thorough history is the best and most cost-effective source of useful health information. Medical and occupational information is obtained via questionnaire. Questionnaires are an efficient means of collecting a standardized set of information and provide documentation of changes in symptoms or the onset of health problems over time. The questionnaire should be reviewed with the worker to clarify answers and obtain more detail for responses that suggest a potential health effect.

Medical history: The medical history may identify a worker at potentially high risk in a particular exposure setting and helps clinicians to interpret laboratory data obtained in the surveillance program. For example, a person with documented asthma is at increased risk in a job where exposure to respiratory irritants or sensitizers is possible. Symptoms discovered in the medical history may serve as an early warning to the HCW of a potential problem (e.g., a sentinel health event). Symptom questions should focus on organ systems that are targets for the hazardous agent or agents in question. The preplacement medical history should be very detailed. Periodic evaluations can be less exhaustive, focusing on signs and symptoms

related to HD exposure and changes in health status since the previous evaluation.

Recording symptoms thought to be caused by HD exposure may give insight into drug handling practices and alert HCWs to a potential problem. For more than 30 years, acute health effects have been reported in antineoplastic drug handlers with variable use of recommended handling procedures. These include lightheadedness, nausea, headache, coughing and burning in the respiratory system, skin irritation, lacrimation, eye irritation, dizziness, hair loss, and others (Constantinidis et al., 2011; Crudi, 1980; Krstev et al., 2003; Ladik, Stoehr, & Maurer, 1980; Momeni, Danaei, & Askarian, 2013; Rogers & Emmett, 1987). Other examples of exposure-related symptoms are found in case studies. One describes a nursing assistant who was seen in her facility's employee health office after experiencing pruritic, disseminated rashes following two separate occasions of handling patient waste. Both patients were treated with vincristine and doxorubicin, and it was concluded that one or both of these agents caused the reaction (Kusnetz & Condon, 2003). Another case report described a nurse who developed throat irritation, chronic nasal congestion, and sinusitis that occurred while employed at an oncology outpatient clinic. A histamine release test with etoposide showed her to be sensitive to that drug (Meyer & Skov, 2010).

These symptoms and others known to occur in HD-treated patients should be investigated when reported by exposed HCWs. Further symptom questions should focus on the known target organs of the agent of exposure. For antineoplastic drugs, special emphasis should be given to the skin and hematopoietic, hepatic, reproductive, and urinary systems. Significant unintentional weight loss, fever, malaise, and unexplained fatigue may be associated with anemia and hematologic malignancies (Appelbaum, 2000; Shipp & Harris, 2000). Constitutional symptoms should be included in a checklist and pursued in detail if they are present. Changes in the occurrence or frequency of symptoms over time can be an important clue to health changes.

Special consideration should be given to the reproductive history of employees handling HDs. Questions regarding problems conceiving and poor reproductive outcomes (e.g., spontaneous abortions, congenital malformations) should be included. Male employees should provide information about the reproductive history of their female partners. For female employees, it is useful to request a complete reproductive history of each pregnancy, including dates, outcome, and work history during pregnancy. Figure 16 shows a sample medical history questionnaire.

Work history: Estimating drug handling history serves as a surrogate measure of the potential exposure dose. Knowing whether drug handlers wear PPE, such as gowns, gloves, face shields, or eye protection, will assist HCWs in determining the opportunity for exposure. Use of a BSC during preparation of HDs should be recorded. Documentation of past events, such as accidents and spills, assists occupational health professionals in estimating the likelihood and intensity of exposure. The frequency and duration of HD handling should be reviewed during the periodic medical examination.

Physical Examination

A physical examination is the least helpful source of surveillance data, given the health outcomes of concern in HD exposed workers. However, a baseline examination is useful for documenting preexisting conditions. Periodic examinations should focus on the skin and mucous membranes. The clinician should look for rash, irritation, or other evidence of acute exposure. Evaluation of other target organ systems is desirable. For example, hepatomegaly, splenomegaly, and lymph node enlargement may be associated with hematologic malignancies (Appelbaum, 2000; Shipp & Harris, 2000). In general, the hematopoietic, hepatic, renal, and urinary systems are more easily evaluated with laboratory studies, and significant illness is likely to be identified from the medical history and symptom queries.

Laboratory Studies

A tiered approach in selecting laboratory studies for surveillance has been recommended by ONS in the past (Polovich, 2011). In the first tier, a study that is desirable, at least as a baseline measure, is a complete blood count with differential to monitor hematopoietic function (NIOSH, 2013). Second-tier measures that are less essential are studies of organ-specific endpoints considered targets of HDs, such as a reticulocyte count as an indication of bone marrow reserve. While this has been suggested in the past, the utility of additional testing has not been studied systematically. Altered liver function test results and evidence of liver damage, for example, have been reported in nurses handling antineoplastic drugs (Sotaniemi et al., 1983), but little evidence exists from more recent reports. One study from Italy reported increased total bilirubin and reduced monocyte count, which the authors attributed to HD exposure (Caciari et al., 2012); however, the exposure assessment, engineering controls available, handling history, and observance of safety practices were not well described, making attribution to work exposure difficult. Several antineoplastic agents (e.g., cisplatin) have toxic effects on the kidneys in patients receiving therapeutic doses (Cronin & Henrich, 2000). Neither the presence nor absence

Figure 16. Sample Medical History Questionnaire for Hazardous Drug Handlers

Medical History

1. In the course of the past year, have you had any changes in your general health? ☐ YES ☐ NO

   If yes, please describe: _____

   _____

2. In the course of the past year, have you had any of the following symptoms?

	Yes	No	Have you noticed that these symptoms occur in relation to your work (e.g., either during the workday or immediately after)?
Bruising			
Dizziness			
Facial flushing			
Fever			
Gastrointestinal complaints			
Hair loss			
Headache			
Nausea			
Nosebleed			
Respiratory symptoms			
Skin rash			
Sore throat			
Vomiting			
Wheezing			
Other (Specify):			

Unintentional weight loss ☐ YES ☐ NO If yes, how many pounds? _____

3. In the course of the past year, or since you last completed this questionnaire, have you had any of the following reproductive events listed below?

   a) Have you or your partner had a problem conceiving a child? ☐ YES ☐ NO

   b) Have you or your partner consulted a physician for a fertility, or other reproductive, problem? ☐ YES ☐ NO

      If yes, who consulted the physician? ___ Self ___ Partner ___ Self and partner

      If yes, please state the diagnosis that was made: _____

   c) In the past year, have you or your partner conceived a child resulting in a miscarriage, stillbirth, or birth defect? ☐ YES ☐ NO

      If yes, please specify the type of outcome: _____ Miscarriage _____ Stillbirth _____ Birth defect

      If the outcome was a birth defect, please specify the type or describe: _____

      _____

   d) What is the occupation of your spouse or partner? _____

   e) For women only: In the past year, have you had any menstrual irregularities? ☐ YES ☐ NO

      If yes, please specify the type of menstrual irregularity: _____

      If yes, how many episodes of this irregularity did you have (in the past year)? _____

(Continued on next page)

Figure 16. Sample Medical History Questionnaire for Hazardous Drug Handlers *(Continued)*

Work History

1. How many hours a week do you usually work with hazardous drugs (either handling or in the area where they are being handled)? _____

2. Has this schedule changed over the past year? ☐ YES ☐ NO

   If yes, how has it changed? _____

3. In the course of the past year, have you been around an antineoplastic drug spill? ☐ YES ☐ NO

   If yes, please give approximate date or dates (if this occurred more than once): _____

   If yes, approximately how large was the spill? __ Less than 5 ml __ More than 5 ml

   If yes, did you clean it up? ☐ YES ☐ NO

   If yes, what protective clothing were you wearing when the spill occurred? _____

4. In the course of the past year, have you accidentally ingested, breathed in, or had skin contact with an antineoplastic drug or solution? ☐ YES ☐ NO

   If yes, how often? _____

5. Please check the most appropriate answer as it applies to your antineoplastic drug handling practice:

	Always	Often	Sometimes	Rarely	Never
I wear disposable gloves.					
I wear double gloves.					
I change my gloves according to the guidelines on my unit.					
I wear disposable gowns.					
I wear eye protection (goggles).					
I wear a protective mask.					
I wear disposable booties.					
I wear disposable hair covers.					
If I mix drugs, I use a biosafety cabinet.					

