Controlling Occupational Exposure to Hazardous Drugs

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Acronyms

ALARA
As Low As Reasonably Achievable
API
Active Pharmaceutical Ingredient
ASCO
American Society of Clinical Oncology
ASHP
American Society of Health-System Pharmacists (formerly American Society of Hospital Pharmacists)
ASTM
American Society for Testing and Materials
BSC
Biological Safety Cabinet
BUD
Beyond-Use Date
CACI
Compounding Aseptic Containment Isolator
CAI
Compounding Aseptic Isolator
CDC
Centers for Disease Control and Prevention (Department of Health and Human Services)
CFR
Code of Federal Regulations
CSTD
Closed System Drug-Transfer Device
CP
Cyclophosphamide
C-PEC
Containment Primary Engineering Control
C-SCA
Containment Segregated Compounding Area
C-SEC
Containment Secondary Engineering Control
CSP
Compounded Sterile Preparations
DNA
Deoxyribonucleic Acid
DOL
U.S. Department of Labor
EPA
U.S. Environmental Protection Agency
FDA
U.S. Food and Drug Administration
GHS
Globally Harmonized System

HCS
Hazard Communication Standard
HCWs
Healthcare Workers
HD
Hazardous Drug
HEPA
High-Efficiency Particulate Air "or Arrestor"
IARC
International Agency for Research on Cancer
IM
Intramuscular
IND
Investigational New Drugs
ISO
International Organization for Standardization
IT
Intrathecal
IV
Intravenous
ONS
Oncology Nursing Society
NIOSH
National Institute for Occupational Safety and Health
OEL
Occupational Exposure Limit
OSHA
Occupational Safety and Health Administration (Department of Labor)
PEC
Primary Engineering Control
P&P
Policy and Procedure
PPE
Personal Protective Equipment
SCE
Sister Chromatid Exchange
SDS
Safety Data Sheet (formerly Material Safety Data Sheet)
SOP
Standard Operating Procedure
SQ
Subcutaneous
TJC
The Joint Commission
USP
US Pharmacopeial Convention
WHO
World Health Organization

I. INTRODUCTION

A. **Management of Hazardous Drugs in the Workplace**
The Occupational Safety and Health Administration (OSHA) first published guidelines for the management of cytotoxic (antineoplastic) drugs in the work place in 1986 (OSHA, 1986), and the guidelines were made available in the peer-reviewed literature that same year (Yodaiken, 1986). OSHA updated the guidelines in 1995 and subsequently posted them to OSHA's website in 1999 (OSHA, 1995; OSHA, 1999). Since OSHA last updated the guidelines, governmental and professional organizations have contributed substantial quantities of scientific investigation results, "best-practices", and policy recommendations, which broadened the evidence base underlying the current practices for safe hazardous drug (HD) handling. NIOSH and the American Society of Hospital Pharmacists (ASHP) (ASHP, 1990) redefined the term "hazardous drug" beyond directly cytotoxic drugs to include additional agents that exhibit specific characteristics in human and animal toxicity [See sec. II.A., Figure 1]. The

World Health Organization (WHO) estimates that the number of cancer patients will almost double in the next two decades (WHO, 2014), and the number of healthcare workers (HCWs) needed to care for those patients will grow commensurately. The National Institute for Occupational Safety and Health (NIOSH) estimates that somewhere around 8 million HCWs are potentially exposed (NIOSH, 2009).

This informational guidance document outlines OSHA's current recommendations for addressing the health and safety hazards faced by healthcare workers who handle HDs, and the background evidence underlying those recommendations.

Although work practices and safe HD handling practices have improved in the years since OSHA first published guidance on the subject in 1986 (OSHA, 1986), workplace exposure to HDs remains a problem (Valanis, 1992; Connor, 1999; Connor, 2010). Several recent publications have documented the ongoing failure of employers to adopt, or consistently use, recommended safety practices for handling HDs (Boiano, 2014; Polovich and Martin, 2011). This failure, in conjunction with many information requests from the public on how to safely handle HDs, and the growing population of HCWs with potential HD exposure in their work prompted OSHA to review and revise its recommendations for hazardous drug handling. Most agents that are considered HDs are covered under the Hazard Communication Standard (HCS)[29 CFR 1910.1200], which has undergone a significant update since OSHA's 1995 hazardous drug guidance was issued (OSHA, 2012b). Note that the requirements of the HCS are superseded by those of OSHA's Laboratory Standard, 29 CFR 1910.1450, when an employer is engaged in the "laboratory use of hazardous chemicals" (i.e., use of relatively small quantities of hazardous chemicals on a non-production basis), but this document focuses on the HCS requirements that apply to most healthcare employers.

These recommendations apply to all healthcare settings where employees are occupationally exposed to HDs, such as hospitals, physicians' offices, and home healthcare agencies. Because many of the same drugs used to treat humans are also used to treat animals, this guidance is applicable to veterinary practices as well. Sections dealing with work areas and prevention of employee exposure to HDs at a workplace refer to workplaces where pharmaceuticals are used in concentrations appropriate for patient therapy. In settings where employees work with drugs in a more potentially hazardous form (e.g., a more concentrated form encountered in certain components of pharmaceutical manufacturing), measures that afford employees a greater degree of protection from exposure are commonly employed and should be used. Many manufacturers have internal occupational exposure limits, but those limits are not generally available to regulatory agencies; workers may inquire about those limits from the manufacturers separately from the information available in this document.

B. **Purpose of Review**

This review will:

1. Provide criteria for classifying drugs as hazardous;
2. Summarize and update the evidence supporting the management of HDs as an occupational hazard;
3. Discuss the elements of a comprehensive safety and health plan for HDs and the recommended worker education, as well as the legal requirements of applicable standards for the protection of workers exposed and potentially exposed to HDs;
4. Update the important aspects of medical surveillance; and
5. Reference and describe the NIOSH HDs list that is currently in use.

Anesthetic agents are not considered in this review, even though exposure to some of these agents is a well-recognized health hazard (NIOSH, 2007). A separate OSHA document on this topic is available at: https://www.osha.gov/dts/osta/anestheticgases/index.html (OSHA, 2000).

II. CATEGORIZATION OF DRUGS AS HAZARDOUS

A. **Characteristics**

While OSHA's 1986 guidelines focused on cancer chemotherapy drug safety (OSHA, 1986), OSHA's 1995 instruction enlarged the focus to include additional agents with toxicity profiles of concern. These additional agent categories were defined as hazardous drugs ("HDs") by the American Society of Health-System Pharmacists (ASHP), formerly American Society of Hospital Pharmacists, in a 1990 publication (ASHP, 1990) based on four specific criteria, which are listed below in Figure 1.

In 2004, a NIOSH work group authored a NIOSH Alert: "Preventing Occupational Exposure to Antineoplastic and Other HDs in Healthcare Settings," (NIOSH, 2004), a now internationally-referenced guidance document that revised ASHP's definition of HDs, including adding two more characteristics, as Figure 1 depicts.

Figure 1: Hazardous Drug Definition

American Society of Hospital Pharmacists (ASHP) (1990)	National Institute for Occupational Safety and Health (NIOSH) (2004)
Genotoxicity	Genotoxicity

Carcinogenicity	Carcinogenicity
Teratogenicity or fertility impairment	Teratogenicity/Developmental toxicity
Serious organ toxicity at low dose	Reproductive Toxicity
	Organ toxicity at low doses
	Structure/toxicity profiles of new drugs that mimic existing HDs

The NIOSH work group split ASHP's "teratogenicity or fertility impairment" characteristic into two characteristics - "teratogenicity/developmental toxicity" and "reproductive toxicity" - to differentiate between insults that develop in offspring (such as a malformation) and impairments to reproductive function or capacity of the parent. The NIOSH work group also added a sixth criterion to address "structure and toxicity profiles of new drugs that mimic existing drugs determined [to be] hazardous by the above criteria."

Finally, the NIOSH work group added helpful refinements to one of the original criteria, "organ toxicity at low doses." Here, the work group added a qualitative and quantitative discussion of the continuum of toxicity that may be exhibited by a drug. To help readers interpret the "low dose" description, the NIOSH work group cited a series of publications authored by pharmaceutical industry toxicologists that describe industry "performance" practices for defining "low dose" effects. The citation notes that "…a daily therapeutic dose of 10mg/day or a dose of 1mg/kg per day in laboratory animals that produce serious organ toxicity, or developmental or reproduction toxicity…" has been used by the pharmaceutical industry to develop internal "occupational exposure limits" (OELs) of less than 10µg /m3 with the application of safety factors (Sargent and Kirk, 1988; Naumann and Sargent, 1997; Sargent et al. 2002). NIOSH's citation further notes that "in house" OELs in this range are typically established for drugs referred to in the pharmaceutical industry as "potent compounds" (NIOSH, 2004).

Under the NIOSH approach, characterizing a drug as "hazardous" requires a "hazard identification" process, in which the descriptive criteria of the drug are reviewed and screened against the six HD characteristics. The presence of any one of the HD characteristics is enough to define a drug as hazardous. As such, this analysis does not comprise a complete four-step risk assessment.

It is important to understand the rationale and logic that is used to identify a drug as "hazardous" so that employers can independently assess the hazardousness of new drugs that have not yet been evaluated by NIOSH. Moreover, investigational new drugs (IND), which may be undergoing clinical trials in a given healthcare setting, are new chemicals for which there is often little information on potential toxicity. Structural or activity similarities to other chemicals and in vitro data can be considered when determining the potential toxic effects of INDs. Investigational new drugs should be prudently handled as HDs unless adequate information becomes available to exclude them. In vitro data may also assist in determining if INDs should be considered a HD (See U.S. Environmental Protection Agency [EPA], 1986, for guidance [EPA, 1986]).

B. **Hazard Definition Based on Pharmacology/Toxicology**

When designating a drug as hazardous, professionals trained in pharmacology and toxicology have historically considered several factors (McDiarmid, 1991) that are similar to the considerations used in NIOSH's approach, including:

1. Is the drug designated as Therapeutic Category 10:00 (Antineoplastic Agent) in the American Hospital Formulary Service Drug Information?
2. Does the manufacturer suggest the use of special isolation or other techniques in its handling, administration, or disposal?
3. Is the drug known to be a human mutagen, carcinogen, teratogen or reproductive toxicant?
4. Is the drug known to be carcinogenic or teratogenic in animals or mutagenic in multiple bacterial systems or animals?
5. Is the drug known to be acutely toxic to an organ system?

In addition to publishing the 2004 Alert on HD safe handling, NIOSH biennially updates their HD list to reflect newly Food and Drug Administration (FDA)-approved agents, and also to address any listings which may be modified in light of newly published scientific literature or other governmental agency determinations.

See the NIOSH Alert parent document (NIOSH, 2004) and the subsequent shorter HD listing updates (NIOSH, 2010; NIOSH, 2012; NIOSH, 2014b) for further details.

III. BACKGROUND: HAZARDOUS DRUGS AS OCCUPATIONAL RISKS

In the thirty years since the publication of OSHA's technical guidance on HD safe handling, the scientific literature on this topic has grown tremendously. In the years since the 2004 NIOSH Alert was issued, over 400 papers on HDs have been published in the peer-reviewed literature. These reports document how vial contamination, preparation, administration,

disposal, and other HD handling activities may expose pharmacists, nurses, physicians, and other HCWs to potentially significant workplace levels of these chemicals.

It is difficult to set safe levels of exposure to HDs on the basis of current scientific information because the degree of absorption that takes place during work, and the significance of early biological effects on each individual, are difficult to assess and may vary depending on the HD. However, several lines of evidence support the toxic potential of these drugs if handled improperly. In addition, most HCWs are exposed to multiple agents during any work shift, yielding a "mixed exposure" scenario. Therefore, it is essential to minimize exposure to all HDs. Summary tables of much of the data presented below can be found in the scientific literature (Sorsa, 1985; Rogers, 1987; Connor and McDiarmid, 2006).

A. **Mechanism of Action**
While most commonly used HDs are members of several chemically unrelated classes of agents, most of those used for anti-cancer chemotherapy exert their action by binding to cellular macromolecules, including deoxyribonucleic acid (DNA), or through disruption of DNA and protein synthesis (Skeel, 1987; Chabner and Longo, 2010). The potential fates of a cell exposed to a HD include transformation to malignant potential, mutation, cell death, or, through repair, a normal cell may remain (Harris, 1976). Importantly, HDs do not distinguish between normal and cancerous cells, thus normal cells are often affected during treatment.

B. **Animal Data**
Numerous studies document the carcinogenic, mutagenic, and teratogenic effects of HD exposure in animals. They are well summarized in the pertinent International Agency for Research on Cancer (IARC) publications (IARC, 1975; IARC, 1976; IARC, 1981; IARC, 1982; IARC, 1987; IARC, 1990; IARC, 2012). Alkylating agents present the strongest evidence of carcinogenicity (e.g., cyclophosphamide, mechlorethamine hydrochloride [nitrogen mustard]). However, other classes, such as the Topoisomerase II inhibitors (Pedersen-Bjergaard, 2002) and some anthracycline antibiotics, have been implicated as well. Extensive evidence for mutagenic and reproductive effects can be found in all antineoplastic classes. The antiviral agent ribavirin has additionally been shown to be teratogenic in all rodent species tested (Harrison, 1988; Kilham and Ferm, 1977). The ASHP recommends that drugs that are carcinogenic and/or teratogenic in animals and those that exhibit reproductive toxicity or organ toxicity at low doses in animals be considered potential human occupational hazards (ASHP, 1990).

C. **Human Data at Therapeutic Levels**
Many HDs are known carcinogens for which there is no safe level of exposure. The development of secondary malignancies in cancer patients is a well-documented side effect of chemotherapy treatment (Sieber, 1975; Weisburger, 1975; Pedersen-Bjergaard, 2002; Choi, 2014). Leukemia is the most frequent adverse outcome, but other secondary malignancies, such as bladder cancer and lymphoma, have been documented in patients treated for other primary malignancies (Socie, 1991; Bermejo, 2009; Krishnan, 2007). Chromosomal aberrations can result from chemotherapy treatment as well (Chabner and Longo, 2010). Numerous case reports have linked chemotherapeutic treatment to adverse reproductive outcomes (reviewed in NTP, 2013). Testicular and ovarian dysfunction, including permanent sterility, has occurred in male and female patients who have received anti-cancer HDs, either singly or in combination (Chapman, 1984; Ajala, 2010). In addition, most antineoplastic agents are known or suspected to be present in breast milk (Briggs, 2014).

The literature also documents the effects of these HDs on other organ systems. Extravasation of some agents can cause severe soft-tissue injury, consisting of necrosis and sloughing of exposed areas (Duvall and Baumann, 1980; Perry, 2008; Rudolph, 1979). Other HDs, such as zidovudine (formerly AZT), are known to have significant side effects (i.e., hematologic abnormalities) and some monoclonal antibodies (biologics) may cause malignancy and reproductive effects in treated patients (Anderson, 1982; Henderson and Gerberding, 1989; Hansel, 2010). Serum transaminase elevation has also been reported in treated patients (Anderson, 1982; Henderson and Gerberding, 1989).

D. **Occupational Exposure: Environmental Measures**
Initial air sampling results often showed very low concentrations of measurable HDs. However, they were questioned because of evidence suggesting that sampling methods were not sufficiently robust to capture drug that existed not only as a particulate, but also in gaseous form emanating from high efficiency particulate arrestor (HEPA) filters (Larson, 2003; Kiffmeyer, 2002) through sublimation. In addition, scientific interest in work surface contamination grew following the initial observation of work surface contamination in early studies, and observations using the biologic evidence of exposure (described below).

With the development of sensitive assays for certain marker HDs, the past several decades have seen a large effort to assess HD work environments using wipe samples of work surfaces, such as BSCs and countertops, and of the wider work environment, such as floors and door handles. These studies frequently found widespread contamination (Minoia, 1998; Connor, 1999; Hedmer, 2004; Nygren and Aspman, 2004). While the concentrations of drug measured were often not high, the frequency of positive (measurable) results, the frequency of positive (measurable) results suggested extensive contamination, and thus exposure opportunities for workers. For example, one multi-site study in the U.S. and Canada found that 75 percent of samples in pharmacies and 65 percent in

nursing treatment areas showed measurable results of HDs (Connor, 1999).