Note. Based on information from McDiarmid & Curbow, 1992.

of renal toxicity has been documented to date in HD handlers; therefore, the usefulness of serum creatinine to assess renal toxicity is uncertain for these workers. These laboratory tests are relatively inexpensive, however, and if already part of the employee health evaluation program, they should be examined for trends on a group basis, which could be attributed to HD exposure.

Additional testing may be indicated as a follow-up to health questionnaire responses by the employee. Laboratory tests may evaluate an employee's health status or organ system function. If a health condition is present, this may place the employee at increased risk of harm from HD exposure. In the absence of symptoms or health changes, the frequency of laboratory studies in periodic surveillance can be flexible, does not necessarily need to occur annually, and can be integrated into other existing surveillance schedules.

Biologic Monitoring

Biologic monitoring is the measurement of a specific agent or its metabolite in the body fluid of an exposed worker (Lauwerys & Hoet, 2001; McDiarmid & Curbow, 1992). With the exception of following a worker subsequent to a major spill, the value of performing biologic monitoring for a specific drug is limited because workers who handle HDs may be exposed to multiple agents. This makes it difficult to choose which agent or agents to monitor. It is not feasible to perform such monitoring on all employees for the many agents in regular use.

Measures of Genotoxicity

Difficulties in the interpretation of mutagenicity measures and cytogenetic (clastogenic) endpoints are a major limitation to their inclusion in routine medical surveillance. It is not possible to offer an accurate interpretation of an individual's positive urine mutagenicity test or to predict individual disease development for most cytogenetic outcomes, nor is it possible to definitively link any single positive result to occupational exposure. A positive result may provoke unnecessary anxiety in individuals for whom its importance cannot be adequately explained. Until more clarification of the clinical implications of these test results at the individual level is available, measuring genotoxic outcomes is not a recommended component of routine medical surveillance for HD handlers. There may be a role for these endpoints in research studies of exposure and outcomes.

Acute Exposure Follow-Up

For management of acute exposure, such as after a spill on the skin or mucous membranes, see the Acute Exposure Management section in this book.

Following acute exposure, any worker should have a postexposure evaluation. This evaluation is tailored to the type of exposure (e.g., spill, needlestick). An assessment of the extent of exposure is made and included in an incident report or report of employee injury. The physical examination focuses on the involved area (e.g., the pulmonary system for an aerosolized HD exposure) as well as other organ systems commonly affected (e.g., skin, mucous membranes). Treatment and laboratory studies follow as indicated and should be guided by emergency protocols. The occupational health professional should evaluate the need for specific follow-up based on the known toxicity of the agent in question and consult the package insert and SDS as per the OSHA Hazard Communication Standard (OSHA, 2012).

The following are general suggestions for acute exposure follow-up:

- Perform a physical examination for acute findings at the site of exposure (e.g., skin, inhalation). Other aspects of the examination focus on target organs for the drug(s) involved.
- Obtain blood for baseline counts and archiving (spin and freeze) so that there is something to compare in case of changes over time. When collected immediately after an exposure, laboratory findings are almost as good as a pre-exposure draw.
- Determine appropriate follow-up times based on drug half-life and, for example, expected nadir of counts.
- Provide counseling to the individual as appropriate to the situation, which may include waiting several (typically three) months before trying to conceive, what symptoms to report, and recommended medical follow-up.

Record Keeping

In addition to the periodic review of individual and grouped data to detect trends over time, OSHA (2016) recommends that an ongoing facility registry be maintained of all employees who routinely handle HDs. In the same way that a record is kept of the lifetime dose of certain chemotherapy drugs received by a patient, a drug handling history should be maintained in the worker's employee health record. It is not necessary to record every instance of drug preparation and administration, although that would be ideal. The record should track by HCW the date and duration of assignment to an HD handling job and the historical use of BSCs, safe work practices, and PPE. The drug handling history is used as a surrogate for exposure dose, although "drug dose handled" and "exposure dose to the worker" are obviously not equivalent. The record can, however, be used to estimate the relative exposure intensity and duration and may help in the interpretation of medical surveillance results.

The resources of an individual hospital or health system best determine the mechanics of a record-keeping program. The increasing use of computerized data systems to organize medical information provides the opportunity to incorporate records of occupational drug handling into the current databases.

Pharmacies that issue computerized labels for each drug prepared may be able to modify their electronic labeling systems to internally record an identifier for the drug preparer. Practices and pharmacies that use a manual record-keeping system may generate several drug labels that could be used in tracking the nurses who administer the drug. For example, a label could be placed in the patient's chart and another label could be placed in a HD logbook, with both labels initialed by the nurse. The pharmacy preparation log and administration log could be reviewed periodically to compile a drug handling history for each employee (McDiarmid, 1990). Electronic pharmacy systems that use bar codes to track drug preparation and administration may use electronic identification numbers to track personnel, which is another potentially useful means of estimating HD exposure for HCWs.

The employee health service and the safety committee should assist in implementing a record-keeping

program to track employees who handle HDs. Data extraction from computerized information systems could result in automatic updates of exposure duration and intensity once the procedures are in place. These records would provide guidance in the interpretation of results from periodic medical surveillance of exposed employees.

Essential Components for Medical Surveillance of Hazardous Drug Handlers

Limited resources may preclude the implementation of a comprehensive medical surveillance program for HCWs who handle HDs. For institutions that do not have the means to develop a comprehensive surveillance program, a few key elements may serve to track employees' exposures (McDiarmid & Curbow, 1992). In healthcare institutions or practices where some form of periodic employee health evaluation is already in place, new elements of surveillance (e.g., drug handling history [exposure proxy]) and reproductive history may be added to existing surveys to screen HD handlers for specific health changes.

At a minimum, the essential components that should be in place for medical surveillance of HD handlers include the following:

- Maintain a list of all workers who are exposed to HDs as a part of their job.
- Have all HD handlers complete periodic questionnaires to track the frequency and duration of contact with these agents, their use of PPE, and any health events that are potentially related to HD exposure.
- Conduct periodic observations of drug preparation and administration practices to determine the need for refresher training in work practices that reduce exposure.
- Carefully document spills, spill cleanup activities, and accidental exposures.
- Confidentially share the results of medical surveillance with the employees who handle HDs.
- Settings without employee health professionals should consult independent occupational health service providers or develop policies that provide guidance for employees to pursue surveillance through their primary care providers.

Temporary Reassignment/Alternative Duty

While not an aspect of medical surveillance, employee health providers assist employers to manage the reproductive toxicity of HDs. Handling HDs may result in reproductive risk, and both male and female HCWs who handle HDs are accountable for notifying their employers about such situations. Upon notification, employers should provide alternative duty that does not include preparation or administration of HDs. Collaboration with employees' primary care physicians and obstetricians should occur. One way of minimizing reproductive toxicity is to provide temporary reassignment or alternative duty for HCWs handling HDs during specific vulnerable periods. Such an administrative policy is appropriate when exposure cannot be sufficiently controlled by engineering containment, work practices, and use of PPE alone. Added vigilance is appropriate because reproductive or developmental effects may occur at lower exposure concentrations than would cause acute systemic effects in an exposed adult (U.S. General Accounting Office, 1991). Some HDs may exert their effect during a limited or single exposure episode if it occurs during a vulnerable "window" of risk in early stages of pregnancy. Additionally, there is evidence that some HDs affect germ cell (sperm and egg) development (Bradbury & Schilsky, 2010).

The majority of regulatory public health decisions made about chemical hazards, such as the setting of permissible exposure limits, are not based on reproductive or developmental effects but on other toxicities, such as cancer or acute effects. A report prepared for the U.S. Senate by the U.S. General Accounting Office (1991) found that "protection against reproductive and developmental toxicity offered to the public by current regulation is uncertain at best" (p. 3). Although this study is dated, no subsequent, systematic review of this issue has been conducted since this report was published.

Several other investigational activities and literature reviews have occurred recently that inform decision making in recommending alternative duty. The U.S. Department of Health and Human Services National Toxicology Program (NTP) recently completed a systematic review on the use of cancer chemotherapy during pregnancy. Although the focus was on treatment of pregnant patients, NTP included a comment regarding the exposure of HCWs. The report suggested that the safety of chemotherapy treatment during pregnancy may benefit from studying the pregnancy and long-term outcomes of oncology workers' offspring, as their exposures "are usually unrecognized, may occur over a longer period of time and may involve a greater number of chemotherapy agents" (U.S. Department of Health and Human Services NTP, 2013, p. 188).

Two publications from NIOSH reinforce the need for vigilance regarding reproductive health risks from occupational exposure to HDs. In a follow-up of the Harvard nurses study cohort, Lawson and colleagues examined birth outcomes of nurses reporting first trimester exposure to HDs. They found a statistically significant 2-fold increase in spontaneous abortions,

which grew in effect size to a 3.5-fold excess in nulliparous women (Lawson et al., 2012). The nurses were exposed as recently as the early 1990s, 10 years after the first ONS and ASHP safe handling guidance, which implies that some safe handling practices were likely in place compared to earlier studies.

In a second monograph, which reviewed the evidence of HDs as a hazard to reproduction and development in exposed workers, a NIOSH team performed a structured literature review of 18 peer-reviewed English language publications on the topic. Results indicated that HD exposure appears to raise the occurrence of both congenital malformations and miscarriage. Endpoints of infertility and time to pregnancy also indicate a likely risk of subfertility (Connor et al., 2014). The authors suggested that additional precautions to prevent exposure during vulnerable periods should be considered. One such additional precaution is alternative duty that does not include HD handling activities.

In addition to occupational exposure, the medical history of affected workers and their personal risk factors (e.g., history of spontaneous abortion, infertility) may suggest that temporary reassignment is needed. ONS, other professional organizations, and some large healthcare employers currently recommend that temporary reassignment be made available during pregnancy (Coyne, 2014; USP, 2016a).

A program of temporary reassignment can be explained to workers as part of the hazard communication training regarding HDs, which is already in place at the work site. A mechanism for HCWs to notify employers of pregnancy and thus the need for reassignment can be explained in this training session. Collaboration with the risk management department and the employee health service, as well as employee involvement in the planning of a policy, is key for successful implementation.

Alternative duty does not mean withdrawal from work but rather refers to reassignment of duties, often within the same job, to avoid the handling of HDs or HD waste. Various nursing or pharmacy duties may be redistributed among a team of workers, or the organization of work may be altered to allow those needing reassignment to still work in many aspects of their typical jobs. In some instances, however, a true position reassignment may be necessary to avoid exposure.

Discussions with affected individuals, supervisors, and employee health professionals will assist in identifying scenarios where temporary duty assignments will provide additional protection to affected workers and still allow them to perform as part of the care team. Such scenarios and task reassignments are much less disruptive to the delivery of care when they are planned for prior to their need. Management concerns regarding the need for alternative duty may be minimized when an employee's private physician initiates the request. The private physician validates the need for alternative and protective work.

Preventive reassignment for working women who are pregnant and breastfeeding is a well-established policy throughout many European countries and in some provinces of Canada. Similarities exist among Danish, Finnish, and Quebecois provincial programs, including the initiation of the request by the working pregnant woman, a validation of occupational risk by occupational medicine physicians, and the obligation of the employer to provide a place of employment that is safe (Plante & Malenfant, 1998; Romito & Saurel-Cubizolles, 1992; Taskinen, Olsen, & Bach, 1995). For example, the mixing of anticancer drugs by pregnant HCWs is expressly prohibited in Finland (Taskinen et al., 1995). Both anesthetic gas and antimitotic drug exposure during pregnancy appear on a "List for Risk Assessment Concern for Exposure of Pregnant and Breast-feeding Women at Work" in Denmark (summarized in Taskinen et al., 1995).

The Safe Maternity Experience Program of Quebec has afforded alternative duty under the *Retrait Preventif* ("preventive withdrawal") legislation for more than 30 years. This policy is initiated via a physician-validated "certification" (the physician signs a document called the "Preventive Withdrawal and Reassignment Certificate for a Pregnant or Breast-feeding Worker"), which documents the belief on the part of the worker's physician that a job hazard exists that threatens the pregnancy. This triggers a series of administrative reviews at the work facility to assess potential risk of exposure to a hazard and to determine a remedy that may include alternative duty (Commission de la Santé et la Securité du Travail, 2014). A risk assessment approach to assess hazards to reproduction also is recommended by the UK Health and Safety Executive (2013), a public health agency similar to OSHA in the United States.

The American College of Occupational and Environmental Medicine (ACOEM) Position Statement/Guidelines on Reproductive Health Hazard Management Options may be a resource for organizations planning reassignment strategies (Meyer, McDiarmid, Diaz, Baker, & Hieb, 2016). ACOEM delineates several circumstances and presents case studies and suggested approaches for when alternative, temporary reassignment should be considered for employees who work with reproductive hazards:

- Pregnancy—an employee notifies her employer she is pregnant.
- Preconception—a male or female employee indicates an intention to have a child.
- Infertility—a couple has sought medical consultation for infertility and no cause has been discovered.

Temporary reassignment should be extended to breastfeeding mothers who handle HDs. This is supported by the fact that a large number of HDs are secreted in breast milk and almost all HDs have cautionary warnings regarding their administration to women who are breastfeeding (Briggs, Freeman, & Yaffe, 2011). While patients' exposure is greater and more direct, it can be a surrogate for the exposure experienced by the HCW who handles these drugs over a period of time on a daily basis.

Summary

A number of OSHA standards affecting the healthcare industry have medical surveillance provisions, including standards related to ethylene oxide, formaldehyde, and bloodborne pathogens. Therefore, including medical surveillance in a comprehensive approach to controlling adverse health outcomes from HD exposures in the healthcare setting is not novel. Tailoring existing preplacement or periodic health evaluations performed at many institutions can integrate HD surveillance into an existing employee health program. When adverse outcomes are detected through medical surveillance, appropriate preventive actions should be taken to address any existing hazard. Engaged HCWs and employers, working in concert with employee health professionals, can successfully develop and implement a surveillance program and alternative-duty policies that enhance health protection and promote a work environment where these useful therapeutic agents can be safely handled.

Staff Education and Training

Key Points

- Comprehensive didactic education and documentation of clinical competence is required for all HCWs prior to handling HDs and must be reassessed at least every 12 months (USP, 2016a).
- Annual education regarding safety procedures is required to update and reinforce knowledge.
- Institutional administration should monitor adherence to PPE use and safe handling procedures and take measures to ensure compliance.

Education and training are necessary components of an HD safe handling program. All nurses who handle HDs must be fully informed about the risks of exposure and the strategies to mitigate those risks. A safe handling of HD agreement can be used to document employee awareness of risks and strategies to mitigate those risks (see Appendix A). Although nurses may know and understand the recommendations for safe handling, compliance with safe handling precautions continues to be a problem (Polovich & Clark, 2012). Strategies designed to change attitudes and beliefs, in addition to enhancing knowledge and verifying skills, should be used to motivate the behavioral change necessary to increase compliance with recommendations and guidelines. Factors in the work environment also influence safe handling practices, such as nurse–patient ratio, climate of safety, and availability of PPE (Friese et al., 2012; Polovich & Clark, 2012).

Most oncology nurses are knowledgeable about chemotherapy exposure and safe handling precautions (Polovich & Clark, 2012); however, some clinicians do not perceive that they are personally vulnerable to the associated health risks (e.g., "I have been doing this for years without wearing a gown and I am fine," "I am beyond the childbearing years"). For example, nurses might choose to wear a laboratory coat instead of a chemotherapy-designated gown. These findings indicate that knowledge alone is insufficient to influence HD precaution use. Safe handling education must be designed to affect not only knowledge but also skills and attitudes.

Initial Education and Training

All HCWs who may be exposed to HDs—including nurses, assistive personnel, physicians, pharmacists, housekeepers, and workers involved in receiving, transport, or storage—should participate in education and training specific to their roles and job requirements prior to handling HDs.