More than 80 studies of the ambient work environment have been published during the past few decades, with the majority having yielded detectable results for at least one of several drugs for which sampling was performed. See NIOSH website: https://www.cdc.gov/niosh/topics/antineoplastic/sampling.html.

Several studies also linked environmental sampling results to bio-monitoring results of drug levels in workers' urine, documenting an uptake of drug levels in contaminated work environments (Minoia, 1998; Wick, 2003; Mason, 2005; Connor, 2010; Hon, 2015). These studies raise the question of whether the skin contact pathway may be not only a common but also biologically important exposure route of absorption for under-protected workers for at least some agents (Kromhout, 2000).

Even prior to drug compounding, exposure opportunity exists for oncology workers, as studies have documented that drug contamination can occur from handling the outside of new, unopened drug vials (Connor, 2005; Nygren, 2002a; Sessink, 1992a; Power, 2014).

The special case of administration of drugs via aerosol nebulizer treatment can lead to measurable air concentrations in the breathing zone of workers who provide the treatment (Harrison, 1988) and, depending on the medication, air concentrations may result in symptoms in exposed workers (Balmes, 1995). Aerosolized medication safety recommendations are available from the Society of Infectious Disease Pharmacists (Le, 2010).

E. **Occupational Exposure: Biological Evidence of Absorption**

1. **Urinary Mutagenicity**. Falck et al. were the first to note evidence of mutagenicity in the urine of nurses who handled cytotoxic drugs (Falck, 1979). This effect increased over the course of the work week, implying a dose-response. With improved handling practices, a decrease in mutagenic activity was seen (Falck, 1981). Researchers have also studied pharmacy personnel who reconstitute antineoplastic drugs. These employees showed increasingly mutagenic urine over the period of exposure; when they stopped handling the drugs, activity fell within two days to the level of unexposed controls (Anderson, 1982; Nguyen, 1982). They also found that mutagenicity in workers using horizontal laminar flow hoods (which blow into the face of the preparer) decreased to control levels with the use of vertical flow containment hoods, which protect the breathing zone of the preparer and now represent standard equipment (Nguyen, 1982).
2. **Urinary Metabolites/Biologic Monitoring.** While the earlier literature focused on various methods for indirectly documenting worker exposure, such as the urine mutagenicity studies described above, more recent studies have used actual bio-monitoring of exposed workers to measure specific agents or their metabolites in body fluids. Such direct exposure assessment approaches eliminate some of the challenges of interpreting the results of indirect exposure measurements. However, bio-monitoring studies present their own challenges. These include the selection of the agent(s) to be measured when oncology clinical workers handle multiple different drugs each day and choosing timing of sample collection in light of the drugs' half-life and elimination kinetics in the body. Nevertheless, positive results are undeniable evidence of drug uptake by workers. However, the converse is not necessarily true: the absence of positive results cannot be used to document lack of actual absorption, given drug detection thresholds in the urine. Thus, bio-monitoring is generally not included in post-spill assessment.

In the past thirty years, bio-monitoring studies have become quite commonplace, with more than 100 reports in the literature, about two-thirds of which documented drug uptake by measuring these drugs or their metabolites in the urine of at least some exposed HCWs. Bystander uptake of drug in non-drug handling health workers, including support staff, has also been reported (Sessink, 1992b; Hon, 2015).

F. **Occupational Exposure: Human Effects**

1. **Cytogenetic Effects**. Since the 1995 OSHA guidance was issued, scores of studies have been published assessing cytogenetic effects on workers, including chromosomal aberrations, with the majority documenting an excess of cytogenicity markers of (Baker and Connor, 1996; Sessink and Bos, 1999; Connor and McDiarmid, 2006; Suspiro, 2011). Differing results between the studies are to be expected given the challenge of quantitating exposure and the variability in personal protective equipment (PPE) use and work practices. These earlier studies, however, documented the plausibility of a biologically relevant effect occurring as a result of an occupational exposure to drugs. A variety of markers for genetic damage have been examined since 1995 (see https://www.cdc.gov/niosh/topics/antineoplastic/), including sister chromatid exchange (SCEs), a measure of point mutations.
   More recent evidence suggests that structural chromosomal damage (e.g., gaps, breaks, translocations and copy number differences (aneuploidy)) may be prognostic of an increased cancer risk at least when considered on a population basis (i.e., exposed vs. non-exposed, groups), thus making it a more potentially meaningful marker of effect (Hagmar, 1998). Micronuclei frequency, a count of chromosome remnants that mark flawed chromosomal segregation during cell division (Fenech, 2008), are also considered to be epidemiologically prognostic of a future cancer risk at the group level (Bonassi, 2007; Bonassi, 2008; Bonassi, 2011).

Importantly, specific chromosomal markers of HD damage, typically observed in therapeutically treated cancer patients, have also been reported in oncology pharmacy and nursing personnel as a function of drug handling frequency (McDiarmid, 2010; McDiarmid, 2014).

2. **Reproductive Effects**. In the 1980s, robust epidemiological studies from the Nordic countries documented both congenital malformations (Hemminiki, 1985) and spontaneous abortions (Selevan, 1985) in statistical excess among oncology nurses. A study of U.S. nurses during that time frame also documented a higher proportion of adverse pregnancy outcomes in oncology nurses who mixed and administered HD (Rogers, 1987). Subsequent studies of reproductive effects in workers are reviewed in Connor and McDiarmid (2006). Because many of the studied agents are well known animal and human reproductive and developmental toxicants, these early epidemiologic observations were biologically plausible.
   The concern regarding reproductive risks associated with occupational exposure to HDs derives from both the mechanism of action of many of the drugs (interference with DNA replication or protein synthesis) and from the well-documented reproductive and developmental toxicity observed in therapeutically treated patients (Perry, 2008). While the focus of concern has been on pregnancy, several HDs have significant male mediated reproductive effects as well (Chapman, 1984; Roche, 1996).

   With the advent of safe handling controls in the mid-1980s, the hope was that these adverse reproductive outcomes, which, unlike a cancer risk, could theoretically result from a brief, acute exposure, would be eliminated. To be sure, outcome studies conducted after safe handling guidelines were issued have shown some decrease in exposure (Connor & McDiarmid, 2006), but several recent studies still have shown excess reproductive loss even with the use of BSCs (Martin, 2003; Lawson et al., 2012, reviewed in Connor et al., 2014).

   In the most recent study on this topic, using the Harvard Nurses' Study cohort, NIOSH investigators found a statistically significant, two-fold increase in the risk of spontaneous abortion in nurses who reported first trimester HD exposure from 1990 through 2001 (Lawson, 2012). A review of the reproductive health risks associated with occupational exposure to HDs can be found in Connor (2014).

   Several of these studies, including the Harvard Nurses' Study, report on a period after the initial safe handling guidance was promulgated in the mid-1980s and imply that some safe handling practices were being implemented. Notably of the 184 drugs that NIOSH identifies as HDs in its 2014 list (NIOSH, 2014), about 80 percent are classified by the FDA as Pregnancy Category D or X, which indicates a potential for fetal harm when used during pregnancy (FDA, 1997). This categorization has been changed to the Pregnancy and Lactation Labeling Rule (PLLR) that became effective June 2015. However, a drug's characteristics that allowed it to be designated as D or X remain unchanged and thus these older designations may be helpful to organizations assembling their own HD list (see https://womensmentalhealth.org/posts/fdas-new-labeling-rule-clinical-implications/).

   In addition, the secretion of HDs into human milk of treated patients suggests an additional concern for exposed and pregnant workers who plan to breast feed (MotherRisk, 2014).

3. **Cancer**. Concern about the potential for cancer to develop in exposed HCWs, similar to the risk of therapy-related malignancies (such as leukemia observed in treated patients), drove early efforts to limit occupational exposure. As described above, many of these agents are known animal carcinogens and have been extensively reviewed by the IARC, which has classified 18 of these agents as Group 1 human carcinogens; 12 as Group 2A, probable human carcinogens; and 11 as Group 2B, possible human carcinogens, based on their toxicity and epidemiology in treated patients (IARC, 1975; IARC, 1976; IARC, 1981; IARC, 1982; IARC, 1987; IARC, 1990; IARC, 2012).
   Epidemiologic data assessing occupational cancer in oncology workers, however, has been difficult to obtain, primarily because the U.S. lacks a national cancer registry. A fragmented set of state registries collects cancer data, but the occupation of patients is not typically included. The best studies performed to date were in Denmark, where linkage of health and employment records allowed this question to be studied. An increased risk of leukemia was found for physicians with at least six months of exposure, but this excess did not reach statistical significance and participant numbers were small (Skov, 1990). A subsequent publication by these same investigators found an increased risk among oncology nurses in the Danish registry, and these excesses did reach significance (Skov, 1992).

   While not specifically targeting oncology workers, other types of available epidemiologic evidence bolsters the Danish cancer registry reports described above. For example, a Danish study of female pharmacy technicians found a statistically significant increased risk of non-Hodgkin's lymphomas (Hansen, 1994), a cancer seen in excess in cancer patients following certain therapies (Krishnan and Morgan, 2007). A study of occupational risk factors for breast cancer among nurses found a non-statistically significant raised odds ratio of 1.65 (95 percent CI 0.53-5.17) among nurses working with cytotoxic HD drugs (Gunnarsdottir,

1997). A large U.S. cancer mortality study of HCWs in 24 states found a 30 percent excess of myeloid leukemia among nurses and a two-fold excess in pharmacists (Petralia, 1999). Other cancers were also observed to be in excess in these workers. A population-based study of worker occupation and leukemia in two Midwestern U.S. states also found an increased risk of leukemia in nursing and health care workers (HCW) (Blair, 2001).

A series of case reports of possible occupational cancer risks have also been published, including bladder cancer in a female pharmacist (Levin, 1993) and naso-pharyngeal cancer in an oncology nurse (Gabriele, 1993). In both cases, no safe handling precautions were used.

4. **Other Effects**. While studies more commonly consider the chronic exposure effects of HDs, such as reproductive loss or cancer development, it is important to recall that acute exposure effects, such as nausea and vomiting, skin rashes, and hair loss, were reported in HCWs who were exposed years before chronic exposure considerations emerged, and may still occur (NIOSH, 2004). Symptoms such as lightheadedness, dizziness, nausea, headache, and allergic reactions have also been described in employees who prepared and administered antineoplastic drugs in unventilated areas (Doll, 1989; Baykal, 2009; Constantinidis, 2011). In occupational settings, these agents are known to be toxic to the skin and mucous membranes, including the cornea (McLendon, 1978; Reich, 1975).
Generally, the same effects of HDs on the target organs of treated patients may also be observed in under-protected employees. For example, hepatocellular damage has been reported in nurses working in an oncology ward, and the damage appeared to be related to the intensity and duration of their work exposure to HDs (Sotaniemi, 1983).

   The use of nebulizers to administer HDs presents a specific challenge to the respiratory system and exposes HCWs to the "fugitive" aerosol of the drug. For example, pentamidine was associated with reversible respiratory dysfunction in one worker who administered aerosol treatment and subsequently experienced a decrease in diffusing capacity of the lung that improved after exposure ceased (Gude, 1989). The onset of bronchospasm in a pentamidine-exposed worker has also been reported (Doll, 1989). Employees involved in the aerosol administration of ribavirin have noted symptoms of respiratory tract irritation (Lee, 1988). With the potential increase in aerosol administration of HDs, exposure controls should be applied to minimize widespread environmental contamination and protect HCWs.

   A number of medications, including some HDs, psyllium, and various antibiotics, are known respiratory and dermal sensitizers. Exposure in susceptible individuals can lead to asthma or allergic contact dermatitis (Kusnetz and Condon, 2003).

IV. WORK AREAS

Risks to personnel working with HDs are a function of the drugs' inherent toxicity and the extent of exposure. Early speculation noted inhalation was the primary route of exposure. However, with the advent of more sensitive drug assays, surface wipe sampling of a number of "marker" HDs has provided a method of examining work areas for HD residue (Sessink, 1992a & b; Sessink, 1997; Kopp, 2013; Fransman, 2005; Fransman, 2007). Numerous studies have shown that surfaces in areas where HDs are stored, mixed, administered, and wasted, as well as where patients are cared for, are contaminated with measurable levels of HD residue (Connor, 1999; Connor 2002; Acampora, 2005; Connor, 2010; Hon, 2013). Studies have detected the presence of HDs in the urine of HCWs who have handled these drugs, and in others who did not work directly with the drugs but who were only in the work area (Sessink, 1997; Wick, 2003; Fransman, 2004; Suspiro, 2011; Hon, 2015). Current belief is that dermal absorption of HD residue from contaminated surfaces is the primary route of exposure for at least some agents, such as cyclophosphamide (Kromhout, 2000; Fransman, 2004; Fransman, 2005). Inhalation, especially of drugs that vaporize, is an additional exposure route, and at least one study of automatic dispensing machines of oral tablets indicates that these devices may generate dust of active pharmaceutical ingredients (APIs) during the counting and dispensing process (Fent, 2014). Exposure is also likely to result from ingestion of contaminated food or drink or through mouth contact with contaminated hands or cigarettes. Accidental injection from the use of needles or contact with broken glass fragments is also of concern.

Opportunity for exposure to HDs may occur at many points in the process of handling these drugs. NIOSH has included pharmacy and nursing personnel, physicians, operating room personnel, environmental services workers, workers in research laboratories, veterinary care workers, and shipping and receiving personnel in the workers who handle HDs (NIOSH, 2004). The US Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide. USP's drug standards are enforceable in the United States by the Food and Drug Administration. USP chapter 797 ("Pharmaceutical Compounding—Sterile Preparations"), notes that when compounding sterile preparations of HDs, they should be handled with caution at all times during receiving distribution, stocking, inventorying, preparation, and disposal (USP 797, 2012). USP's general chapter 800 ("Hazardous Drugs—Handling in Healthcare Settings" published 2/1/2016 in USP 39-NF 34, First Supplement) cautions that both clinical and nonclinical personnel may be exposed to HDs when they create or use aerosols, generate dust, clean up spills, or touch contaminated surfaces during the receipt, preparation, administration,

cleaning, or disposal of HDs (USP 800, 2016). NIOSH, ASHP, and others have reported on studies that found drug residue on the outside of HD vials when they arrive at the workplace from the manufacturer or distributor (NIOSH, 2004; ASHP, 2006; Power, 2014). Packing cartons have also been identified as sources of measurable HD contamination (Kiffmeyer, 2000).

A. **Pharmacy or Other Compounding or Dispensing Areas**

1. HDs may be dispensed as sterile intravenous (IV), intramuscular (IM), intrathecal (IT), subcutaneous (SQ), or other doses, which must be compounded prior to administration, oral doses of solids or liquids which must be prepared or packaged, or occasionally as a topical preparation that may require special mixing. Sterile doses of HDs must be compounded to preserve the quality of the dose for patient safety, as well as to protect the worker and the environment. USP Chapter <797> describes appropriate facilities, worker training, and work practices to ensure safe compounding of sterile preparations, including HD doses, and is focused primarily on *patient safety* (USP 797, 2012). The tenets of USP <797> are supported by many state boards of pharmacy, and are included in Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (NABP, 2014). In large oncology centers and other facilities that follow USP <797>, sterile HDs are usually compounded in the pharmacy by trained pharmacists or technicians. However, in small hospitals, outpatient treatment areas, and physicians' offices they may be compounded by physicians or nurses without appropriate engineering controls and protective apparel (Christensen, 1990; Crudi, 1980; Martin and Larson 2003; Hon, 2011; Kopp, 2013; Friese, 2014). USP Chapter <800> describes appropriate facilities, worker training, and work practices for protecting, patients, workers, and the environment while handling both sterile and non-sterile HDs in all healthcare settings (USP 800, 2016).
2. Many HDs must be reconstituted, transferred from one container to another, or otherwise manipulated before administration to patients. Even if care is taken, opportunity for absorption through inhalation or direct eye or skin contact can occur (Kromhout, 2000; Fransman, 2004; Fransman, 2005; Fransman, 2007; Friese, 2012; Suspiro, 2011).
3. Examples of manipulations that can cause escape of HD residue by splattering, spraying, and aerosolization include:
   - piercing drug vial septa with needles or dispensing pins;
   - withdrawal of needles or pins from drug vials;
   - drug transfer using syringes and needles or dispensing pins;
   - breaking open of ampules;
   - drug transfer from ampules using filtered needles or filter straws;
   - expulsion of air from a drug-filled syringe;
   - piercing injection ports of IV bags or bottles with needles to inject HDs;
   - spiking delivery ports of HD-containing IV bags or bottles with the sharp spike of IV administration sets; and
   - removing air from the IV administration sets by running HD containing fluid through the set (i.e., priming the line).