Beyond oncology nurses and pharmacy personnel, workers who come in contact with HDs both in hospitals and other settings include the following:

- Nursing assistants and patient care technicians who care for or handle the excreta of patients receiving HDs
- Nurses who work in areas such as rheumatology, ophthalmology, the emergency department, and maternal-child areas and other non-oncology nurses who administer HDs
- Homecare nurses, nursing assistants, and formal and informal caregivers
- Physicians, nurse practitioners, and physician assistants involved in the administration of HDs (e.g., during intrathecal or intraventricular injection)
- Transport personnel who deliver HDs from pharmacy preparation areas
- Transport personnel who move hazardous waste from satellite sites in patient care areas to storage areas
- OR or radiation therapy staff
- Environmental staff who clean patient rooms or administration areas
- Environmental staff who are tasked with HD spill response and cleanup
- Workers who receive and process HD shipments
- Nursing home workers
- Veterinary workers
- Laundry personnel

All staff potentially at risk for HD exposure should be identified and included in systematic training programs (ASHP, 2006; USP, 2016a). Any worker expected to contain and decontaminate following an HD spill must receive comprehensive training on spill cleanup and the use of PPE. OSHA (2016) and USP (2016a) recommend that HD training be provided when a worker is first assigned to a work area, prior to handling HDs, with competency evaluated at least every 12 months. Educational content should reflect institutional policies and be tailored for specific roles and job requirements.

Initial training and education should address some or all of the following elements, depending on job responsibilities:

- Institutional HD list
- Institutional policies and procedures for HD handling
- Potential health effects of HD exposure
  - Genotoxicity
  - Reproductive toxicity
  - Carcinogenicity

  - Acute toxicities
- Workplace environmental contamination
- Routes of occupational HD exposure
  - Dermal absorption
  - Ingestion
  - Inhalation
  - Injection
- PPE
  - Glove selection and use
  - Gown selection and use
  - Face and eye protection
  - Respiratory protection (including fit testing and training for staff who wear NIOSH-approved respirators, in accordance with OSHA's Respiratory Protection Standard (Respiratory Protection, 2012)
  - Other equipment required for spill cleanup
- Engineering controls
  - BSCs or CACIs
    * Proper installation and location
    * Maintenance and use
  - CSTDs
    * Rationale for use
    * Proper use
  - Use of PPE
    * Rationale for proper use to decrease workplace contamination
    * Appropriate application, removal, and disposal of PPE
  - Drug storage practices
  - Drug preparation techniques that minimize exposure
    * Centralized drug preparation areas
    * Location of drug preparation areas
    * Staff assignment for drug preparation
    * Changing gloves at appropriate intervals and when contaminated
    * Wiping down drug containers to remove drug residue
    * Dispensing HDs in sealed bags
    * Handwashing
    * Wiping down surfaces within the C-PEC
    * Priming all tubing with nondrug solution before adding HDs
    * Using CSTDs
    * Selecting the correct size of syringe to avoid overfilling
    * Capping syringes and transporting them without needles
    * Labeling of HDs with warning labels
    * Appropriate disposal techniques
  - Drug transport techniques to limit exposure
    * Use of containment devices, including placing in a clear, sealable plastic bag
    * Drug transportation process
  - Drug administration techniques to limit worker exposure
    * Use of locking connections
    * Use of CSTDs
    * Avoiding spiking and unspiking
    * Avoiding glass bottles
    * Avoiding venting of tubing
    * Using dry spiking and backpriming technique when needed
    * Wiping down the outside of drug containers
    * Considering the infusion tubing, connectors, and pumps available to determine the optimal technique for connecting IV HDs
    * Using plastic-backed absorbent pads to absorb leaks
    * Using gauze squares around injection ports or connections to absorb leaks with disconnect
    * Placing a Luer end-cap on the IV tubing, after disconnecting, to prevent drips during disposal
    * Avoiding ejecting air from syringes for IM or SC injections outside the C-PEC
    * Managing exposure (e.g., skin, mucous membrane, ocular contamination)
    * Spill kit contents and use
    * Spill containment and management, including use of a NIOSH-approved respirator
- Patient care
  - Appropriate PPE
  - Handwashing
  - Handling of contaminated fluids and excreta
  - Cleaning of contaminated areas and equipment
  - Handling of linens
  - Skin protection of incontinent patients
  - Safe handling issues in the home
- Proper disposal of HDs and HD-contaminated materials
- The medical surveillance program

Didactic content should be evaluated through some form of knowledge assessment, such as a quiz or test after a live educational program or following completion of a computer-based training program. In addition to knowledge assessment, competency for specific skills, such as spill cleanup, should be evaluated by direct observation. A checklist, such as that found in Appendix B, provides one method of documenting competence in HD safe handling skills. Similar checklists reflecting institutional policies should be developed.

Periodic Education and Training

Each employee involved in HD handling should receive annual updates regarding new HDs; SDSs; and HD policies, procedures, and other guidelines.

Annual updates should review initial training, based on employee role, and should also include a review of engineering controls, PPE, medical surveillance if available, spill management, and acute exposure response. Training should include special attention to workers who do not speak English so that they recognize the warning signs and labels of HDs.

Special Educational Needs

Unique routes of administration, such as intravesical, IP, and intraoperative therapies, require that staff learn additional safe handling content (see Appendix C). Intravesical therapy using an indwelling catheter, for example, necessitates handling of a large volume of drainage from the bladder via a closed system. Appropriate containment equipment, such as CSTDs, should be evaluated and made available. In all of these settings, safe handling procedures, adequate training, and supervised practice with necessary equipment should be provided prior to the initiation of treatments.

HDs administered in the home setting may pose additional challenges to ensuring that safe handling practices are implemented. Less control over the environment by professional staff with possible breaches in good practice can contribute to potential environmental contamination and caregiver exposure. Homecare programs should ensure that nursing staff members receive adequate training in all aspects of HD administration, patient care, safe handling, and patient and family education about safe handling practices.

Educational Strategies

Education and training designed to teach nurses and others about safe handling of HDs generally aims to augment knowledge about the potential hazards and how to avoid them, to develop specific psychomotor skills, and to engage in specific behaviors, such as the following:

- Work practice controls, such as wearing PPE and prepriming IV bags with nondrug fluids, are taught as strategies to improve safe handling.
- Proper engineering controls, such as a BSC, CACI, or CSTD, are used for drug preparation and administration.
- Administrative controls, such as requiring nurses to have initial and ongoing didactic training, and annual competency testing are employed.

Some professional groups, such as those of nurses and pharmacists, have access to education and training developed by their professional organizations. Nurses who administer HDs perform their work in a variety of settings and with wide variation in their professional experience and specialized training. Many nurses participate in ONS's two certificate courses, the Chemotherapy and Biotherapy: Fundamentals of Administration Course and the ONS/Oncology Nursing Certification Corporation Chemotherapy Biotherapy Certificate Course (Polovich et al., 2014). Safe handling content is a component of these courses. As ONS guidelines recommend, nurses should complete a clinical practicum before administering chemotherapy (see Appendix C). The ONS (2015) position titled "Education of the Oncology Nurse Who Administers and Cares for the Individual Receiving Chemotherapy and Biotherapy" states that introductory and annual competency reassessment programs for RNs include content regarding principles of safe preparation, storage, labeling, transportation, and disposal of chemotherapy and biologic agents and appropriate use and disposal of PPE. In a joint position statement with the American Society of Clinical Oncology (ASCO) and the Hematology/Oncology Pharmacy Association, ONS reiterated the importance of "education, training, and competency evaluation" about the risks of HD exposure, the recommended precautions for reducing exposure, and handling acute exposure (ONS, ASCO, & Hematology/Oncology Pharmacy Association, 2016).

As part of this component of their training, nurses should be precepted by experienced nurses in the actual administration of HDs and educated on the associated institutional policies. Certificate renewal requires additional periodic continuing education, thereby ensuring that knowledge will be updated and that the learner will review current trends and practices, including information about new therapies.

Adult Learning

Adult learning takes place across three domains as described in Bloom's taxonomy: knowledge (cognitive), psychomotor (skills and behaviors), and affective (attitudes) (Knowles, Holton, & Swanson, 2012). A clinical practicum blends all of these domains in the delivery of patient care. Programming on safe handling should address the requisite knowledge, skills, and attitudes to handle HDs safely and should incorporate the larger components of an organizational safety culture.

Learners use concrete experience, reflective observation, abstract conceptualization, and active experimentation as they attempt to integrate new learning (Kolb, 2015). For example, nurses who have completed a chemotherapy educational program can

return to their clinical setting and, through the clinical practicum or preceptor experience, engage in a variety of behaviors to continue their learning. As nurses learn to handle HDs safely, they gain insight from their new experience, make observations about their own practice and the practice of other nurses, conceptualize how they would handle a specific scenario (e.g., a drug spill), and then use their integrated knowledge to solve problems and make decisions in practice.