   Evaluation of these preparation techniques, using fluorescent dye solutions, has shown contamination of bag ports, gloves, and the sleeves and chest of gowns (Stellman, 1987; Spivey and Connor, 2003). HD contamination has also been identified and quantified on gloves and other PPE through the use of sensitive assays of marker drugs of cyclophosphamide, fluorouracil, and methotrexate. (Sessink, 1992a; Sessink, 1992b; Sessink, 1997; Minoia, 1998; Fransman, 2004; Fransman, 2005; Mason, 2005).

4. Horizontal laminar airflow workstations (HLFW) provide an International Organization for Standardization (ISO) Class 5 environment for the compounding of sterile preparations (USP 797, 2012). However, these units provide no containment of HD residues, which allows these residues to contaminate workers and the work environment (NIOSH, 2004). HLFW and horizontal workstations, i.e., horizontal hoods, have been contraindicated in the compounding of HDs since 1995 (OSHA, 1995). Similar restrictions are included in ASHP's 1990 publication, USP <797> (since its revision in 2008), and USP <800> (ASHP, 1990; USP 797, 2012; USP 800, 2016). Smoking, drinking, applying cosmetics, and eating where HDs are prepared, stored, or used, also increase the chance of exposure and should be prohibited in these areas. To ensure that compounded sterile preparations of HDs are prepared safely, USP <797> has identified facility and equipment specifications (USP 797, 2012). These standards are harmonized with the NIOSH 2004 Alert and with ASHP 2006 guidance (NIOSH, 2004; ASHP, 2006). USP <800> identifies appropriate equipment, personal protective equipment (PPE) and work practices for handling both sterile and non-sterile preparations of HDs (USP 800, 2016).

B. **Administration of Drugs to Patients**

Administration of HDs to patients is generally performed by nurses or physicians. The potential for occupational exposure exists for every route of drug administration. Common methods include injection (e.g., intravenous, intra-arterial, intramuscular, subcutaneous), IV infusion, oral or enteral tube, intracavitary (e.g., intravesicular, intraperitoneal, or intrapleural), topical, intraspinal, and inhalation (Polovich, 2011).

1. Exposure may occur by absorption when liquid forms of HDs leak or spill during connecting or disconnecting tubing or syringes, spiking IV containers, priming air from infusion sets or syringes, or from accidental disconnection in any drug delivery system. Work area surfaces that are contaminated with drug residues are a common source of dermal exposure (Connor, 1999; Connor, 2010; Hon, 2014a & b; Kromhout, 2000; Sessink, 2011; Siderov, 2010).
2. Exposure may occur by inhalation when HD dust or droplets are generated during drug administration. HD dust may result from crushing solid oral forms. Aerosols can be produced during inserting of or removing tubing from IV containers, expelling air from syringes, or clipping or crushing needles or syringes. HD aerosols may escape and expose healthcare workers during administration of drugs by inhalation.
3. Exposure may occur by ingestion when foods or beverages are consumed in drug administration areas, or by hand-to-mouth transfer of drug residue from HD contaminated surfaces (ASHP, 2006).
4. Exposure may occur by accidental injection from needle sticks or other sharps contaminated by HDs.
5. Excreta from patients who have received HDs is another source of exposure for health care workers. Patients' urine, stool, emesis and sweat contain varying concentrations of drugs or their hazardous metabolites. For example, patients receiving cyclophosphamide excrete up to 36 percent of the drug dose as well as mutagenic metabolites in their urine (Hedmer, 2008a). Temsirolimus is eliminated in feces, and is present in stool for up to 14 days (Wyeth, 2014). Methotrexate has been found in emesis and sweat of patients, leading to worker exposure (Mader, 1996).

C. **Disposal of Drugs and Contaminated Materials**

HDs and contaminated materials should be disposed of in accordance with federal, state, and local laws. Any discarded HDs greater than residue amounts should be evaluated as to whether they are a hazardous waste under federal U.S. EPA regulations, and if so, be disposed of in accordance with 40 CFR part 261 (EPA, 1991a and b). In addition, any discarded antineoplastic HDs should be managed as hazardous waste as a best practice, and as required by some states. Since the EPA lists of hazardous wastes have not been updated since the 1980s, EPA's Office of Inspector General has strongly recommended that EPA conduct a review of drugs that have entered the market since that time, particularly chemotherapy agents, to determine which drugs should be managed as hazardous waste, in order to protect human health and the environment EPA OIG, 2012). An independent commentary article on the EPA report (Eckstein, 2012), provides context to the issue of the future regulation of pharmaceutical waste.

Overtly contaminated materials, such as may occur during a spill or the cleanup of a spill, should also be managed as a hazardous waste (EPA, 2008). Trace contaminated materials used in the preparation and administration of HDs, such as gloves, gowns, syringes and vials, also present a hazard to clinical support and housekeeping staff. These items should be disposed of in properly labeled, covered, and sealed disposal containers and handled by trained and protected personnel. Since sharps and potentially infectious materials may also be included in the trace contaminated materials, such containers should be managed as biohazardous waste under the Bloodborne Pathogens Standard [29 CFR 1910.1030(d)(4)(iii)] (OSHA, 2012a). Treatment should occur at a regulated medical waste incinerator rather than an autoclave or microwave to prevent aerosolization. Spills involving HDs can also represent a hazard, and employers should ensure that all employees are familiar with appropriate spill procedures, as outlined in the Chemotherapy Safety Standards issued by the American Society of Clinical Oncology/Oncology Nursing Society (ONS, 2013).

D. **Surveys of Current Work Practices**

Recent studies of HD handling practices have found deviations from the recommendations for personnel training, use of work practices, and personal protective equipment. Formal training for HD handlers is not universally provided. For example, among nurses and pharmacists responsible for HD preparation, 9-13 percent reported never having received HD training, and for those who had received training, most reported that it was more than a year earlier (Boiano, 2014). Individuals responsible for HD preparation reported failure to wear protective gowns 20-36 percent of the time and failure to wear chemotherapy gloves 8-10 percent of the time (Polovich, 2012; Boiano, 2015). For HD administration, use of protective gowns ranged from 50-65 percent, use of chemotherapy gloves ranged from 78-85 percent, and double-gloving was particularly low, at only 11-20 percent (Polovich, 2011, 2012; Boiano, 2014). Such failure to use appropriate precautions results in occupational exposure, with 4-17 percent of employees reporting known skin or mucous membrane contact with HDs in the previous year (Friese, 2012; Boiano, 2014; Boiano, 2015). These findings demonstrate that employers have failed to sufficiently protect all personnel potentially exposed to HDs.

E. **Special Locations**

Healthcare workers may be occupationally exposed to HDs in many different types of settings. Drug preparation can take place in pharmacies (hospital, retail, mail-order, or compounding) or clinic settings. Drug administration occurs in hospital inpatient and outpatient units, operating rooms, interventional radiology departments, respiratory therapy departments, treatment centers, physician offices, veterinary clinics or hospitals, extended care facilities, and home care agencies.

Exposure potential is related to the manipulations required to prepare and administer HDs, the type of equipment available in the specific setting, the work practices, and personal protective equipment used by the personnel.

Specialized settings (e.g., operating room or interventional radiology departments) may infrequently be involved in HD handling. Procedures should be evaluated step-by-step for the likelihood of drugs being released into the environment so that exposure can be minimized.

Settings where HDs are administered by inhalation or nebulizer should be equipped with appropriate engineering controls to prevent workers' inhalation of fugitive aerosols (CDC, 2003). Additionally, drug aerosols may be deposited on skin and surfaces, resulting in dermal exposure.

V. PREVENTION OF EMPLOYEE EXPOSURE

A. **Hazardous Drug Safety and Health Plan**

Where HDs are used in the workplace, sound practice dictates that employers develop a written Hazardous Drug Safety and Health Plan. As many HDs are also hazards that are identified in the revised HCS, the requirements of the HCS must also be met [29 CFR 1910.1200] (OSHA, 2012b). Such a plan assists in:

- Protecting employees from health hazards associated with HDs, and
- Keeping exposures as low as reasonably achievable (ALARA).

The HD Safety Plan should be readily available and accessible to all employees, including temporary employees, contractors, and trainees. The comprehensive plan should address all aspects of safe handling of HDs throughout the facility, be developed using a collaborative effort including all affected departments, and specify measures that the employer is taking to ensure employee protection. The Joint Commission (TJC) released a monograph in 2012 to stimulate greater awareness of the potential synergies between patient and worker health and safety activities by comparing TJC standards and OSHA mandates and guidance (TJC, 2012). This monograph will help employers to develop a HD Safety Plan that includes both patient and worker safety under a generalized "culture of safety." OSHA has also prepared a comparison of the OSHA Safety and Health Management Systems and Joint Commission Standards to further assist employers to develop comprehensive safety programs (OSHA, 2013). The NIOSH 2004 Alert on HDs and the ASHP 2006 HD Guidelines provide recommendations for similar safety programs that also include these elements (NIOSH, 2004; ASHP, 2006):

Standard operating procedures (SOPs) or policy and procedures (P&Ps) that provide a comprehensive safety program to deal with all aspects of the safe handling of HDs should be in place. These SOPs and P&Ps should address receiving, storage, transport, preparation, administration, spill cleanup, handling HD waste, handling patient waste, and disposal of HDs in order to protect the safety and health of all health care workers who are responsible for handling HDs.

- HDs that have been identified as requiring safe handling precautions should be clearly labeled at all times during their transport and use (USP 800, 2016);
- A list of HDs in use in the facility is required by the HCS, and is also recommended by the TJC, as Elements of Performance for Medication Management (MM).01.01.03 (OSHA, 2012b; TJC, 2015);
- Safety Data Sheets (SDS) must be available for all HDs on the facility list;
- Areas and procedures for HD storage and preparation should be designated (USP 800, 2016);
- Specific control measures should be used to reduce employee exposure to HDs, including appropriate ventilation controls, personal protective equipment, work practices, and ancillary devices, such as closed system drug-transfer devices (USP 800, 2016);
- Ventilation controls should be used to protect personnel from HD exposure, such as biological safety cabinets and containment isolators (USP 800, 2016);
- Appropriate personal protective equipment must be available and used based on the type of HD handling activities [29 CFR 1910.132] (USP 800, 2016);
- Ventilation systems and other protective equipment should function properly, and specific measures to ensure proper and adequate performance of such equipment should be in place (USP 797, 2012);
- Safety programs must identify and include all workers who may be at risk of exposure;
- Information and training for personnel responsible for HD handling must be provided;
- Medical surveillance and methods of protection of personnel responsible for HD handling should be provided; and
- The Safety Plan should be reviewed annually, updated as necessary, and evaluated for effectiveness.

The NIOSH HD Alert of 2004, ASHP HD Guidelines of 2006, USP <797> of 2012, and USP <800> of 2016 all address the need to handle HDs using containment facilities, special equipment, and appropriate ventilation (NIOSH, 2004; ASHP, 2006; USP 797, 2012; USP 800, 2016).

HD handling areas should be established for sterile and non-sterile compounding:

- Under USP <800>, storage areas for antineoplastic HDs requiring manipulation other than counting or

repackaging of final dosage forms and any HD API should be separated from non-HDs in a manner that prevents contamination and personnel exposure. These should be stored in an externally vented, negative-pressure room with at least 12 air changes per hour (ACPH) (USP 800, 2016).

- Appropriate ventilated compounding equipment for sterile and non-sterile HD compounding should be available (NIOSH, 2004; USP 797, 2012; USP 800, 2016).
- USP <800> advises that sterile and non-sterile HDs should be compounded within a Containment Primary Engineering Control (C-PEC) located in a Containment Secondary Engineering Control (C-SEC) (USP 800, 2016).
  - All C-PECs used for manipulation of sterile HDs should be externally vented (USP 800, 2016).
  - C-PECs used for manipulation of non-sterile HDs should be either externally vented (preferred) or have redundant-HEPA filters in series (USP 800, 2016).
  - The C-SEC used for sterile and non-sterile HD compounding should be externally vented through HEPA filtration; be physically separated (i.e., a different room from other preparation areas); have an appropriate air exchange (e.g. ACPH); and have a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas (USP 800, 2016).
- All ventilated equipment should be certified operational using the appropriate standards.
  - All ventilation and exhaust systems should be certified operational at least every six months (USP 797, 2012; NIOSH, 2004).
  - NIOSH recommends proper installation and maintenance of all types of ventilated cabinets (NIOSH, 2004).
- Decontamination procedures for BSC, CACI, other ventilated enclosures and other surfaces, including HD vials, should be performed regularly (ASHP, 2006; USP 800, 2016).
- Procedures for safe removal of all contaminated waste should be used by all workers (ONS, 2013; USP 800, 2016).
- USP <800>, TJC, NIOSH, and ASHP include periodic evaluations of the HD list, facilities, and worker training. (NIOSH, 2004; ASHP, 2006; TJC, 2015; USP 800, 2016).

B. **Drug Compounding Precautions**

1. **Work Area**

   NIOSH, USP, and ASHP recommend that HD compounding be performed in a restricted and preferably centralized area.

   a. Compounding of sterile doses of HDs should be done in a facility that meets USP <797> and USP <800> (USP 797, 2012; USP 800, 2016).
   b. Compounding of non-sterile HDs should meet the recommendations of the NIOSH Alert and USP <795> and USP <800> (NIOSH, 2004; USP 795; 2013; USP 800, 2016).
   c. Per USP <800>, all C-PECs used for manipulation of sterile HDs should be externally vented (USP 800, 2016).
      - Sterile HD compounding should be performed in a C-PEC that provides an ISO Class 5 or better air quality, such as a Class II or III BSC or Compounding Aseptic Containment Isolators (CACI) (USP 800, 2016).
      - Class II BSC types A2, B1, or B2 are acceptable. For most known HDs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC. Class II type B2 BSCs are typically reserved for use with volatile components (USP 800, 2016).
   d. The C-PEC for sterile compounding should be located in a C-SEC, which may either be an ISO Class 7 buffer room and ante-room (preferred) or an unclassified containment segregated compounding area (C-SCA). If the C-PEC is placed in a C-SCA, the beyond use date (BUD) of all compounded sterile preparations (CSPs) so prepared should be limited as described in USP <797> for CSPs prepared in a SCA (USP 800, 2016).
      - If the C-SEC for sterile compounding is an ISO Class 7 buffer room, the C-SEC should be externally vented; provide 30 ACPH; and have a negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas (USP 800, 2016).
      - The ISO Class 7 ante-room or non-HD buffer room should maintain a positive pressure of at least 0.02 inches of water column to all adjacent unclassified areas (USP 800, 2016).
      - If the C-SEC for sterile compounding is a C-SCA, the C-SEC should be externally vented; provide 12 ACPH; and be at negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas (USP 800, 2016).
   e. Non-sterile HD compounding should be performed in a C-PEC that provides for personnel and environmental protection, such as a Class I BSC or a Containment Ventilated Enclosure (CVE) (USP 800, 2016).
   f. The C-PEC for non-sterile HD compounding should be placed in a C-SEC that is externally vented, have at least 12 ACPH, and be at negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas (USP 800, 2016).

g. Signs identifying that HDs are in use and restricting the access of unauthorized personnel should be prominently displayed. Eating, drinking, applying makeup, and the presence of foodstuffs should be avoided in HD work areas (ASHP, 2006).
h. NIOSH and ASHP recommend that workers be trained to clean up spills (NIOSH, 2004; ASHP, 2006). Spill kits and procedures for spill management should be kept in the HD work area (NIOSH, 2004; ASHP, 2006).
i. ASHP also recommends having procedures and kits for immediate treatment of workers with direct skin or eye contact with HDs (ASHP, 2006). USP <800> states that a sink should be available for hand washing. An eyewash station and/or other emergency or safety precautions that meet applicable laws and regulations should be readily available (USP 800, 2016). USP <800> notes that water sources and drains should not interfere with ISO classifications where required and should be located at least one meter away from the C-PEC (USP 800, 2016).