Effective continuing nursing education incorporates principles of adult learning in content delivery. Adults prefer self-directed educational experiences that are centered on action, based on their experience, focused on real-life problems, and driven by solutions. As adult learners, HCWs bring a wealth of personal and practical clinical experience to their professional practice. Respecting that expertise, drawing upon it, and building upon its foundation are important aspects of effective adult education. Creating connections between the material to be learned and content that the learner has already mastered is essential. In a culture where evidence-based practice is valued, highlighting new evidence can be an effective strategy to modify learner behavior.

Adults learn using different styles, and programming ideally should be offered in several formats to appeal to most learners. For some, visual presentations work best, so computer-based training or other visual strategies, such as reading a journal article or a self-study guide, might be the preferred learning mode. For those who are auditory learners, podcasts or recorded presentations might be used. Combined audiovisual presentations, such as recorded lectures with visuals, podcasts, or video programs, appeal to a wide range of learners. Distance-learning formats featuring computer-based training or blended formats allow learning to take place anywhere, at the time and setting of the learner's choice—a concept well suited to self-directed adult learners. Others learn best by doing, so experiential exercises, one-on-one coaching, and clinical practicums offer an ideal learning venue. Over time, comprehensive safe handling education can engage participants in discussion, journal clubs, reviews, practice-based scenarios, case studies, role play, and experiential exercises to keep the learning experience fresh and interesting.

Overcoming Barriers to Safe Handling Practices

Even the best teaching methodologies will fail to convince a certain segment of HCWs who feel that they are not susceptible to the adverse outcomes associated with handling HDs or who practice in a setting where the organizational culture minimizes the importance of safe handling recommendations. Barriers to safe handling of HDs include inconvenient access to equipment, inadequate supplies, gloves that do not fit or are difficult to put on, gowns that are uncomfortable, knowledge deficits, faulty belief systems, lack of time, and habitual outdated practices.

Compliance with recommended practices evolves not only from knowledge but also from personal beliefs and even peer pressure. Improvements in knowledge and skills, therefore, are insufficient to change the behavior of some nurses. Effective safe handling education also should seek to change attitudes and perceptions, targeting affective change in the learner as well as organizational culture in the work setting.

Educational strategies to address the affective domain of learning prove to be more elusive and may be neglected in the planning and execution of nursing education. Influencing attitudes is much more complex than changing behaviors or increasing knowledge. Long-standing beliefs (e.g., "I was pregnant while handling chemotherapy, and my child is fine," "Patients will be frightened if I give their drugs dressed in a Hazmat suit") can be powerful forces in a clinical setting and may set the norms for accepted practice and safe handling behavior. Teaching strategies in this domain of learning assist learners to internalize values and to demonstrate behaviors consistent with these values (e.g., "I will wear PPE consistently even if my coworkers do not").

Hennessy and Dynan (2014) engaged staff in a quality improvement program that utilized education followed by compliance monitoring of the use of PPE. Leadership support and frontline staff involvement were paramount to the success of this program.

Informal Education

HCWs may have benefited from formal continuing education or in-services, and others may have learned about handling practices through on-the-job training or by self-study or consulting colleagues. Settings of care may have varying practices, and staff members may have wide ranges of experience (Polovich & Clark, 2012). As a result, informal on-the-job training may be inconsistent. Specialized centers may have more access to local expertise while some in more rural settings may have fewer experienced staff members available or may lose staff with expertise through attrition.

Much of the knowledge transmitted in the clinical setting is conveyed from one practitioner to the next through conversation and dialogue, often occur-

ring in the context of a preceptor or mentorship relationship. One example is that of experiential learning through conversation, a process during which learners make sense of what they have learned and what they are experiencing through reflection (Kolb, 2015). Two individuals, such as a staff nurse and an advanced practice nurse, collaborate, and through the sharing of ideas and experiences these professionally oriented conversations can be opportunities for learning. In these moments of informal teaching, the rationale for the use of PPE can be reinforced and the significance of specific work practice controls can be highlighted in the context of practice. What may have been unclear in the classroom or in front of a computer screen comes alive in the clinical setting under actual practice conditions using real experiences in context.

Staff educated in the importance of safe handling should consistently role-model safe handling behaviors and compliance. Role modeling of recommended practices by experienced and respected practitioners is invaluable in shaping the behaviors of new or less experienced staff. The converse is also true: the reluctance of more seasoned staff to change their practice to reflect current recommendations can be detrimental to the knowledge, practice, and attitudes of those they mentor. Informal educational interactions provide a perfect opportunity to stimulate a different perspective on these issues and to create an impetus for adapting recommended safe handling practices. Experienced staff should be educated about the fact that noncompliance with safe handling of HDs causes workplace environmental contamination, putting other staff members and caregivers in the area at risk. One nurse's decision to be noncompliant can affect other staff and caregivers in the environment.

Educating caregivers and patients also is an important strategy. Explaining the importance of staff and caregiver safety is a necessary component of the initial teaching of patients who receive HDs. This explanation can begin with the mechanism of action of HDs in the treatment of cancer. Patients may even advocate for staff and caregiver safety if they notice inconsistencies.

Innovative Strategies

Simulated practice has been used extensively in the teaching of cardiopulmonary resuscitation and holds promise as an oncology nursing education tool as well. Scenarios featuring a progressive simulation of a patient receiving HDs and the care required to administer the HDs could be created, such as using a CSTD, implementing recommended drug administration work practices, donning and removing PPE correctly, disposing of HD waste, handling patient excreta, cleaning up spills, and caring for patients in the home setting. Simulated safe handling learning situations allow learners to achieve learning goals without actual exposure to HDs.

In summary, all personnel who are responsible for any aspect of HD handling must be properly trained according to their specific role. While knowledge alone is insufficient to ensure safe handling, it is an essential component of an HD safe handling program.

Patient and Family Education

Key Points

- Research studies have demonstrated that surface contamination can occur in the homes of patients who are receiving HDs, potentially exposing family members and caregivers.
- Patients and caregivers must be taught about sources of and ways to minimize exposure.
- Information should be provided both verbally and in writing.

Nurses administering antineoplastic therapy routinely provide patient and family education regarding the treatment schedule, anticipated side effects, and symptom management (Polovich et al., 2014). Patients require a significant amount of information to cooperate with the treatment plan and to minimize treatment toxicity. The fact that exposure to HDs is possible for patients' family members or caregivers makes safe handling an important aspect of patient education.

If patients are not taught about the sources of exposure and what can be done to minimize exposure, their loved ones may be unnecessarily put at risk. This section will discuss the importance of patient and family education related to the safe handling of HDs.

Bystander Hazardous Drug Exposure

Although ample research exists related to occupational HD exposure, exposure of family members of patients receiving chemotherapy has received little attention until recently. Nurse researchers in Japan conducted small studies in the households of patients being treated with chemotherapy. The studies included both environmental monitoring and biologic monitoring of urine for chemotherapy residue. They found detectable levels of chemotherapy agents on environmental surfaces in more than 60% of homes that were studied (Yuki et al., 2013; Yuki, Takase, Sekine, & Ishida, 2014). Cyclophosphamide was measured in the urine of all patients in the studies for at least 48 hours and for up to five days after the drug was administered (Yuki et al., 2015). In two studies by the same researchers, drug residue was above the LOD in 21% (representing 6 of 10 family members) and 100% (3 of 3 family members) of urine samples from cohabitating family members of the patients (Yuki et al., 2013, 2015). Drug residue on household surfaces occurred frequently and was the presumed source of family members' exposure. The observed level of environmental contamination in the homes was surprisingly similar to that previously reported in healthcare settings (Maeda et al., 2010; Yoshida et al., 2011).

The extent of bystander exposure to HDs outside of healthcare settings in the United States is currently unknown. Even though the sample sizes in the few studies related to chemotherapy exposure outside of healthcare settings were small, the frequency of environmental contamination and documented exposure is concerning. The amount and quality of education that family members receive about safe handling precautions or how often they use them also is unknown. The opportunities for exposure, combined with even the limited evidence of household exposure, suggests that patient education must include safe handling information. Family members, significant others, and caregivers must receive the same information.

Content of Patient Education for Safe Handling

Safe handling education for patients and caregivers should be a planned and purposeful activity that is incorporated into the teaching plan for all patients undergoing treatment with HDs. Education should be provided based on the patients' preferred learning style while considering barriers to learning (Polovich et al., 2014). Information should be provided both verbally and in writing so that patients can refer to the instructions after leaving the healthcare setting (Neuss et al., 2016). The content of safe handling education must include procedures for the safe handling, storage, and management of medications; the handling of body secretions and waste following treatment (Neuss et al., 2016); and any procedures that are specific to the type of treatment.

Routes of Exposure

The routes of HD exposure for those who live with or participate in the care of treated patients are the same as those for HCWs: drugs or drug residue can be absorbed, inhaled, ingested, or injected. Patients and family members should be taught to avoid direct contact with HDs. Dermal absorption of HD residue can occur from touching IV bags, tubing, or infusion pumps and from touching tablets or capsules. Leaks or HD spills should be reported immediately to the healthcare provider. Family members should be told not to

have food or drinks in the drug administration area to minimize the chance of ingestion of HD residue.

Absorption, inhalation of aerosols, or accidental injection of HDs can occur during preparation or administration of injectable HDs at home. If patients or their caregivers are responsible for injection of HDs at home, they must be taught about safe sharps disposal. Sharps container disposal programs vary from state to state. Staff must be familiar with the local requirements, such as supervised collection sites, hazardous waste sites, mail-back programs, and residential special waste pick-up services (U.S. FDA, 2016). For more information, call Safe Needle Disposal at +1-800-643-1643 or e-mail safeneedle disposal@needymeds.org for state-specific guidelines.

Although HCWs understand that drugs are metabolized and eliminated by the body and that the end products of HDs may be harmful to others, patients and family members may not be aware of this. Body fluids and excrement of treated patients may contain varying amounts of HD residue. Body fluids, including urine, stool, saliva, emesis, vaginal secretions, and semen, should be considered potentially hazardous during the time that the drugs are expected to be excreted. While safe handling precautions have traditionally been recommended for 48 hours after HD administration, the excretion time of many HDs is longer than 48 hours (see Table 7). If evidence exists of prolonged drug excretion, this information must be provided to the patient and family. For example, a recent study in Japan documented urinary excretion of cyclophosphamide for more than 48 hours after drug administration in 63% of patients; some patients excreted the drug for as long as five days (Yuki et al., 2015). For oral HD regimens, excrement likely will contain HD residue for the entire duration of therapy and for 48 hours after the last dose (Yuki et al., 2013).

Healthcare facilities should carefully consider the safety of children when they visit patients undergoing treatment with HDs. When children are allowed to visit, patients and family members should be instructed to prevent young children from touching infusion pumps, IV equipment, and HD waste containers. Patients and families must receive information to safeguard children from HD exposure in the home.

Personal Protective Equipment

PPE provides barrier protection from HD exposure and is one of the essential interventions from the hierarchy of controls. Early research suggested that some nurses were concerned about patients being frightened, worried, or upset when seeing staff wear PPE while administering HDs (Valanis, McNeil, & Driscoll, 1991; Valanis & Shortridge, 1987). Today, despite the fact that PPE is commonplace for infection prevention, and gown and glove use is "familiar" to patients, this attitude persists in some settings (Polovich & Clark, 2012). Although this has not been studied in the context of safe handling, it is reasonable to assume that patient objections can be overcome by education regarding the purpose of PPE.

Nurses should inform patients that staff will wear PPE while administering HDs. Patients should be told that nurses will wear gowns to protect their clothing, gloves to protect their hands, and, when needed, face shields or respirators to prevent contact with drugs that might leak during administration. Nurses should explain that staff handle multiple HDs on a daily basis, that no benefit from the drugs exists for people who do not need treatment, and that potential harm can occur from repeated exposure because of the side effects of the drugs. Patients should be reassured that the need for PPE is the result of the hazardous nature of the drugs and not because the patients themselves are "contaminated" or a source of harm.

In healthcare settings, when patients require help with bedpans, urinals, and emesis basins, they should be taught to ask staff, rather than family members, for assistance. Staff members have access to PPE and are trained to measure and dispose of excreta carefully. Patients who are ambulatory should be encouraged to use the toilet for body waste rather than bedpans or urinals.

PPE is indicated for family members who participate in the care of patients during HD therapy. Parents should be taught to wear gloves when changing diapers of infants or toddlers receiving chemotherapy. When assisting patients with oral HDs, family members should use "no-touch" technique (e.g., pour tablets into the cap of the container) or wear gloves for handling. When preparing and administering HDs for injection, caregivers should wear gloves.

Safe Handling of Oral Medications

Teaching about safe handling precautions is necessary when oral HDs are part of therapy in home settings. Patients must be taught to store all oral antineoplastic medications in their labeled containers, away from food, drink, cookware, and other medications. This minimizes the chance of transferring HD residue to household surfaces. HDs should be stored away from areas that may be accessed by children and pets or in areas where they may be mistaken for other medications. Zipper-lock bags can be used for storage of the drug containers if they require refrigeration.

Patients should be taught to avoid crushing or breaking oral HDs unless absolutely necessary. Specialty pharmacies should be encouraged to provide HDs that require manipulation (e.g., crushing or splitting of tablets) in a

ready-to-administer (i.e., unit-dose) form (Polovich et al., 2014). If the drug is not provided in unit-dose packaging, the patient should be the one to handle the HD whenever possible. If caregivers must assist the patient, they should wear chemotherapy-tested gloves.

Although EPA does not regulate household waste, improper disposal of HDs has safety implications. Patients should be taught the proper handling of HD-contaminated equipment and leftover hazardous medications at home. This varies depending on the geographic region and how the patient received the medication for home use. The responsibility for proper disposal may rest with homecare agencies if the drugs are provided by them. If HD waste containers are provided, patients should be taught how to seal them and how the containers will be handled when full. For unused oral HDs, clear instructions for proper disposal should be provided to the patient and family.

Safe Handling Following Bladder Instillation

Intravesical HD treatment is not systemic, so excretion of the drugs occurs over a few hours. Current recommendations suggest that urine should be handled as hazardous for six to eight hours after treatment (Washburn, 2007). Instruct the patient to avoid sitting down for the first six hours following treatment to decrease risk of splashing. If a biologic agent, such as BCG, is used, the toilet can be disinfected by adding two cups of household bleach to the toilet water and letting it stand for 15–20 minutes before flushing (Organon Teknika Corp. LLC, 2009).

Safety Regarding Normal Activities of Daily Living

In the home setting, prudent practice suggests that patients and family members should be taught to use separate toilets for 48 hours after HD administration if possible. This eliminates the risk of family members' contact with contaminated body waste. In households with only one bathroom, education should address ways to reduce others' exposure to excreted HDs. Patients can keep disinfecting sanitizing wipes near the toilet to clean the toilet seat and rim after use. The wiping action physically removes HD residue from surfaces. Following toileting and cleaning, patients should wash their hands with soap and water before touching other surfaces or items. At the end of 48 hours, the toilet and bathroom floor should be washed.

Patients should be told to refrain from sexual intercourse for the first 48 hours after treatment because of the possible presence of HD residue in vaginal fluid or semen. Alternatively, barrier contraception should be used for sexual activity (White, 2012).

Preventing Surface Contamination at Home

Sources of surface contamination with HDs at home include leaks or spills of liquid drug preparations, dispersal of drug powders, and spills of contaminated body fluids. Safe handling education should address the specific exposure risks associated with the route of drug administration. When drug preparation is necessary, patients should be taught techniques that will minimize contamination of the household environment. For example, family members should be told to avoid contact with drugs, drug containers, IV bags, and infusion pumps as much as possible. For HDs that require manipulation, the preparation should be limited to one area of the home. The preparation surface should be one that can be cleaned easily, such as a washable counter. Those responsible for handling HDs should be taught to protect preparation surfaces with a towel and wipe down the surface with soap and water when finished. If injections are necessary, handlers should be reminded to dispose of sharps carefully.

Family members should be told to avoid contact with contaminated body fluids as much as possible. HD-tested gloves should be worn for touching contaminated urine, stool, and emesis. If patients are incontinent, disposable diapers should be used to contain the excrement. Reusable items that are contaminated with body fluids during and for at least 48 hours after therapy should be handled with gloves and washed with soap and water. Handwashing with soap and water should be performed at the end of HD handling activities to remove residue and prevent the transfer of contamination from hands to surfaces.