2. **Containment Primary Engineering Controls (C-PEC) and Ventilated Cabinets**
USP <800> states that sterile and non-sterile HDs should be compounded within a Containment Primary Engineering Control (C-PEC) located in a Containment Secondary Engineering Control (C-SEC) (USP 800, 2016).

USP <800> has identified C-PECs as the appropriate ISO Class 5 cabinets for sterile compounding (USP 800, 2016). C-PECs for compounding sterile HDs include Class II and Class III BSCs and ISO Class 5 CACIs that meet or exceed the standards set in USP <797> (USP 797, 2012).

a. If a C-PEC (BSC or CACI) is unavailable, for example, in a private practice office, accepted practice is the sharing of a cabinet (e.g., several medical offices share a cabinet) or sending the patient to a center where HDs can be prepared in a C-PEC. Alternatively, preparation can be performed in a facility with a C-PEC and the drugs transported to the area for administration.
b. Use of a dedicated C-PEC, where only HDs are prepared, is prudent practice. Per USP <800>, a BSC or CACI used for the preparation of HDs should not be used for the preparation of a non-HD. An allowance is made if the non-HD preparation is placed into a protective outer wrapper during removal from the C-PEC and is labeled to require PPE handling precautions (USP 800, 2016).
c. Examples of C-PEC for non-sterile compounding include a Class I BSC, a containment ventilated enclosure (CVE), and an isolator intended for containment applications (USP 800, 2016).

3. **Biological Safety Cabinets**
Class II Biological Safety Cabinets (BSC) that meet the current NSF/ANSI standard 49 (NSF 49, 2012) should reduce exposure to HDs during preparation. A study done in 1982 showed that the Class II BSC reduced the exposure of pharmacy compounding staff to HDs as measured by urine mutagenicity detected by the Ames test (Anderson, 1982). More recent studies, using analytical methods specific to HDs and significantly more sensitive than the Ames test, have shown environmental and worker contamination occurs in HD workplaces despite the use of a Class II BSC (Connor, 1999; ASHP, 2006; Connor, 2010; Wick, 2003). Contamination with marker HDs has been found on the work surface, front lip and grill of the BSC, on areas around the BSC, and on the floor in front of the Class II BSC. Marker HDs have also been measured in the urine of workers where a Class II BSC is the PEC (Wick, 2003). The exact cause of HD contamination is undetermined and there are a number of issues that could contribute to the apparent failure of the BSC to contain HD residue.

- Drug residue may be present on the outside of vials received from manufacturers and distributors (Kiffmeyer, 2000; Nygren, 2002a; Mason, 2003; Favier, 2003; Connor, 2005; Gilbar, 2005; Touzin, 2008; Schierl, 2010; Hama, 2011; Power, 2014). If vials are not cleaned before they are stored in HD work areas or placed in the buffer areas or in the Class II BSC, the residue on the outside of drug vials may transfer to other surfaces and/or onto gloves, which may further transfer the residue.
- The Class II BSC is dependent on operator technique to prevent residue from escaping through the open front. Some HDs have the potential to pass through HEPA filters and may escape from BSCs that are not exhausted to the outside. (Connor, 2000; Larson, 2003; Kiffmeyer, 2002).

When used in a total safety program that includes good work practices, excellent technique, and consistent cleaning and decontamination, Class II BSCs are a valued tool for reducing occupational exposure to HDs during compounding. Per ASHP's 2006 guidelines, workers should understand that the Class II BSC does not prevent the generation of contamination within the cabinet and that the effectiveness of such cabinets in containing HD contamination depends on operators' use of proper technique (ASHP, 2006).

4. **Types of BSCs**
Four main types of Class II BSCs are available. They all have downward airflow and HEPA filters. They are differentiated by the amount of air recirculated within the cabinet, whether this air is vented to the room or the outside, and whether contaminated ducts are under positive or negative pressure. These four types are described below:

a. Type A1 cabinets recirculate approximately 70 percent of cabinet air through HEPA filters back into the cabinet; the rest is discharged through a HEPA filter into the preparation room. Contaminated ducts are under positive pressure.
b. Type A2 cabinets have a higher inflow velocity, have recirculated air within the cabinet similar to the A1 and may exhaust HEPA filtered air back into the work area or to the environment through properly functioning exhaust canopies, and have all contaminated ducts and plenums under negative-pressure or surrounded by negative-pressure ducts and plenums.
c. Type B1 cabinets have higher velocity air inflow, recirculate about 30 percent of the cabinet air and exhaust the rest through a dedicated duct to the atmosphere after passing it through a HEPA filter, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums.
d. Type B2 (total exhaust): These Class II BSCs maintain a minimum inflow velocity of 100 feet/minute, have HEPA filtered down-flow air drawn from the work area or the outside, exhaust all air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the work area, and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums.

Class III BSCs are totally enclosed with gas tight construction. The entire cabinet is under negative pressure, and operations are performed through attached gloves. All air is HEPA filtered. All exhaust is to the outside. The exhaust air is treated by double HEPA filtration or single HEPA filtration/incineration. Passage of materials in and out of the cabinet is generally performed through pass-through chambers that can be decontaminated between uses.

Class II BSC types A2, B1, or B2 are acceptable for compounding HDs. For most known HDs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC. Class II type B2 BSCs are typically reserved for use with volatile components (USP 800, 2016).

The exhaust fan or blower of the Class II or Class III BSC should be on at all times, except when the cabinet is being mechanically repaired or moved. If the blower is turned off, the BSC should be decontaminated before reuse (ASHP, 2006). Each BSC should be equipped with a continuous monitoring device to allow confirmation of adequate air flow and cabinet performance. Open front Class II BSCs should preferably be placed in ISO 7 buffer areas with minimal air turbulence (USP 797, 2012). If the Class II BSC is placed in a C-SCA, the beyond use date (BUD) of all compounded sterile preparations (CSPs) so prepared should be limited as described in USP <797> for CSPs prepared in a SCA (USP 800, 2016).

C. **Compounding Aseptic Containment Isolators (CACI)**

USP <797> defines a CACI as a form of isolator specifically designed for compounding pharmaceutical ingredients or preparations, designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes, and designed to provide an aseptic environment for compounding sterile preparations (USP 797, 2012). Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile HDs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation. USP <797> has specific performance criteria for the CACI (USP 797, 2012):

- The isolator should provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.
- Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site should maintain ISO Class 5 levels during compounding operations.
- Not more than 3,520 particles (0.5 mm and larger) per m3 should be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer (USP 797, 2012).

The manufacturer of the CACI should provide documentation that the device will meet this standard when located in environments where the background particle counts exceed ISO Class 8 for 0.5-mm and larger particles. When CACI are used for sterile compounding, the recovery time to achieve ISO Class 5 air quality should be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations. CACIs should be certified to CAG-002-2006 or current (CETA, 2008; USP 797, 2012).

When a CACI is placed in a C-SCA, the beyond use date (BUD) of all compounded sterile preparations (CSPs) so prepared should be limited as described in USP <797> for CSPs prepared in a SCA (USP 800, 2016).

The CACI is no more resistant to HD contamination than the Class II BSC as the same limitations (vial contamination,

technique, cleaning and decontamination) apply. Transfer of contaminated items into or out of the CACI will result in contamination on outside surfaces. The CACI, like all isolators, should have the fixed gloves changed multiple times per day to perform HD compounding. Sleeves, gauntlets, and glove assemblies develop pinholes and other damage and should be monitored for this. As the CACI is negative pressure to the surrounding area, damage to gloves or sleeves will bring particulates into the ISO 5 work area, creating a risk of microbial contamination of sterile preparations. USP <797> standards and other guidance documents do not exempt the CACI from the use of appropriate PPE for HD compounding (USP 797, 2012; ASHP, 2006; NIOSH, 2004). Gowns and additional gloves should be worn by HD compounders using a CACI.

1. **Decontamination, Deactivation, and Cleaning**
   The C-PECs used to compound HDs should be cleaned according to the manufacturer's instructions. Additional cleaning information may be found in the SDS for specific drugs. Per ASHP, decontamination may be defined as cleaning or deactivating (ASHP, 2006). Per USP <800>, all areas where HDs are handled and all reusable equipment and devices should be deactivated, decontaminated, and cleaned (USP 800, 2016). Sterile compounding areas and devices should be subsequently disinfected (USP 800, 2016). Deactivating a hazardous substance is preferred, but no single process has been found to deactivate all currently available HDs. The use of alcohol for disinfecting (deactivating microbial contamination) the C-PEC will not deactivate any HDs and alcoholic solutions may result in the spread of contamination rather than any actual cleaning (Sessink, 1992b; Dorr, 1992; ASHP, 2006; Le, 2013). Disinfection should be done routinely when using C-PEC for sterile compounding.

   Attempts to remove marker HD contamination with detergents and vaporized hydrogen peroxide have been met with mixed success depending on the HD and the cleaning method (Roberts, 2006). Several studies examining cleaning techniques in HD compounding and administration areas have found residual HD contamination after cleaning in most instances (Acampora, 2005; Hedmer, 2008b; Touzin, 2010; Turci, 2011; Chu, 2011). One study found a commercial sodium hypochlorite/sodium thiosulfate product to be more successful at removing cyclophosphamide (CP) when compared to other cleaning solutions (Touzin, 2010). Combining various cleaning techniques, however, resulted in even less residual concentration of CP after cleaning was performed (Touzin, 2010).

   This success in reducing CP contamination, however, may have limited usefulness when attempting to clean other drugs. A recent study of 10 HDs, which were divided into "hydrophilic" or "hydrophobic" groups, assessed the potential of several chemical solutions to decontaminate stainless steel and glass work surfaces (Lamerie, 2013). The authors chose to test "elimination type" solutions (cleaners), whose main action is to dissolve chemical products on the surface, and "degradation type" (deactivating) solutions, which react with the chemical structure of compounds leading to their degradation and, possibly, the formation of expected non-cytotoxic compounds. Sodium hypochlorite 0.5 percent, a degradation type solution, showed the highest overall effectiveness, with removed 98 percent contamination all 10 drugs from both surfaces. The authors did not report using detergent or neutralizer with this bleach solution.

   One elimination type surfactant, dish washing liquid, was found to be an effective cleaning solution (91.5 percent of contaminants removed), but the exact formulation of the solution was unknown. Solutions containing 10-2 M anionic surfactants and 20 percent isopropyl alcohol had the highest global effectiveness at around 90 percent. Their efficacy was the highest for the most hydrophilic compounds and around 80 percent effective for anthracyclines. Another interesting finding was that adding isopropyl alcohol to surfactant solutions enhanced their decontamination efficiency on the least hydrophilic molecules. Additional research is needed, but this study provides much needed information on the cleaning of C-PECs, as well as drug vials. When cleaning C-PECs, one must ensure that they appropriately rinsed, and that the cleaning and rinsing materials are collected and disposed of as contaminated waste. Per ASHP, a C-PEC that runs continuously should be cleaned before the day's operations begin, at regular intervals, or when the day's work is completed (ASHP, 2006). For a 24-hour service, the cabinet should be cleaned two or three times daily (ASHP, 2006).

   Initial decontamination (cleaning) should consist of surface cleaning with water and detergent followed by thorough rinsing. Detergents, as surfactants, may assist in removing HD residue from the C-PEC (Lamerie, 2013). No single accepted method of chemical deactivation for all HDs has been identified (Castegnaro, 1985; Benvenuto, 1993; Castegnaro, 1997). Several studies have shown standard cleaning methods may leave HD residue or result in moving the residue to other areas (Sessink, 1992b; Turci, 2011). Cleaning systems that provide decontamination and deactivation using sodium hypochlorite, detergent, and thiosulfate neutralizer have shown some success (Touzin, 2010). Newer agents, such as high level disinfectants containing hydrogen peroxide and peracetic acid, may provide alternatives to bleach when used in HD equipment cleaning programs. C-PECs used for sterile compounding should be disinfected routinely, per USP <797> (USP 797, 2012).

Class II BSCs and CACIs that have laminar flow in the work area may have a removable work tray as the work surface. The area under this tray should be physically cleaned routinely. USP <800> describes a cleaning process and recommends at least a monthly clean of this area (USP 800, 2016). The interior of the Class II BSC and the CACI should be thoroughly cleaned and rinsed prior to accessing the area under the tray. During cleaning, the worker should wear PPE similar to that used for spills. The sash on the Class II BSC should remain down during cleaning and the front of the CACI should remain closed. The exhaust fan/blower should be left on. Cleaning should proceed from the least to the most contaminated areas. Any trough area should be cleaned at least twice since it can be heavily contaminated. All materials from the decontamination process should be handled as HDs and disposed of in accordance with federal, state and local laws (ASHP, 1990; ASHP, 2006).

Vial cleaning and decontamination of storage areas should be done routinely to reduce HD residue in the work area. The outer surface of HD vials has been shown to be contaminated with HD residue in numerous studies (Sessink, 1992b; Kiffmeyer, 2000; Connor, 2005; Touzin, 2008; Power, 2014). This residue may transfer to workers when receiving HDs, storing HDs, performing inventory control, selecting HDs for compounding, and all other times when workers interact with potentially contaminated vials. Limited studies have been done to select an appropriate and successful cleaning procedure for HD vials (Touzin, 2008; Lamerie, 2013). Cyclophosphamide (CP) was removed, to varying extents, from vial surfaces by using several methods of wiping with a tissue wetted with soapy water, followed by a dry wipe and a wipe down with a pre-wetted commercial wiper (Touzin, 2008). A larger study used wipers wetted with selected cleaning solutions to wash off vials of 10 different HDs (Lamerie, 2013). Sodium hypochlorite 0.5 percent solution in water, dish washing liquid in water, and anionic surfactants in 20 percent isopropyl alcohol all achieved greater than 90 percent removal of most of the 10 drugs (Lamerie, 2013). Wiping solutions for both studies were selected due to their ease of use and lack of toxicity. Though more studies are needed, these methods of wiping HD vials would remove much of the initial contamination and reduce the transfer of HD residue to storage and compounding areas. Storage areas should be cleaned and decontaminated routinely to avoid transfer of HD residue to gloves and other surfaces. Sodium hypochlorite solution, detergent, neutralizer and rinsing have been shown to be effective on hard surfaces (Touzin, 2010).

2. **Service and Certification**
   USP <797> notes that a C-PEC used for sterile compounding be certified by a qualified technician every six months using an approved procedure, such as the Controlled Environment Testing Association (CETA)-approved procedure. Contract workers certifying or servicing these devices should be made aware of the HD risks posed by these tasks and should use the same PPE that compounding staff uses when cleaning HD spills (USP 797, 2012).

   ASHP recommends that BSCs be serviced and certified by a qualified technician every six months, or any time the cabinet is moved or repaired (ASHP, 1990; ASHP, 2006). Technicians servicing these cabinets or changing the HEPA filters should be aware of HD risks through hazard communication training from their employers and should use the same PPE as recommended for large spills. CACIs should be serviced and certified, per the CETA guidance (CETA, 2008).

3. **Personal Protective Equipment**
   The C-PECs generally used for handling HDs require personal protective equipment (PPE) to provide a barrier between the worker and the HD during episodes of potential contact, and OSHA requires employers to provide and to require the use of PPE that protects employees against the hazards to which they are exposed [29 CFR 1910.132]. Multiple studies show that workers have continued physical contact with HD contaminated surfaces in the many work areas where HDs are handled. A recent study used pre-moistened tissue to wipe the hands of workers who were preparing or checking HDs, as well as workers who were in the preparation area but were not involved in preparing the HDs (Hon, 2011). Of 18 wipes tested, 28 percent had measurable levels of the marker drugs, including those not directly involved with preparing HDs. A study of ambulatory care oncology nurses was conducted in 2010 to examine self-reported skin or eye contact with HDs during the previous work year (Friese, 2012). The survey found that the overall rate of exposure to the skin or eyes was 16.9 percent. NIOSH prepared a Workplace Solution in 2009 on Personal Protective Equipment for Health Care Workers Who Work with HDs to provide guidance on the PPE needed to safely handle HDs (NIOSH, 2009). PPE is especially important during administration, spill control, handling of drug waste, and handling of patient waste because no C-PECs are in place for these activities. During sterile compounding of HDs, barrier garments should be worn to prevent the shedding of human skin and hair cells, and the deposition of mucus or respiratory residue into the compounding area. USP <797> specifies that compounding garb for sterile doses should include the following (USP 797, 2012):

   - Sterile, powder-free gloves;
   - A non-shedding gown that closes in the back, has sleeves that fit snugly around the wrists and is

enclosed at the neck;
- Face masks;
- Dedicated shoes or shoe covers;
- Head and facial hair covers (e.g., beard covers in addition to face masks [see also 3.c. Respiratory Protection]).

a. **Gloves**. Research indicates that most of the surfaces in an HD environment are contaminated with drug residue, and that this contamination has been measured in workers handling HDs or who are in areas where HDs are handled (Sessink, 1992a; Sessink, 1992b; Sessink, 1997; Connor, 1999; Connor, 2002; Wick, 2003; Fransman, 2004; Acampora, 2005; Fransman, 2005; Fransman, 2007; Connor, 2010; Suspiro, 2011; Kopp, 2013). Gloves are essential for handling HDs and should be worn at all times when handling drug packaging, cartons, and vials, including while performing inventory control procedures and when gathering HDs and supplies for compounding a batch or single dose (ASHP, 2006). Not all gloves offer adequate protection from dermal exposure to HDs, and employers should review test information provided by the glove manufacturer that demonstrates permeation resistance to specific HDs (NIOSH, 2009). However, current standards are only available for testing "chemotherapy gloves" (American Society for Testing and Materials [ASTM], 2013), and information may not be available for other types of HDs (NIOSH, 2009). NIOSH, ASHP, Oncology Nursing Society, and USP recommend using gloves that have been tested according to ASTM's D6978 specifications (NIOSH, 2009; ASHP, 2006; ASTM, 2013; Polovich, 2014; USP 800, 2016). Health care employers must ensure that gloves purchased for HD use are tested to the correct standard in order to ensure that they protect their employees against the hazards of the particular HDs used. NIOSH recommends wearing two pairs of gloves when compounding, administering, and disposing of HDs (NIOSH, 2009). ASHP also recommends double-gloving, both to reduce permeation and to improve work practices, because wearing and removing a single glove allows skin to be exposed to a number of contaminated surfaces (ASHP, 2006). Prudent practices from NIOSH and ASHP include:
   - Inspect gloves for defects before use and change gloves on a regular basis;
   - Changing recommendations vary from 30-60 minutes (NIOSH, 2004; ASHP, 2006). Whenever gloves are damaged or contact with a drug is known or suspected, carefully remove and dispose of them properly;
   - Use powder-free gloves since the powder can contaminate the work area and can absorb and retain HDs; and
   - Wear two pairs of gloves when compounding, administering, and disposing of HDs;
   - Sterile chemotherapy gloves should be used for compounding of sterile preparations under USP Chapter <797> (USP 797, 2012);
   - Wear the inner glove under the gown cuff and the outer glove over the cuff. Place gloves with long cuffs over the cuff of the gown to protect the wrist and forearm (NIOSH, 2009; ASHP, 2006; Polovich, 2014);
   - When compounding sterile preparations, sanitize gloves with sterile 70 percent alcohol. Do not spray gloves that are possibly contaminated with HDs to avoid transferring HD residue to other surfaces or into the environment. Spray a wiper and wipe the gloves and allow them to dry; ensure that the selected gloves are not degraded by alcohol;
   - Remove outer gloves after wiping down final preparation but before labeling or removing the preparation from the C-PEC (ASHP, 2006);
   - Outer gloves should be placed in a containment bag while in a BSC (ASHP, 2006);
   - In a CACI, a second glove should be worn inside the fixed-glove assembly; the fixed gloves or gauntlets should be surface cleaned after compounding is completed to avoid spreading HD contamination to other surfaces (ASHP, 2006);
   - In a CACI, clean gloves (e.g., the clean inner gloves) should be used to surface decontaminate the final preparation, place the label onto the final preparation, and place it into the pass-through (ASHP, 2006);
   - In a CACI, don fresh gloves to complete the final check, place preparation into a clean transport bag, and remove the bag from the pass-through (ASHP, 2006);
   - When removing double gloves, remove them one at a time (e.g., outer glove, then inner glove) turning the gloves inside-out so that contaminated surfaces do not touch uncontaminated surfaces (NIOSH, 2009); and
   - Wash hands thoroughly with soap and water both before donning and after removing gloves (ASHP, 2006; NIOSH, 2009).

b. **Gowns**. Proper gowns protect the worker from spills and splashes of HDs and waste materials. Gowns should not have seams or closures that could allow drugs to pass through. They should have long sleeves with tight fitting cuffs (NIOSH, 2009). Disposable gowns made of polyethylene-

coated, poly-propylene, or other laminate materials offer better protection than those of non-coated materials (NIOSH, 2004; ASHP, 2006). There is no specific standard for gowns or gowning materials to be tested for permeation by sample chemotherapy or other HDs. ASTM F739-12 is a test method for permeation by liquids and gases through protective clothing materials under conditions of continuous contact, but it does not specify drugs or concentrations to be tested (ASTM, 2012). It has no performance standard for an acceptable resistance to HD permeation. Some gowns are tested using the F739-07 parameters and the chemotherapy drugs and concentrations from D6978. This practice has not been studied for effectiveness or safety. Cloth laboratory coats, surgical scrubs, or other absorbent materials permit the penetration of HDs, and can hold spilled drugs against the skin and increase exposure (NIOSH, 2009).
Follow these recommended work practices when wearing gowns:

- Dispose of gowns after each use. Reusing gowns increases the likelihood of exposure to HDs (NIOSH, 2009);
- Wear gowns during compounding, administration, when handling waste from patients recently treated with HDs, when cleaning up spills of HDs, and whenever there is a possibility of splash or spill (ASHP, 2006; NIOSH, 2009);
- Do not wear gowns outside the compounding or administration area to avoid spreading drug contamination to other areas and possibly exposing non-protected workers (NIOSH, 2009);
- If no permeation information is available for the gowns in use, change them every 2 to 3 hours or immediately after a spill or splash (ASHP, 2006);
- Remove gowns with care to avoid spreading contamination. Specific procedures for removal should be established and followed (ASHP, 2006);
- Contain and dispose of used gowns as contaminated waste (ASHP 2006); and
- Wash hands after removing and disposing of gowns (ASHP, 2006).

c. **Respiratory Protection**. An appropriate respirator must be used whenever there is a possibility of exposure from aerosolization of HDs (for example, when actively containing a spill or handling a damaged shipping carton). For most activities requiring respiratory protection, a NIOSH-certified N-95 or more protective respirator is sufficient to protect against airborne particles (NIOSH, 2005). However, N-95 respirators offer no protection against gases and vapors and little protection against direct liquid splashes. A surgical N-95 respirator provides both the respiratory protection of an N-95 respirator and the splash protection provided by a surgical mask through its tested and approved moisture resistance, with additional certification by FDA. Surgical masks alone do not provide respiratory protection from drug exposure and should not be used to compound or administer drugs (NIOSH, 2004).
Whenever respirators are used, OSHA's Respiratory Protection Standard (RPS) [29 CFR 1910.134] (OSHA, 2011b) must be followed, which includes requirements for respirator selection, medical evaluation, fit testing and training. NIOSH and ASHP have provided the following guidance on the selection respirators to protect against exposure to HD:

- Use an appropriate, full-face piece, chemical cartridge-type respirator 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, 2005; NIOSH, 2009);
- A respirator of correct size and appropriate to the aerosol size, physical state (i.e., particulate or vapor), and concentration of the airborne drug should be available at all times (ASHP, 2006); and
- Surgical masks do not provide respiratory protection (ASHP, 2006).

d. **Eye and Face Protection**. Proper eye and face protection is needed whenever HDs may splash in the eyes, nose, or mouth since many HDs are irritating to eyes and mucous membranes and may be absorbed by the eyes. Chemical-barrier face and eye protection must be provided and used in accordance with OSHA's Eye and Face Protection Standard [29 CFR 1910.133].
NIOSH has recommended the following practices to provide eye and face protection to employees working with HD (NIOSH, 2009):

- Use eye and face protection when compounding a drug outside a C-PEC (e.g., in the operating room), working at or above eye level, cleaning a BSC or CACI, or cleaning a spill;
- Use face shields in combination with goggles to provide a full range of protection against splashes to the face and eyes;
- Face shields alone do not provide full eye and face protection;
- Eyeglasses with temporary side shields are inadequate protection to the eyes from splashes;
- A full-facepiece respirator also provides eye and face protection; and
- Eyewash facilities should also be made available.

4. **PPE Disposal and Decontamination**
   All gowns, gloves, and disposable materials used in HD preparation should be disposed of according to the facility's HD waste procedures and as described under this review's section on Waste Disposal (Section IV. C.). Goggles, face shields, and respirators, except the filter elements, may be cleaned with mild detergent and water for reuse by wiping reusable items with wetted wipers. Discard all cleaning materials as hazardous waste.

5. **Containment Supplemental Engineering Controls**
   In 2004, NIOSH formulated a generic definition to describe a device used in the compounding and administration of sterile HD doses that was designed to reduce the aerosol and drug residue that may escape during a traditional needle and syringe and open IV set technique (NIOSH, 2004). A "closed system drug-transfer device" is a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system (NIOSH, 2004). This device has been abbreviated in the literature as CSTD, although NIOSH never used this acronym. A CSTD is classified by FDA as a Class II Medical Device and is cleared through the 510(k) process, which requires a submitted device to have "substantial equivalence" to another legally U.S.-marketed device, commonly known as the "predicate" device (FDA, 2014). The FDA's 510(k) process does not establish independent performance standards for devices submitted as "substantially equivalent." Some CSTDs have been shown to limit the potential for generating aerosols during compounding and to avoid leakage and disconnects during administration, which results in less measurable HD surface contamination in HD work areas. There are a number of devices marketed as CSTDs but there is currently no performance standard by which all CSTDs are evaluated for containment. Until a protocol or evaluation method is established, users should carefully evaluate performance claims associated with marketed CSTDs (USP 800, 2016).

   Some CSTDs have been shown in peer-reviewed studies to reduce HD contamination in the workplace (Connor, 2002; Clark, 2013; Harrison, 2006; Nygren, 2002 b; Nygren, 2008; Nyman, 2007; Sessink, 2011; Sessink, 2013; Tans, 2004; Wick, 2003; Zock, 2011). The persistent presence of HD contamination in compounding and administration areas, despite adherence to HD safe handling guidelines, has generated an interest in supplemental containment controls, especially for administration areas where primary engineering controls are not available. CSTDs are not a substitute for good work practices or pre-cleaning of HD vials.

   - NIOSH and ASHP recommend the use of a CSTD in conjunction with engineering controls, PPE, and work practices (NIOSH, 2004; ASHP, 2006).
   - CSTDs are not a substitute for ventilated engineering controls and should not be used outside of an appropriate C-PEC (NIOSH, 2004; ASHP, 2006; USP 800, 2016).
   - CSTDs should be used when compounding HDs when the dosage form allows (USP 800, 2016).
   - CSTDs should be used when administering HDs when the dosage form allows (USP 800, 2016).

D. **Work Equipment**
   Worker exposure to HDs may occur in handling both sterile and non-sterile doses. Work equipment for HDs should be suitable for the task and reduce the risk of exposure to the HD. Equipment should either be disposable as HD contaminated waste, or, if reusable, should be able to be decontaminated with a suitable chemical without adding exposure risk to the worker and contamination risk to the environment (USP 800, 2016).

   For sterile compounding, only supplies and drugs essential to compounding the dose or batch should be placed in the work area of the C-PEC (USP 800, 2016). BSCs and CACIs should not be overcrowded to avoid unnecessary contamination with HD residue and possible interference with laminar flow for puncturing critical sites (ASHP, 2006; USP 797, 2012; USP 800, 2016). For non-sterile compounding, the ventilated controls should be cleared of unnecessary supplies to avoid transfer of HD contamination to them during compounding tasks (USP 800, 2016). All items placed in C-PECs should be able to be decontaminated or discarded as HD contaminated waste (ASHP, 2006; USP 800, 2016).

   1. **Preparation Pads**
      Plastic-backed absorbent pads are commercially available and may be used to cover work surfaces in the C-PECs or other areas to absorb HD leaks or small spills. In a Class II BSC, one study suggested the use of such a pad may interfere with the airflow through the open front or block exhaust grills (Minoia, 1998). Another study determined that a flat, firm pad did not block the grills of the Class II BSC and had no effect on airflow (NuAire, 2003). The use of a pad that is large enough to block the front and/or rear grills of a Class II BSC or a CACI should be avoided. As such a pad may absorb small spills, it may become a source of HD contamination, and that contamination may be transferred to other surfaces (ASHP, 2006). Preparation pads should be replaced and discarded after the preparation of each batch and frequently during extended batch compounding (ASHP, 2006; USP 800, 2016). Pads that are used outside of the C-PEC should be replaced regularly and monitored for excessive contamination, such as a spill. Preparation pads should be

discarded as HD contaminated waste.

2. **Waste/Sharps Containers**
   A small waste/sharps container may be placed along the sidewall toward the back of the C-PEC as long as it does not interfere with airflow in the ventilated cabinet or negatively impact on the particle count within an ISO 5 PEC (ASHP, 2006). Studies show HD contamination on the floor in front of the Class II BSC could occur when workers reach out of the cabinet to discard waste in receptacles located on the floor (Connor, 1999; Connor, 2010). Closed front cabinets, like the CACI, may have chutes from the cabinet work area that go directly to waste containers. Waste handling, especially sharps waste, presents a risk of HD exposure. Care should be taken in manipulating sharps at all times. Waste containers stored inside the C-PEC should be sealed and decontaminated before removing from the C-PEC for discard, due to the potential HD contamination on the outside of the container (ASHP, 2006).

   HD containment bags are a valuable tool for containing contaminated gloves, wipers, preparation pads, and other things that should not be discarded directly into large waste containers. These bags should be sealed and then discarded. As the larger waste containers are frequently not covered, or the cover is opened throughout the day, the containment bag provides additional protection from exposure. ASHP advocates the use of these bags for waste containment and for transport (ASHP, 2006). Transport bags should never be placed in the BSC or the isolator work chamber during compounding to avoid inadvertent contamination of the outside surface of the bag (ASHP, 2006).

3. **Use Luer-Lock Fittings**
   Use Luer-Lock fittings for all needleless systems, syringes, needles, infusion tubing, and pumps. Luer-Lock fittings avoid separation during use for HD compounding and during administration. Syringe size should be large enough so that they are only 3/4 full when containing the entire drug dose to prevent loss of the plunger during manipulation and to allow space to manage the dose. Per ASHP, many devices labeled as "chemo adjuncts" are currently available (ASHP, 2006). Many feature a filtered, vented spike to facilitate reconstituting and removing HDs during the compounding process.

   These devices do not lock onto the HD vial, allowing them to be transferred from one vial to another, creating an opportunity for both environmental and product contamination (ASHP, 2006). Many of the "chemo adjunct devices" have large spikes that damage the septum of the HD vials. None of these devices may be considered a CSTD, and none has been formally studied with results published in peer-reviewed journals to demonstrate that they reduce exposure to the worker (ASHP, 2006). NIOSH, ASHP, and USP state that CSTDs (or any other ancillary devices) are not a substitute for using a ventilated cabinet (NIOSH, 2004; ASHP, 2006; USP 800, 2016).

E. **Work Practices**
   Correct work practices are essential to worker protection. Without appropriate compounding work practices, both workers and patients are at risk. Protective equipment and environments should be accompanied by a stringent program of work practices, including operator training and demonstrated competence, contamination reduction, and decontamination (ASHP, 2006).