Linen Handling at Home

Bed linens and towels in the home can be handled as usual unless they are contaminated by an HD spill or by body fluids during the time that HD excretion is expected. If contaminated, linen should be handled separately from other laundry and washed with detergent twice in hot water. The contaminated items should be placed directly into the washing machine to avoid contamination of any intermediary storage container. If possible, the patient should handle these linens so as to decrease exposure of other members in the household (refer to Linen Handling [p. 51]). If patients are unable to handle their own linens, family members or

caregivers should handle the linens with gloves. Bleach should be used when feasible, considering the fabric, for its role in deactivating HDs.

Hazardous Drug Spills in the Home

When patients are sent home with a continuous infusion of an HD, they and their caregivers must be educated about the risk of exposure from malfunction of the pump, the IV tubing, the insertion site, and the medication container. Spill kits should be provided, along with written step-by-step instructions on using the spill kit. Patients and family members should be able to verbalize how to manage a spill should one occur (Polovich et al., 2014). Facilities responsible for managing home chemotherapy should provide a phone number to patients for notification about a spill and encourage them to report spills or leaks immediately.

Several resources are available to supplement verbal instructions for patients and their caregivers related to HD safe handling (National Institutes of Health Clinical Center, 2014a, 2014b; OncoLink, 2016). Figure 17 summarizes important teaching points for various HD handling activities.

A comprehensive safe handling education plan is essential to the health and safety of patients being treated with HDs and their caregivers so that they understand what they need to do to ensure safety both in healthcare facilities and at home. Open communication is crucial. Nurses must provide information in such a way that raises appropriate concern without causing fear.

Figure 17. Patient and Family Education for the Safe Handling of Hazardous Drugs

IV Drug Safety
- Wash your hands well with soap and water before and after touching the IV pump or bag.
- Do not let children or pregnant women touch the IV pump or bag.
- Wear disposable gloves when touching the IV pump or bag. Do not use gloves with tears or holes.
- Remove used gloves one at a time, turning them inside out. Try not to touch the outside of the gloves.
- If given a special waste container, keep the lid closed. Keep it away from children and pets.
- Place used gloves in a plastic bag and seal it before throwing it away in the chemo waste container. Otherwise, use the regular trash.
- Check your pump regularly to make sure it is working and there are no leaks.
- If you find a leak or spill, stop the pump and clamp your line. Notify the clinic or hospital as instructed.

Oral Drug Safety
- Wash your hands well with soap and water before and after handling your medication.
- Do NOT let others touch your drugs unless they have been told how to do so safely. Do not let children or pregnant women touch your drugs.
- Do NOT touch the tablets or capsules with bare hands. Wear disposable gloves. Do not use gloves with tears or holes.
- Pour the tablet(s) from the bottle into the cap. For unit-doses, open the package carefully. Use a disposable plastic medicine cup or oral syringe for liquids.
- Place used gloves in a plastic bag and seal it before throwing it away in the waste container. Otherwise, use the regular trash.
- Keep your drugs out of reach from children and pets.
- Keep your drugs separate from any other medications.
- Keep your drugs in the original containers. Do not use a pill box.
- If your drugs require refrigeration, keep them separate from foods. Store them in a separate crisper drawer or in a zipper-lock bag.

Drug Safety for Injections
- Wash your hands well with soap and water before and after touching the drugs.
- Do NOT let others touch your drugs unless they have been told how to do so safely. Do not let children or pregnant women touch your drugs.
- Wear disposable gloves when touching the drugs and syringe. Do not use gloves with tears or holes.
- Use a towel to protect the counter from leaks when preparing the drugs for injection.
- Follow the separate instructions for preparing and giving the chemo injection.
- Handle needles carefully. Throw away needles and syringes in rigid container to protect others from being stuck.

Drug Safety When Handling Body Fluids
- Be aware that your body eliminates drugs in urine, stool, saliva, emesis, and other body fluids over hours or days.
- Do NOT let others touch your body fluids unless they have been told how to do so safely. Do not let children or pregnant women touch your body fluids.
- Use a toilet rather than a bedpan or urinal whenever possible. If using a bedpan or urinal, handle it with gloves and wash it with soap and water after use.
- If you share a bathroom with others at home, wipe the toilet seat and rim with a sanitizing wipe after use.
- Wear disposable gloves when touching body fluids. Do not use gloves with tears or holes.
- Do NOT have sexual intercourse for 48 hours after taking the drug, or use a condom.

The Hazardous Drug Handling Policy Landscape

Key Points

- HD policies are developed, implemented, and evaluated at federal, state, professional, and institutional levels.
- Nurses can make meaningful practice improvements by developing and evaluating policies in their workplace.

A complex and fragmented political landscape threatens evidence-based HD policy implementation. Despite these challenges, HCWs have advocated successfully for reforms across states, and professional organizations have heightened awareness. The Conceptual Model for Nursing and Health Policy posits that nurses can support policy efforts across governmental, institutional, and organizational settings (Russell & Fawcett, 2005). This section will review the current landscape and future opportunities across these settings. The section concludes with advocacy opportunities to reform HD handling policies.

Federal Efforts: Occupational Safety and Health Administration and National Institute for Occupational Safety and Health

A review of studies that link HD exposure and health (see Evidence for Occupational Hazardous Drug Exposure section) and the documented health risks to exposed workers (see Adverse Effects of Hazardous Drug Exposure section) shows that while exposures and health risks are implicated in HDs, two key scientific gaps pose noteworthy challenges to federal intervention. First, few longitudinal studies show that HD exposures cause health events, and second, few studies establish dose–response relationships between HD exposures and health events.

The Occupational Safety and Health Act of 1970 established OSHA as part of the U.S. Department of Labor (OSHA, n.d.), with a charge to protect the health and safety of the American workforce. As a regulatory agency, OSHA establishes and enforces safety standards for U.S. workers. The act requires each state to establish specific standards and enforcement plans, which enables flexibility but also potential confusion. OSHA inspects facilities (either announced or unannounced) for adherence to standards and fines facilities that deviate from standards. However, OSHA cannot enforce advisories, such as guidelines and recommendations.

Two enforceable OSHA standards exist that pertain directly to HDs. Section 1910.1020 requires employers to report incidents, including HD exposures, and permits employees to view their incident records (Access to Employee Exposure and Medical Records, 2014). OSHA also can view these records for reporting purposes. Section 1910.1200, titled Hazard Communication (2014), requires manufacturers and users of hazardous substances to inventory and label them properly, maintain SDSs, and ensure that workers who handle hazardous substances receive training. Our analysis of 2013–2014 data suggests that OSHA fined 29 physician offices a total of $10,360 for violations of the Hazard Communication Standard. For violations of the same rule, 11 outpatient care centers cumulatively received fines of $1,440, and 17 hospitals received fines of $11,842. The available data do not specify clinical specialty nor provide details of the infractions. Although under the "General Duty" clause (Section 5) OSHA also can cite employers for failing to provide a safe and healthy work environment, this is rarely done.

On June 25, 2015, OSHA published a memorandum that announced increased oversight of HCWs' injuries (OSHA, 2015). Primarily motivated by a National Public Radio report on nurses' back injuries, the directive stated that new inspections of inpatient facilities and nursing homes will focus on musculoskeletal disorders, workplace violence, bloodborne pathogens, tuberculosis, and slips, trips, and falls (Zwerdling, 2015). In addition, inspections may include reviews of exposure to drug-resistant organisms and hazardous chemicals, including drugs. The directive excludes ambulatory settings, where the majority of antineoplastic drugs in the United States are administered.

A more effective method of controlling workers' exposure to HDs would be establishment of occupational exposure limits (OELs). However, as outlined previously in these guidelines, the causal relationship between HD exposure and worker health changes has not been clearly established. OELs also are based on airborne exposures, and HCWs are exposed through multiple routes. Consequently, OSHA cannot establish OELs for these substances. In contrast to other work settings, the absence of HDs OELs precludes meaningful enforcement of drug handling guidelines.

Also established in 1970 as an education and research (rather than regulatory) agency, NIOSH, currently part of CDC, investigates the causes, conse-

quences, and interventions for workers' injuries. Primarily, NIOSH conducts its own research but has a relatively small extramural research program. In partnership with external stakeholders, NIOSH issues guidelines for injury prevention across many occupational sectors. However, these guidelines are advisory and not enforceable.