   1. **Compounding Technique**
      HD compounding may be both sterile and non-sterile. Sterile compounding requires competence in aseptic technique, and that is assumed in this section. The general principles of aseptic technique, therefore, will not be detailed here.

      a. Vertical airflow C-PECs (Class II or III BSC or CACI) differ from horizontal airflow devices in several ways that require special precautions. Manipulations should not be performed close to the work surface of a vertical airflow C-PEC, as the quality of the air is poorest in that area. Critical sites should be accessed in "first air" which is close to the HEPA filter and not obstructed in any way (USP 797, 2012).
      b. Good organizational skills are essential to minimize contamination and maximize productivity during compounding (ASHP, 2006).
      c. Gather all needed supplies before beginning compounding to avoid exiting and reentering the work area of the C-PEC (ASHP, 2006).
      d. Disinfect supplies placed in the compounding area when sterile compounding in the C-PEC (USP 797, 2012).
      e. Reduce the HD contamination burden in the C-PEC by wiping down HD vials before placing them in the C-PEC (ASHP, 2006; USP 800, 2016).
      f. Transport bags should never be placed in the C-PEC work chamber during compounding to avoid inadvertent contamination of the outside surface of the bag (ASHP, 2006).
      g. Final preparations should be surface decontaminated within the C-PEC and placed into the

transport bags in the BSC or in the isolator pass-through, taking care not to contaminate the outside of the transport bag (ASHP, 2006).

h. Once compounding is completed, decontaminate the C-PEC. Seal all contaminated materials (e.g., gauze, wipes, towels, wash or rinse water) used in cleaning or decontaminating the C-PEC in bags or plastic containers and discard as contaminated waste (ASHP, 2006).
i. CACI gloves or gauntlets should not be replaced before completing decontamination within the cabinet (ASHP, 2006).
j. For sterile compounding, hands should be washed before donning gloves, and then sanitized routinely during compounding activities (USP 797, 2012).
k. Additional guidance for the use of a C-PEC within a classified buffer area and the appropriate garbing and cleansing procedures for sterile compounding of HDs can be found in USP <797> and USP <800> (USP 797, 2012; USP 800, 2016).

2. **Labeling**
In addition to standard pharmacy labeling practices, all syringes and IV bags containing HD's should be labeled with a distinctive warning label, such as:

SPECIAL HANDLING/ DISPOSAL PRECAUTIONS

3. **Using Needles**
As clipping or crushing used HD needles generates aerosols of HD, this process is strongly discouraged. HD needles used on patients present a bloodborne pathogen hazard as well. NIOSH recommends placing sharps, such as needles and syringes, in HD waste containers designed to protect workers from injuries (NIOSH, 2004). ASHP recommends that drug syringes (with the needle attached) be discarded directly into a HD waste container (ASHP, 2006). Sharps contaminated with blood or other infectious material must be placed in puncture-resistant, leak-proof, and appropriately labeled containers as soon as possible after use and kept in such containers until properly reprocessed [29 CFR 1910.1030(d)(2)(viii)].

4. **Spiking and Priming**
Spiking an IV set into a solution containing HDs or priming an IV set with HD solution in an uncontrolled environment should be avoided. Attaching and priming the IV set to the final container in the C-PEC before adding the HD is a prudent practice (ASHP, 2006). An alternative is the use of a CSTD adaptor, which should achieve a dry connection between the administration set and the HD final container. This connection allows the container to be spiked with a secondary IV set and the set to be primed by backflow from a primary non-HD solution. This process may be done outside the C-PEC, reducing the potential for surface contamination of the outside of the IV set during the compounding process (ASHP, 2006). Once attached, the IV set should never be removed from an HD dose, thereby preventing the residual fluid in the bag, bottle, or tubing from leaking and contaminating personnel and the environment (ASHP, 2006).

5. **Handling Vials**
Pressurizing HD vials should be avoided, as it strains the septum and may cause the HD to aerosolize and escape the vial as a powder or liquid (Nygren, 2002; Spivey, 2003, Tans, 2004). While filtered venting devices help equilibrate the pressure, large bore spikes create holes in the septa that may release drug. Devices that do not lock on and may be transferred from one vial to another may increase the release of HD contamination (ASHP, 2006). Special aseptic technique has long been advocated to reduce aerosol formation and leakage of HDs during compounding (Wilson, 1981). Newer and more sensitive measures of HD surface contamination have been used to assess the effectiveness of technique alone. A number of studies using surface wipe sampling to detect marker HDs on surfaces in compounding and administration work areas indicate that traditional syringe/needle and open IV set techniques may be insufficient to control HD contamination (Connor, 1999; Connor, 2010). While HD on the outside of vials should be considered a source of the contamination, rigorous handling practices and cleaning should be used along with meticulous technique to reduce worker exposure (NIOSH, 2004; USP 800, 2016).

6. **Handling Ampules**
HDs that are available in vials should be purchased whenever possible, as the contents of ampules are hard to contain. To withdraw HD from an ampule, gently tap the neck or top to return all liquid to the bottom of the ampule. Wipe the neck with sterile alcohol and allow it to dry. Wrap a sterile gauze pad around the ampule neck before breaking the top (Wilson, 1981; ASHP, 1990; ASHP, 2006). This can protect against cuts and catch airborne HD aerosol. HD solution should be drawn from an ampule with a 5 micron filter

needle or straw to remove any glass that might have entered the solution. Use a syringe large enough that it will not be more than three-fourths full when holding the dose. The needle or straw is exchanged for a needle of similar gauge and length. Any air or excess drug should be ejected into a sterile vial (leaving the desired volume in the syringe). The drug may then be transferred to an IV bag or bottle. If the dose is to be dispensed in the syringe, the plunger should be drawn back to clear fluid from the needle and hub. The needle should be replaced with a locking cap, and the syringe should be surface decontaminated and labeled (ASHP, 2006).

7. **Packaging HDs for Transport**
   The outside of bags or bottles containing the prepared drug should be wiped with moist gauze. Entry ports should be wiped with moist alcohol pads and capped. Transport should occur in sealed plastic bags and in containers designed to avoid breakage (ASHP, 2006). Shipped HDs that are subject to EPA regulation as hazardous waste are also subject to Department of Transportation regulations as specified in 49 CFR 172.101.

8. **Handling Non-Sterile Hazardous Drugs**
   Compounding and handling non-sterile HDs may present opportunities for exposure and require special precautions. All HDs should be labeled and identified to prevent improper handling. Oral solid forms of HDs should not be placed in automated counting machines, as these have been shown to produce "pill dust" in the work area, some of which is active drug (Fent, 2014). ASTM tested "chemotherapy" gloves should be worn when counting and pouring HDs, and C-PEC designed for non-injectable HDs should be used (USP 800, 2016). Double gloves should be worn when crushing HD tablets or opening HD capsules (NIOSH, 2014b [table 5]). When compounding non-sterile HDs (e.g., crushing, dissolving, or preparing a solution or an ointment), PPE should include non-permeable gowns and double gloves (ASHP, 2006). Compounding should take place in a ventilated cabinet (NIOSH, 2004; USP 800, 2016). HDs should be dispensed in the final dose and form whenever possible (ASHP, 2006). Disposal of unused or unusable non-sterile dosage forms of HDs should be performed in the same manner as for sterile hazardous drug dosage forms and waste (ASHP, 2006).

F. **Drug Administration**
   HDs are administered through many different routes, in several types of settings, and for numerous disease states. Safe handling is required for all HDs no matter how they are used. Precautions include using personal protective equipment, work equipment, and work practices designed for safety.

   1. **Personal Protective Equipment**
      All personnel responsible for administering HDs must wear appropriate personal protective equipment as described in the PPE section. Appropriate eye and face protection must be worn when splashing is possible. A NIOSH-approved respirator must be worn when administering aerosolized drugs and for other handling activities that generate aerosols (ASHP, 2006; NIOSH, 2014a; Polovich, 2014).

   2. **Work Equipment**
      Equipment for HD administration depends on the route of drug administration and the delivery system being used. Some IV equipment, such as a CSTD, is designed to minimize drug leaks when HDs are administered (NIOSH, 2004). When CSTDs are not available, equipment should be selected to improve safety.

      a. Needleless devices are preferred to reduce sharps injury (NIOSH, 2004)
      b. Syringes, needles, tubing, and pumps with locking connections (e.g., Luer-Lock) should be used whenever possible to decrease accidental disconnection (NIOSH, 2004; USP 800, 2016).
      c. CSTDs should be used for administration of antineoplastic HDs when the dosage form allows (Polovich, 2011; USP 800, 2016).
      d. Gauze pads can be used to absorb small droplets.
      e. Plastic-backed pads can be used to protect work surfaces from HD contamination (USP 800, 2016)
      f. Sealable bags should be used for transporting HDs (ASHP, 2006; USP 800, 2016).
      g. The following should be readily accessible for disposal of HD contaminated waste: a puncture resistant container for sharps, plastic HD waste disposal bags, and HD waste containers (ASHP, 2006).
      h. All health care settings where HDs are administered should have spill kits and emergency skin and eye decontamination equipment, as well as relevant Safety Data Sheets for guidance in the case of spills or employee exposure (USP 800, 2016).
      i. PPE and administration equipment may be packaged together and labeled as an HD administration kit.

   3. **Work Practices**
      Safe work practices when handling HDs should include the following:

a. Hands should be washed before donning and after removing and discarding PPE (NIOSH, 2004).
b. Employees should work below eye level to reduce the chance for eye exposure.
c. Gowns or gloves that are knowingly contaminated should be changed immediately. Employees must be trained in proper methods to remove contaminated gloves and gowns [29 CFR 1910.132(f)]. After use, gloves and gowns should be disposed of in designated HD waste containers (NIOSH, 2004).
d. Syringe and IV tubing connection sites should be secured with locking connections. Infusion sets and pumps should be observed for leakage during use.
e. When CSTDs are not used, a plastic-backed absorbent pad should be placed under connection sites during administration to catch any leakage. Sterile gauze should be placed around syringe connection sites (ASHP, 2006, Polovich, 2011).
f. Priming IV sets or expelling air from syringes should be carried out in a C-PEC. If priming is done at the administration location, spiking should be performed using an adapter that minimizes leakage, and IV sets should be primed with non-drug containing solution using a backflow method. IV containers with venting tubes should not be used (ASHP, 2006).
g. Needles and syringes should not be crushed or clipped. They should be placed in a puncture-resistant container, then into an HD disposal bag with all other HD-contaminated materials. Sharps contaminated with blood or other infectious material must be placed in puncture-resistant, leak-proof, and appropriately labeled containers as soon as possible after use and kept in such containers until properly reprocessed [29 CFR 1910.1030(d)(2)(viii)].
h. IV administration sets should be disposed of intact. Disposal of the waste bag should follow HD disposal requirements. Unused drugs should be returned to the pharmacy.
i. IV pumps should be wiped clean of any drug contamination after use.
j. All disposable PPE should be removed and disposed of before leaving the patient care area.
k. Reusable PPE should be cleaned with detergent and thoroughly rinsed.
l. If splashing is possible during the administration of oral HDs, appropriate PPE must be used [29 CFR 1910.132]. NIOSH recommends that gloves should be worn and gowns should be in such circumstances (NIOSH, 2014a).
m. For drug administration by a route that is likely to result in leakage, the location should be prepared with plastic-backed absorbent pads, and locking connections should be used if possible. Face and eye protection must be worn if there if splashing is a hazard [29 CFR 1910.133].
n. Handling of investigational HDs should be limited to individuals who have received specific instructions regarding their toxicity and safe administration (Polovich, Olsen, & Lefebvre, 2014).
o. Employees involved in home care HD administration should follow the above work practices and employers should make administration equipment and spill kits available. Home health care workers should have emergency protocols with them as well as information regarding who to contact in the event emergency care becomes necessary. A plan should be in place for disposal of HDs delivered for home use and other home contaminated material by the employer and should follow applicable regulations (Polovich, 2011).

4. **Aerosolized Drugs**
The administration of aerosolized HDs requires special engineering controls to prevent exposure of health care workers and others in the vicinity. These controls include treatment booths or tents with local exhaust ventilation that are designed specifically to isolate aerosolized forms of drugs and negative pressure isolation rooms with separate HEPA filtered ventilation systems. Warning signs should be posted on the door of the room and the door kept closed during treatment. Staff should avoid entering isolation rooms during treatment, but if entry is necessary, they must wear gowns, gloves, eye protection, shoe covers, and a powered air purifying respirator. The environment should be cleaned after each treatment to remove residual drug from surfaces. Patient gowns and linens should be considered contaminated and changed after treatment (Latchford, 2003; Mooney, 2014).

G. **Caring for Patients Receiving HDs**
Patient excreta that is contaminated by HDs should be handled in such a way as to protect health care workers from exposure.

1. **Personal Protective Equipment**. All personnel responsible for handling excreta, including urine, emesis, or feces, from patients who have received HDs in the last 48 hours must wear personal protective equipment as described in the PPE section. Eye and face protection must be worn when splashing is possible. PPE should be discarded after each use or immediately when knowingly contaminated, as detailed under Waste Disposal. Hands should be washed with soap and water after removal of gloves or immediately after contact with the above substances.
2. **Linen Handling**. Linens contaminated with HDs or excreta from patients who have received HDs in the past 48 hours should be handled carefully to minimize employee exposure and contamination of the

environment. Linen soiled with blood or other potentially infectious materials, as well as HD contaminated excreta, must also be managed according to the Bloodborne Pathogens Standard (OSHA, 2012a). Linen contaminated with HDs should be placed in specially marked laundry bags and then placed in a labeled and impervious bag. The laundry bag and its contents should be prewashed, and then the linens added to other laundry for a second wash. Laundry personnel should wear gloves and gowns while handling prewashed material.

3. **Reusable Items**. Glassware or other reusable items contaminated with HDs should be washed twice with detergent by a trained employee wearing personal protective equipment as described in the PPE section (Polovich, 2011; Polovich, Olsen, & Lefebvre, 2014).

H. **Spills**

Emergency procedures to address spills or inadvertent release of HDs should be included in the facility's overall health and safety program (ASHP, 2006; USP 800, 2016). Incidental spills and breakages should be cleaned up immediately by a properly protected person trained in the appropriate procedures (ASHP, 2006; USP 800, 2016). The area should be identified with a warning sign to limit access to the area (ASHP, 2006; USP 800, 2016). The circumstances and management of HD spills should be documented (ASHP, 2006; USP 800, 2016). Incident reports should be filed to document the spill and persons exposed (ASHP, 2006; USP 800, 2016). Information should be included in a confidential data base that the organization manages to track exposures as a formal log.

1. **Personnel Contamination**. Contamination of protective equipment or clothing, or direct skin or eye contact, should be treated by:
    a. Immediately removing the gloves or gown.
    b. Immediate cleansing of the affected skin with soap and water.
    c. Flooding an affected eye at an eyewash fountain or with water or isotonic eyewash designated for that purpose for at least 15 minutes, for eye exposure.
    d. Obtaining medical attention. (Protocols for emergency procedures should be maintained at the designated sites for such medical care. Medical attention should also be sought for inhalation of HDs in powder form.)
    e. Documenting the exposure in the employee's medical record.
2. **Spill Kits**. Spill kits containing all of the materials needed to clean up spills of HDs should be assembled or purchased (ASHP, 2006). These kits should be clearly labeled, should be kept in or near HD preparation and administrative areas, as well as HD receiving and storage areas where spills may occur. Spill kits should be located on HD transport carts and staff transporting HDs should be trained to manage a spill (ASHP, 2006). The HD-specific SDS should include sections on emergency procedures, including appropriate personal protective equipment.

    The ASHP recommends that kits include (ASHP, 2006):

    a. Sufficient supplies to absorb a spill of about 1000mL (volume of one IV bag or bottle).
    b. Appropriate PPE to protect the worker during cleanup, including two pairs of disposable chemotherapy gloves, non-permeable, disposable protective garments (coveralls or gown and shoe covers), and face shield.
    c. Absorbent, plastic-backed sheets or spill pads.
    d. Disposable toweling.
    e. At least two sealable, thick plastic hazardous waste disposal bags (pre-labeled with an appropriate warning label).
    f. One disposable scoop for collecting glass fragments.
    g. One puncture-resistant container for glass fragments.

    In addition, NIOSH recommends eye and face protection and a full-face piece chemical cartridge-type respirator for events such as large spills (NIOSH, 2005; NIOSH, 2009). Respirators should be available near the spill kits.

    Prior to cleanup, appropriate protective equipment should be donned. Absorbent sheets should be incinerable. Reusable protective eye/face gear and respirators should be cleaned with mild detergent and water after use. Items contaminated with HDs should be washed three times with detergent by a trained employee wearing personal protective equipment as described in the PPE section (NIOSH, 2004; Polovich, 2011).

3. **Clean-up of Spills**. Each facility should have SOPs for spill management and all workers possibly involved in spill management should be fully trained. As HDs vary in potency and toxicity, a distinct volume of spill is not useful for assessment of exposure. The size of the spill may determine who is authorized to conduct the cleanup and decontamination, and how the cleanup is managed (NIOSH, 2009). Spill kits should be available in all areas where an HD spill may occur.

    NOTE: An appropriate NIOSH approved respirator must be used for either powder or liquid spills where airborne powder or aerosol is or has been generated (OSHA, 2011b; NIOSH, 2009).

A complete respiratory protection program, including fit-testing, is required to wear respirators, including those contained in some spill kits (OSHA, 2011b). Use NIOSH certified respirators (NIOSH, 2005). Surgical masks do not provide adequate protection (NIOSH, 2004).

ASHP's Recommended General Spill Procedures (ASHP, 2006)

a. Assess the size and scope of the spill. Call for trained help, if necessary.
b. Obtain spill kit and respirator, if needed. Spills that cannot be contained by two spill kits may require outside assistance.
c. Don PPE including double gloves and respirator.
d. Once fully garbed, contain spill using spill kit.
e. Carefully remove any broken glass fragments and place them in a puncture resistant container.
f. Absorb liquids with spill pads or toweling.
g. Absorb powder with damp disposable pads or soft toweling.
h. Spill cleanup should proceed progressively from areas of lesser to greater contamination.
i. Completely remove and place all contaminated material in the HD waste disposal bags.
j. Rinse the area with water and then clean with detergent, sodium hypochlorite solution, and neutralizer (if the area may be bleached; if not, use detergent and rinse 3 times).
k. Rinse the area several times and place all materials used for containment and cleanup in disposal bags. Seal bags and place them in the appropriate final container for disposal as hazardous waste.
l. Carefully remove all PPE using the inner gloves. Place all disposable PPE into disposal bags. Seal bags and place them into the appropriate final container.
m. Remove inner gloves, contain in a small, sealable bag, and then place into the appropriate final container for disposal as hazardous waste.
n. Wash hands thoroughly with soap and water.
o. Once a spill has been initially cleaned, have the area re-cleaned by housekeeping, janitorial staff, or environmental services per facility policy.

ASHP's Recommended Procedures for Spills in a C-PEC (ASHP, 2006)

a. Spills occurring in a C-PEC should be cleaned up immediately.
b. Obtain a spill kit if the volume of the spill exceeds 30mL or the contents of one drug vial or ampule.
c. Additional HD gloves should be worn to remove broken glass in a C-PEC. Care should be taken not to damage the fixed-glove assembly in a CACI.
d. Place glass fragments in the puncture resistant hazardous drug waste container.
e. Thoroughly clean and decontaminate the C-PEC. Clean and decontaminate the drain spillage trough located in the C-PEC if so equipped.
f. If the spill results in liquid being introduced onto the HEPA filter, or if powdered aerosol contaminates the "clean side" of the HEPA filter, use of the C-PEC should be suspended until the equipment has been decontaminated and the HEPA filter replaced.
g. Contaminated reusable items, for example glassware and scoops, should be cleaned with mild detergent and water after use. Items contaminated with HDs should be washed twice with detergent by a trained employee wearing personal protective equipment as described in the PPE section.

I. **Storage and Transport**

1. **Storage Areas**. Drug packages, bins, shelves, and storage areas for HDs should bear distinctive labels identifying those drugs as requiring special handling precautions (ASHP, 2006; USP 800, 2016). These warning labels should be applied to all HD containers, as well as the shelves and bins where these containers are permanently stored. Segregation of HD inventory from other drug inventory improves control and reduces the number of staff members potentially exposed to the danger (ASHP, 2006; USP 800, 2016). Access to areas where HDs are stored should be limited to authorized personnel with signs restricting entry. A list of drugs covered by HD policies and information on spill and emergency contact procedures should be posted or easily available to employees. HDs should be stored in an area with sufficient general exhaust ventilation to dilute and remove any airborne contaminants (NIOSH, 2004). Per USP, HDs should be stored separately from other inventory and the storage area should have sufficient general exhaust ventilation, at least 12 air changes per hour, to dilute and remove any airborne contaminants (USP 797, 2012). Many HDs have sufficient vapor pressures to allow volatilization at room temperature; thus, storage is preferably within a containment area such as a negative pressure room (USP 797, 2012). HD storage facilities should be designed to prevent containers from falling to the floor (e.g., bins with barrier fronts). HDs should be handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking and inventorying (USP 797, 2012). Warning labels and signs must be in English and in other languages if non-English readers work in those areas (HCS, 29 CFR 1910.1200(f)(2)). All personnel who work with or around HDs must be trained to appropriately perform their jobs using the established

precautions and required PPE (HCS, 29 CFR 1910.1200(h)).

2. **Receiving Damaged HD Packages**. The packaging (cartons, vials, ampules) of HDs should be properly labeled by the manufacturer or distributor with a distinctive identifier that notifies personnel receiving them to wear appropriate PPE during their handling (ASHP, 2006). Sealing these drugs in plastic bags at the distributor level provides an additional level of safety for workers who are required to unpack cartons. Visual examination of such cartons for outward signs of damage or breakage is an important first step in the receiving process (ASHP, 2006). Policies and procedures should be in place for handling damaged cartons or containers of HDs (e.g., returning the damaged goods to the distributor using appropriate containment techniques) (USP 800, 2016). These procedures should include the use of PPE (NIOSH, 2004), which must be supplied by the employer in accordance with OSHA's PPE standard [29 CFR 1910.132]. As there may be no ventilation protection in the area where damaged containers are handled, the use of complete PPE, including an NIOSH certified respirator, is recommended, and may be required by OSHA's standards (OSHA, 2011b; NIOSH, 2009; USP 800, 2016).
   Receiving personnel should be trained per the entity's SOP to process damaged packages. Appropriate PPE, including ASTM tested, powder-free chemotherapy gloves, must be worn when handling HDs. A spill kit should be accessible in the receiving area. Per USP <800>, the entity should enforce policies that include a tiered approach, including (USP 800, 2016):

   a. Visual examination of the shipping container for signs of damage or breakage;
   b. If shipping containers appear damaged, USP <800> recommends the following additional action (USP 800, 2016):
      - Don appropriate PPE;
      - Enact facility policies to determine whether the package will be sealed and returned to the supplier or whether it will be opened;
      - If the intent is to return the package to the supplier, enclose the package in an impervious container, label the outside container as "Hazardous", and contact the supplier for instructions.
   c. If the damaged package should be opened, USP recommends the following additional action (USP 800, 2016):
      - Seal the container in plastic or an impervious container and transport it to a Class I containment device for non-sterile HD compounding;
      - Place a plastic-backed preparation mat on the work surface of the Class I device;
      - Open the package and remove usable items;
      - Wipe the outside of the usable items with a disposable wipe;
      - Enclose the damaged item(s) in an impervious container, label the outside container as "Hazardous", and contact the supplier for instructions.
      - Clean the Class I device and discard the mat and cleaning disposables as hazardous waste.

3. **Labeling, Packaging and Transport**. USP <800> recommends standard operating procedures (SOPs) for the labeling, packaging and transport of HDs. The SOPs should address prevention of accidental exposures or spills, personnel training on response to exposure, and use of a spill kit (USP 800, 2016). Personnel should select and use packaging containers and materials that will maintain physical integrity, stability and sterility (if needed) of the HDs during transport (USP 800, 2016). All transport of HD packages should be done in a manner to reduce environmental contamination in the event of accidental dropping. HDs should be transported in containers that minimize the risk of breakage or leakage (USP 800, 2016). HD packages should be placed in sealed containers and labeled with a unique identifier (ASHP, 2006). Carts or other transport devices should be designed with guards to protect against falling and breakage. All individuals transporting HDs should have safety training that includes spill control and have spill kits immediately accessible (ASHP, 2006).
   USP <800> differentiates between transporting from receiving to the storage and compounding area, transporting from compounding to patient areas within the healthcare entity, and transporting from compounding to outside the healthcare entity (USP 800, 2016). USP <800> states that personnel transporting HDs should be trained and their competency documented. Drugs that have been identified as requiring HD handling precautions should be clearly labeled at all times during their transport (USP 800, 2016). Liquid HDs or any antineoplastic HD should not be transported in pneumatic tubes because of potential breakage and contamination (USP 800, 2016).

J. **Training**

As discussed below in more detail below in the section on Hazard Communication, OSHA's Hazard Communication Standard requires all employees to be trained in the hazards of HDs used their work area, the means used to detect HD presence or release, the procedures employers have implemented to protect employees from HDs, and the employer's hazard communication program [29 CFR 1910.1200(h)]. Staff who may be required to wear respirators must be fit tested and trained in accordance with OSHA's RPS (OSHA, 2011b; NIOSH, 2009). This section summarizes additional published guidance on training for workers in work area where HDs are present.

All staff who will be handling HDs should be fully trained in the receipt, storage, handling, and disposal of these drugs (USP 800, 2016). Compounding staff should be trained in the stringent aseptic and negative-pressure techniques necessary for working with sterile HDs. Once trained, staff should demonstrate competence by an objective method, and competency should be reassessed on a regular basis (ASHP, 2006; Harrison, 1996).

Per USP <800>, training should occur prior to preparing or handling HDs, and its effectiveness should be demonstrated by HD handling competencies (USP 800, 2016). Personnel competency should be reassessed every 12 months (USP 800, 2016). This training should include didactic overview of HDs, including mutagenic, teratogenic, and carcinogenic properties, and it should include ongoing training for each new HD (USP 800, 2016).

USP <800> states that compounding personnel of reproductive capability should confirm in writing that they understand the risks of handling HDs. The training should include at least the list of HDs; review of HD handling policies; proper use of PPE, equipment and devices; response to known or suspected HD exposure; spill management; proper disposal of HDs and trace contaminated equipment (USP 800, 2016).

NIOSH recommends that regular training reviews be conducted with all potentially exposed workers in workplaces where HDs are used. Seek ongoing input from workers who handle HDs and from other potentially exposed workers regarding the quality and effectiveness of the prevention program. Use this input from workers to provide the safest possible equipment and conditions for minimizing exposures. This approach is the only prudent public health approach, since safe concentrations for occupational exposure to HDs have not been conclusively determined (NIOSH, 2004).

NIOSH also recommends establishing procedures and providing training for handling HDs safely, cleaning up spills, and using all equipment and PPE properly. Inform workers about the location and proper use of spill kits. Make these kits available near all potential sources of exposure. In addition, establish procedures for cleaning and decontaminating work areas and for proper waste handling and disposal of all contaminated materials, including patient waste (NIOSH, 2004).

VI. MEDICAL SCREENING AND SURVEILLANCE

Like workers who are potentially exposed to other chemical hazards in healthcare, such as ethylene oxide and formaldehyde, those exposed to HDs, which include agents known to be human carcinogens, as well as those which are reproductive and developmentally toxic, should be monitored in a medical surveillance program (ASHP, 1990; ASHP, 2006; OSHA, 1995; ISOPP, 2007; Polovich, 2011; NIOSH, 2013). Medical screening and surveillance is one part of a comprehensive approach for minimizing hazardous exposures, which also includes training, engineering and work practice controls, and use of PPE. The purpose of screening is to identify the earliest reversible biologic effects so that exposure can be reduced or eliminated before the employee sustains irreversible harm. The occurrence of exposure-related disease or other adverse health effects should prompt immediate reevaluation of primary preventive measures (e.g., engineering controls, work practices, and use of PPE). Separately, OSHA views surveillance as the formal evaluation of groups of workers; in this manner, medical surveillance acts as a check on the efficiency and appropriateness of controls already in use (OSHA, 2015).

For detection and control of work related health effects, screening is typically performed at specific intervals:

- Before job placement;
- Periodically during employment;
- Following acute exposures; and
- At the time of job termination or transfer (exit examination).

In addition to review of individual worker results obtained during a screening, the data obtained should be analyzed in a systematic fashion to allow early detection of disease patterns in groups of workers. Such surveillance requires systematic collection of information and, usually, some form of electronic data management system, ideally with exposure tracking.

A. **Pre-Placement Medical Examinations**
    1. As is the case for employees who work with other known carcinogens and highly toxic agents, those handling HDs in the workplace should have an initial evaluation consisting of a medical and work history, a baseline physical exam, and laboratory studies. To assist the healthcare provider in making their assessment, information provided by the employer to the examining physician should include:
        a. A description of the employee's duties as they relate to the employee's exposure.
        b. The employee's exposure levels or anticipated exposure levels, which may include estimates of frequency and/or duration of HD handling.
        c. A description of any personal protective equipment used or to be used.
        d. Information from previous medical examinations of the employee.
    2. The history details the individual's medical and reproductive experience with emphasis on potential risk factors, such as past hematopoietic, malignant, or hepatic disorders. It should focus on the known target organs of commonly used HDs (skin, kidney, bladder, hematopoetic) (Polovich, 2011). A complete occupational history, with information on the extent of past exposures (including environmental sampling

data, if possible) and use of protective equipment, is also obtained. Estimates of worker exposure, in the absence of environmental sampling data, may include:

a. Records of drugs and quantities handled;
b. Hours spent handling these drugs per week;
c. Number of preparations/administrations per week; and
d. Over-exposure events.

3. An initial physical examination is performed, which focuses on the targeted organ systems of commonly used drugs: the skin, mucous membranes, and lymphatic systems. Other organ systems suggested from the medical history should also be assessed.
4. The most valuable test in a laboratory assessment is a complete blood count with differential. This allows for a determination of any pre-existing blood condition that may place the worker at increased risk when handling HDs. Other laboratory testing (liver function tests, blood urea nitrogen, creatinine, and a urine dipstick for blood) may sometimes be appropriate (Polovich, 2011). However, these tests should be conducted only at the discretion of the physician, as a function of the medical history obtained, or as part of a formal surveillance program with well-defined goals.
5. Due to poor reproducibility, inter-individual variability, and difficulty in interpreting individual results, measures of genetic effects (i.e., chromosomal aberrations, micronuclei, or other markers of genotoxic exposure) are not recommended in routine surveillance.
6. Biological monitoring, i.e., the measure of a specific agent or its metabolite in a body fluid (such as a urine 5-FU level), is also not recommended for a screening protocol on a routine basis due to the large number of agents an employee handles on a given work shift.
7. An evaluation for respirator use must be performed in accordance with the RPS [29 CFR 1910.134], if the employee will wear a respirator (for example, during cleaning of the BSC, or in a larger spill response) (OSHA, 2011b).

B. **Periodic Medical Examinations**

The medical, reproductive, and exposure history should be updated on a periodic basis, every one to three years, although many employees are reluctant to divulge details of reproductive history. Another approach is to administer the history annually but use the health and exposure history responses to guide the interval for physical exam and laboratory studies. A primary purpose of the examinations is to explore adherence and identify obstacles to good work practices.

The interval between exams of individual workers depends on the opportunity for exposure, the duration and intensity of exposure, and (possibly) the age of the worker. The worker's health and exposure history may also influence the decision of the occupational medicine physician. Careful updating of an individual's routine drug handling history and any acute accidental exposures are made. The physical examination and laboratory studies follow the format outlined in the pre-placement examination (McDiarmid, 1990). The periodic examination may also be incorporated into an existing, broader, periodic health assessment for an organization's healthcare workers rather than function as a "stand-alone" program.

C. **Post-exposure Examinations**

Post-exposure evaluations are tailored to the type of exposure (e.g., spills or needle sticks from syringes containing HDs). An assessment of the extent of exposure is made and included in the confidential database (discussed below) and in an incident report. The physical examination focuses on the involved area of the body, as well as other organ systems commonly affected (i.e., for a spill, the skin and mucous membranes of the affected area; for aerosolized HDs, the pulmonary system). Treatment and laboratory studies follow as indicated and should be guided by emergency protocols.

The following are general suggestions for acute exposure management (Polovich, 2011):

1. Removal of contaminated clothes, stockings, etc.
2. Decontamination based on SDS for the agent of exposure.
3. Visit to employee health professional to document and assure complete decontamination.
4. Physical examination for acute findings at the site of exposure (e.g., skin or the pulmonary system for an inhalation exposure). Other aspects of the exam focus on target organs for drug(s) involved.
5. Blood for baseline counts and archiving (spin and freeze) after major exposures.
6. The employee health clinician can determine appropriate follow up intervals based on drug half-life and, for example, expected timing of blood count nadir (low point).
7. Counseling should be provided to the individual as appropriate to the situation, and may include a discussion to defer attempts at conceiving for a period of time, what symptoms to report, and recommended medical follow up.