Upon request of employers or employees, NIOSH scientists conduct health hazard evaluations to identify potential workplace hazards and propose solutions. NIOSH has published four evaluations that investigated HD exposures in healthcare settings (Couch & de Perio, 2011; Couch & West, 2012; Page & Couch, 2011; West & Beaucham, 2014). While NIOSH scientists have established recommended exposure limits (RELs) for certain chemicals, such as formaldehyde, no RELs currently exist for HDs (NIOSH, 2007).

The 2004 NIOSH alert on HDs represents the institute's landmark document on research and recommendations to reduce worker exposure. Despite research reports and safe handling guidelines published since the 1980s, NIOSH scientists concluded that workplace contamination and subsequent worker exposure persisted and an alert was necessary (Connor & McDiarmid, 2006). This alert summarized the extant literature on exposure routes, drugs that NIOSH identified as potentially hazardous, and recommendations for workplaces and individual workers to reduce contamination and exposure. Outside experts from occupational health, industrial hygiene, nursing, and pharmacy contributed to the report. Periodically, NIOSH updates research findings, its latest recommendations, and proposed list of HDs (NIOSH, 2017). Before NIOSH officials issue the final report, the public may comment on draft versions.

In 2011, OSHA and NIOSH partnered with the Joint Commission to recommend that facilities seeking accreditation monitor worker health and establish policies, procedures, and training to mitigate HD exposures. With technical assistance from OSHA and NIOSH, Joint Commission surveyors routinely tour infusion clinics attached to hospitals seeking accreditation and observe HD handling procedures. In 2013, this partnership was renewed for five years (OSHA, 2013). However, the majority of infusion clinics in the United States operate outside of hospitals and do not seek Joint Commission accreditation. Consequently, the majority of settings where HD handling occurs are not monitored by the Joint Commission.

Recent State Initiatives

Federal rules set by OSHA are considered the minimum occupational safety standards. In addition to federal OSHA inspections, state authorities may conduct their own inspections and fine offending employers. Selected states have enacted legislation or regulatory reforms that are more stringent than federal standards. Since 2010, increased public attention to the plight of HCWs taken ill after HD exposures has catalyzed state-based efforts to require employers to adhere to NIOSH recommendations. However, a 2014 review of federal and state inspections characterized occupational health oversight as "murky" (Jung & Makowsky, 2014, p. 1).

In July 2010, reporter Carol Smith chronicled pharmacist Sue Crump's diagnosis of metastatic pancreatic cancer; she had compounded HDs with little protection since 1980 (Smith, 2010). Crump's story garnered national attention and support from organized labor leaders and the state nurses' association. In April 2011—less than one year later—Washington State passed two key bills. The first would require all facilities in which HDs are administered to follow the 2004 NIOSH alert recommendations (and subsequent updates). The second bill required employers to track potentially exposed employees through a database (Washington State Department of Labor and Industries, n.d.). Bill requirements are being phased in. The rules to establish databases for exposed workers were not yet finalized at the time of this publication.

With the support of the California Nurses Association, the California Healthcare Institute, and several labor groups, California enacted similar legislation in 2013 and the rulemaking process is underway. At the time of this writing, North Carolina is also in the rulemaking phase after a bill passed in July 2014. In January 2015, bills were filed in the New Jersey General Assembly and the Massachusetts House of Representatives. The legislation in New Jersey passed both chambers in May 2017 and was signed into law by Governor Christie on May 11, 2017. In Massachusetts, the legislation was reintroduced in 2017. In March 2015, Michigan Senate Bill 237 was introduced and referred to the health policy committee. During the 2014 session, Maine's legislature did not pass legislation out of its Joint Standing Committee on Health and Human Services. In contrast to bills introduced into state legislatures, the state of Maryland has discussed changes to their existing regulations. An advisory committee of stakeholders has convened to revise regulations that would undergo public comment before they are finalized.

Professional Organizations

USP is a private, nonprofit organization that establishes standards for drug manufacturing, storage, prep-

aration, and administration, among other activities (USP, n.d.). Organized by chapters, select USP standards are enforced by FDA and similar agencies in 120 countries. USP General Chapter 800 aligns with extant recommendations from NIOSH and others (USP, 2016c). Importantly, chapter 800 is enforceable by state boards of pharmacy and other regulators; previous safe handling sections were considered advisory. The chapter addresses all phases of HD handling, including drug administration and disposal. After collating public comments, the expert panel on compounding HDs finalized the chapter on February 1, 2016. The implementation date is December 1, 2019 (USP, 2017a). Readers are encouraged to review this chapter thoroughly to understand the detailed standards, including requirements for external ventilation of preparation areas and employer-provided PPE and training.

After a 2015 stakeholders meeting in Washington, DC, representatives from ONS, ASCO, and the Hematology/Oncology Pharmacy Association issued a joint position statement to summarize their position on HD handling (Tomkins, 2015). The statement recommends that facilities (a) adopt evidence-based strategies to reduce HD exposure to HCWs, (b) provide engineering controls and tested PPE, (c) educate staff and patients on exposure risks and preventive strategies, (d) provide alternate duty to workers attempting to conceive, and (e) establish sound drug disposal policies. The three organizations also pledged to generate and disseminate evidence-based preventive interventions.

Institutional Policy

The term *policy* often connotes unpleasant images of speaking with legislators, slow progress, and long, unreadable documents. Yet nurses can make meaningful practice improvements by developing and evaluating policies in their workplace. Such policies form the backbone of high-quality, reliable nursing practice. Facilities in which HDs are administered often establish institutional policies that govern the ordering, storage, preparation, administration, disposal, and documentation surrounding HDs. Nursing participation in these efforts can ensure that policies reflect the latest evidence base, are congruent with NIOSH recommendations, and are feasible to implement in practice.

Institutions rarely make HD policies publicly available. Thus, it is challenging to assess their quality and comprehensiveness. As part of the NIOSH-funded Drug Exposure Feedback and Education for Nurses' Safety study, the research team identified substantial variation in the content of institutions' HD handling policies (Friese, Mendelsohn-Victor, et al., 2015). A Canadian team proposed essential elements of a robust institutional policy for HD exposure management, with healthcare executives as the intended audience (Easty et al., 2015). These recommendations may help nurses as they participate in policy development and evaluation. Policies should undergo periodic expert review to incorporate the latest research evidence (Graham, Mancher, Wolman, Greenfield, & Steinberg, 2011).

Conclusions and Implications for Nursing

HD policies are developed, implemented, and evaluated at federal, state, professional, and institutional levels. Nurses have the opportunity to participate across these levels to ensure policies can be implemented effectively (Russell & Fawcett, 2005). Given the limited data available on exposed workers' long-term health, nurses should report HD exposures to their employers and ensure that permanent records are kept. Locally, nurses can develop and revise HD administration policies.

Nursing policy efforts at the state or federal level need not be onerous. Often overlooked, nurses should review both state and federal opportunities to comment publicly on bills or rules that address HD handling. At the federal level, draft regulations for public comment can be viewed at www.regulations.gov. States vary in their public commenting procedures. Policy makers and the public respond positively to personal narrative, and the public views nurses as highly trustworthy professionals (Riffkin, 2014). Through letters to the editor or commentaries, nurses can use poignant personal experiences to raise concerns and propose solutions (Friese, 2015a, 2015b). Nurses can testify before state or federal authorities as they consider legislative or regulatory reforms.

While the impetus for HD handling policy is diffuse, this fragmentation may be viewed as an opportunity for nurses to participate at levels most comfortable to them. Through sustained interest in emerging research findings, evidence-based advocacy efforts, and effective messages to key stakeholders, nurses can play an important role in developing sound HD handling policy that protects workers' safety and health.

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Appendix A. Handling of Hazardous Drugs Employee Agreement

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

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

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

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

RN, MD, NP, LPN only:

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

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

Employee _____

Signature Printed Name Employee # Date

Witness _____

Signature Printed Name Date

Appendix B. Hazardous Drug Administration Safe Handling Checklist

Name: _____ Date of Review and Exam: _____

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

(Continued on next page)

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

Appendix C. Hazardous Drug Administration Practicum for Registered Nurses

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

(Continued on next page)

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

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

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The letter f *after a page number indicates that relevant content appears in a figure; the letter* t, *in a table.*

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