D. **Exit Examinations**

The exit examination completes the information on the employee's medical, reproductive, and exposure histories. Examination and laboratory evaluation should be guided by the individual's history of exposures and follow the

outline of the periodic evaluation.

E. **Exposure-Health Outcome Linkage**
Exposure assessment of all employees who have worked with HDs is important, and the maintenance of existing records is required by 29 CFR 1910.1020 (OSHA, 2011a). The use of previously outlined exposure estimates is acceptable, although actual environmental or employee monitoring data are preferable, when available. Details of the use of personal protective equipment and engineering controls present should be included, as well as maintenance of a confidential database with information regarding the individual's medical and reproductive history, with linkage to exposure information to facilitate epidemiologic review.

F. **Reproductive Issues**
The examining physician should consider the reproductive status of employees and inform them regarding relevant reproductive issues. The reproductive toxicity of HDs should be carefully explained to all workers who will be exposed to these chemicals, and providing this explanation is required for those chemicals that are covered by the HCS. While controversy previously existed as to the degree of hazard that handling HDs presented to pregnant HCWs or those attempting to conceive, data published recently have shown excess reproductive loss in those workers, even with the use of BSCs as mentioned above (Peelen, 1999). Moreover, the most recent U.S. study of nurses working as recently as 2001 (that is, many years after OSHA and professional organizations published safe handling guidance, and presumably influenced safety procedures) documented statistically significant excesses of spontaneous abortion in nurses with first trimester HD exposure (Lawson, 2012).

Due to the reproductive and developmental toxicity profile of many HDs, professional organizations whose members handle HDs and NIOSH now have proposed providing employees who are pregnant or actively attempting to conceive with the option of alternative work assignments that do not involve HD handling (Polovich, 2011; ASHP, 2006; ISOPP, 2007, NIOSH 2015). Also, because many of these drugs are known to enter breast milk, and possess hazard warnings from FDA (FDA, 1997), breast-feeding workers should also have alternative work assignment options. Indeed, NIOSH has recently issued a publication on this topic with suggested implementation approaches (Connor, 2014). Importantly, some HDs possess male mediated reproductive toxicity and, therefore, alternative duty should also be extended to male employees, especially those with a history of inability to conceive (HSE, 2003). The American College of Occupational and Environmental Medicine also suggests that a risk assessment be made and alternative reassignment be considered for HD handlers during these vulnerable periods (ACOEM, 2011).

Organizations should establish a mechanism by which those workers who are actively trying to conceive, are pregnant, or are breast-feeding can request alternative duty or protective reassignment. In European countries and some Canadian provinces where these programs already exist, the working pregnant woman initiates the request (a "notification" of pregnancy) and occupational health physicians validate the occupational risk (Taskinen, 1995; Plante, 1998; Romito, 1992). Discussions with large health care systems in the U.S. have identified that many have established programs but not developed written policies. Implementing such mechanisms generally required collaboration between the employee health unit, human resources personnel, the specific service (nursing, pharmacy), and the worker. Information about reproductive risks of the job and the procedures by which alternative duty can be requested can be part of Hazard Communication training for workers. The healthcare worker's private physician may also play a role in providing "validation" of the worker's request for alternative duty assignment. This may be sought by the employer as a matter of policy, or may be provided by the worker when a personal medical risk factor places them at additional risk of health harm from work exposure. It is important, however, that requests for this protective, alternative reassignment should ideally be made prior to pregnancy to avoid exposure during the vulnerable first months of pregnancy when early stages of development are occurring. Thus, a discussion of alternative duty availability and the administrative mechanisms to request it should be part of the hazard communication discussion. Ongoing review of actions taken should be performed on a regular basis.

VII. HAZARD COMMUNICATION

This paragraph is for informational purposes only and is not a substitute for the requirements of the Hazard Communication Standard (HCS) [29 CFR 1910.1200] (OSHA, 2012b). Note that the requirements of the HCS are superseded by those of OSHA's Laboratory Standard, 29 CFR 1910.1450, when an employer is engaged in the "laboratory use of hazardous chemicals" (i.e., use of relatively small quantities of hazardous chemicals on a non-production basis), but this document focuses on the HCS requirements that apply to most healthcare employers.

A. **Introduction**
1. The HCS is, and always has been, applicable to HDs. Now aligned with the United Nations Globally Harmonized System (GHS) of Classification and Labelling of Chemicals, the updated HCS issued in 2012 describes a series of labeling and hazard training requirements for employers in settings where hazardous chemicals are used.
2. According to the HCS, a "hazardous chemical" means any chemical which is classified as a physical hazard or a health hazard, a simple asphyxiant, combustible dust, pyrophoric gas, or hazard not otherwise

classified.

"Health hazard" means a chemical which is classified as posing one of the following hazardous effects: acute toxicity (any route of exposure); skin corrosion or irritation; serious eye damage or eye irritation; respiratory or skin sensitization; germ cell mutagenicity; carcinogenicity; reproductive toxicity; specific target organ toxicity (single or repeated exposure); or aspiration hazard. The criteria for determining whether a chemical is classified as a health hazard are detailed in Appendix A of the HCS -- Health Hazard Criteria.

"Physical hazard" means a chemical that is classified as posing one of the following hazardous effects: explosive; flammable (gases, aerosols, liquids, or solids); oxidizer (liquid, solid or gas); self-reactive; pyrophoric (liquid or solid); self-heating; organic peroxide; corrosive to metal; gas under pressure; or in contact with water emits flammable gas. See Appendix B of the HCS -- Physical Hazard Criteria.

3. Both human and animal data are to be used in this determination and the appendices listed above describe in detail the approach to classification and sources of data used to perform the classification of covered substances. Generally, HDs would be included under the "health hazard" classification, due to the germ cell mutagenicity, carcinogenicity (known or presumed), and reproductive and developmental toxicity of many of the agents. However, some agents, (e.g., Adriamycin) can be acutely corrosive in a single exposure (Chabner and Longo, 2010).
4. The HCS requires that drugs posing a health hazard (with some limited exception of those in solid, final forms for direct administration to the patient, i.e., tablets or pills) be included on lists of hazardous chemicals to which employees are exposed.
5. SDSs are required to be prepared and transported with the initial shipment of all hazardous chemicals, including covered drugs and pharmaceutical products. This excludes drugs defined by the Federal Food, Drug, and Cosmetic Act that are in solid, final form for direct administration to the patient (e.g. tablets, pills, or capsules), or that are packaged for sale to consumers in a retail establishment. Package inserts and the Physician's Desk Reference are not acceptable in lieu of requirements of SDSs under the HCS.
6. It is important to note that while tablets may be exempt from the HCS, many HDs in tablet form also are manufactured in another formulation, such as liquid or concentrated powder, and require reconstitution for intravenous therapy or for injection; as such, those formulations must conform to the HCS. Also, the toxic properties of drugs in tablet form are the same as when in liquid or powder form, and tablets can be especially hazardous when they are counted out from a bulk container in a way that generates drug powder clouds. Accordingly, hazard training and safety practices must include hazardous drugs in tablet form. OSHA issued a letter of interpretation regarding this topic in 2004, a quote from which follows below:
"...*The intent of the HCS is to protect employees from hazardous exposures. In the situation you described, employees are counting tablets, pills, and capsules in preparation for packaging and are, therefore, handling the drugs in a manner that would potentially result in exposure to the dust from crumbled pills, tablets, or capsules. Where there is potential for exposure, employees are covered by the standard and have the right to know the hazards of the chemicals to which they are exposed. The same principle applies to the processing of any liquids, injections, gels, and ointments, for which there is no exemption under the HCS.*"

(https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=INTERPRETATIONS&p_id=25054.)

B. **Written Hazard Communication Program**

1. Employers shall develop, implement, and maintain at the workplace a written hazard communication program for employees handling or otherwise exposed to chemicals, including drugs that represent a health hazard to employees. The written program will describe how the criteria specified in the HCS concerning labels and other forms of warning, SDSs, and employee information and training will be met. The program must also include the following:
    a. A list of the covered HDs known to be present using a product identifier that is referenced on the appropriate SDS.
    b. The methods the employer will use to inform employees of the hazards of non-routine tasks in their work areas.
    c. The methods the employer will use to inform employees of other hazards at the work site.
2. The employer shall make the written hazard communication program available, upon request, to employees, their designated representatives, and the Assistant Secretary of OSHA in accordance with requirements of the HCS.
3. In accordance with requirements in the HCS, the employer must maintain SDSs accessible to employees for all HDs used in the facility. Specifics regarding SDS content are contained in the HCS. Essential information includes: health hazards, primary exposure routes, carcinogenic evaluations, acute exposure treatment, chemical inactivators, solubility, stability, volatility, PPE required, and spill procedures for each covered HD. SDSs shall also be made readily available upon request to employees, their designated representatives, or the Assistant Secretary of OSHA.

VIII. TRAINING AND INFORMATION DISSEMINATION

A. **Discussion**

All staff handling HDs must be fully trained in the receipt, storage, handling, and disposal of these drugs.

1. In compliance with the HCS [29 CFR 1910.1200] (OSHA, 2012b), all personnel involved in any aspect of the handling of HDs (physicians, nurses, nursing assistants, pharmacists, pharmacy technicians, housekeepers, and other employees involved in receiving, transport, storage, compounding, administering, waste handling and other forms of handling) must receive information and training to apprise them of the hazards of HDs present in the work area. Such information shall be provided by the employer at the time of an employee's initial assignment to a work area where HDs are present, and prior to assignments involving HDs. Information about new HDs must be provided when they are introduced into the work area.
2. According to USP, HD compounding personnel of reproductive capability should confirm in writing that they understand the risks of handling hazardous drugs (USP 797, 2012; USP 800, 2016).
3. NIOSH (NIOSH, 2004) and ASHP (ASHP, 2006) recommend that knowledge and competence of personnel be evaluated after the first orientation or training session, and then on a regular basis. Evaluation may involve direct observation of an individual's performance on the job. Competency programs for evaluating safe handling technique have been established using non-toxic products, such as fluorescein, which fluoresces under ultraviolet light, or red dye, which is visible under normal light. (Harrison, 1996). Non-HD solutions should be used for evaluation of preparation technique.
4. Per USP, training should occur prior to preparing or handling HDs, and its effectiveness should be verified by testing specific HD preparation techniques. Such verification should be documented for each person at least annually. This training should include didactic overview of hazardous drugs, including mutagenic, teratogenic, and carcinogenic properties, and it should include ongoing training for each new HD (USP 797, 2012; USP 800, 2016).
5. USP <797> states that training for compounding personnel should include at least safe aseptic manipulation practices; negative pressure techniques when utilizing a C-PEC and correct use of CSTD devices; containment, cleanup, and disposal procedures for breakages and spills; and treatment of personnel contact and inhalation exposure (USP 797, 2012).

B. **Employee Information**

Employees must be informed of the requirements of the Hazard Communication Standard (HCS) [29 CFR 1910.1200] (OSHA, 2012b) as follows:

1. Any operation/procedure in their work area where drugs that present a hazard are present;
2. The location and availability of the written hazard communication program;
3. The location and availability of the list(s) identifying HDs present in the work area; and
4. The location and availability of safety data sheets for all HDs in the work area.

C. **Employee Training**

Employee training must conform to the requirements of the HCS and other relevant OSHA requirements, such as the PPE standard [29 CFR 1910.132]. Training required under the HCS must include all employees potentially exposed to these agents, which includes not only healthcare professional staff, but also physical plant, maintenance, or others who potentially come into contact with the HDs.

Staff who may be required to wear respirators must be fit tested and trained to all OSHA respirator requirements (OSHA's RPS, 29 CFR 1910.134; NIOSH, 2009). Training should include at least the following elements:

1. The properties of the HDs located in the work area; (OSHA, 2011b)
2. The techniques and safe handling practices that have been implemented in the work area to protect employees from exposure to HDs, such as identification of drugs that should be handled as hazardous, appropriate work practices, safety equipment, and PPE to be used, and emergency procedures for spills or employee exposure; (OSHA, 2012b; NIOSH, 2009)
3. The details of the hazard communication program developed by the employer, including an explanation of the labeling and HD identification system used by the employer, the SDSs, and how employees can obtain and use the appropriate hazard information; (OSHA, 2012b)
4. Proper use of safety equipment such as biological safety cabinets, compounding aseptic containment isolators, and closed system transfer devices; (OSHA, 2012b)
5. Proper donning and doffing of PPE; and (OSHA, 2011)
6. Drug preparation, administration, disposal and spill management procedures that minimize worker and environmental exposure (USP 800, 2016).

IX. RECORDKEEPING

Employee exposure records, including workplace monitoring, biological monitoring, and SDSs, as well as employee medical records related to drugs posing a health hazard, must be maintained and access to them provided to employees in

accordance with 29 CFR 1910.1020 (OSHA, 2011a). That is, records created in connection with HD handling shall be kept, transferred, and made available for at least 30 years, and medical records shall be kept for the duration of employment plus 30 years.

In addition, the HCS does not require training documentation, but sound practice dictates that training records should be created, and include the following information:

- Dates of the training sessions;
- Contents or a summary of the training sessions;
- Names and qualifications of the persons conducting the training; and
- Names and job titles of all persons attending the training sessions.

It is wise to maintain training records for some period of time from the date on which the training occurred but the HCS no longer requires such retention.

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GLOSSARY

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

Alternative Duty - Performance of other tasks that does not include the direct handling of HDs.

Ante Area - Transition area between the general area and the segregated area containing the CPEC. Hand-hygiene, garbing, staging of components, order entry and other particle-generating activities are performed in the ante area. For sterile compounding, the ante area should meet ISO 7 characteristics and also provides assurance that pressure relationships between rooms are constantly maintained (USP 797, 2012; USP 800, 2016).

Batch - More than one unit of a compounded preparation that is intended to have uniform character and quality within specified limits, prepared in a single process, and completed during the same and limited time period.

Beyond-use date - The date or time after which a compounded preparation should not be stored or transported. See Pharmaceutical Compounding - Non-sterile Preparations USP <795> and Pharmaceutical Compounding - Sterile Preparations USP <797> for additional details.

Biohazard - A biological agent, such as a virus or a condition that constitutes a threat to humans.

Biological Safety Cabinet (BSC) - A ventilated cabinet for CSPs, personnel, product, preparation, and environmental protection having an open front with inward airflow for personnel protection, downward high efficiency particulate air (HEPA) filtered laminar airflow for product and preparation protection, and HEPA filtered exhausted air appropriately removed by properly designed building ventilation for environmental protection.

Buffer Area - Part of the compounding area where the primary containment engineering control (CPEC) is physically located. Activities that occur in this area are limited to the preparation and staging of components and supplies used when compounding HDs.

Chemotherapy glove - A medical glove that meets the American Society for Testing and Materials (ASTM) Standard Practice (D6978-05(2013)) for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs.

Cleanroom - A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel are not exceeded for a specified cleanliness class (See USP 36, Chapter <1116>, "Microbiological Control and Monitoring of Aseptic Processing Environments," and also the definition of "Buffer Area").

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

Closed system transfer device (CSTD) - A drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapors concentrations outside the system.

Compounded Preparation - A sterile or non-sterile drug or nutrient preparation that is compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber.

Compounding personnel - Individuals who participate in the compounding process who are competent and knowledgeable, and responsible for the preparation of HDs, using information from Chapter <797> and <800>, the entity's SOPs, and instructions from the compounding supervisor.

Compounding supervisor - The individual who is responsible for developing and implementing appropriate procedures, overseeing facility compliance with Chapter <797> and <800> and other applicable laws, regulations, and standards, ensuring competency of personnel, and assuring environmental control of the compounding areas.

Compounding Aseptic Containment Isolator (CACI) - A compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations (See USP 797, 2012). Air exchanged from the surrounding environment should not occur unless it is first passed through a microbially retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Exhaust air from the isolator should be appropriately removed by properly designed building ventilation.

Compounding Aseptic Isolator (CAI) - A primary engineering control designed for use for non-HDs. A laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) should not be used for the compounding of an antineoplastic HD (USP 800, 2016).

Containment Primary Engineering Control (C-PEC) - A ventilated cabinet, designed to establish primary containment and to minimize worker exposures by controlling emissions of airborne contaminants through the following techniques:

- The full or partial enclosure of a potential contaminant source;
- The use of airflow capture velocities to capture and remove airborne contaminants near their point of generation; and
- The use of air pressure relationships that define the direction of airflow into the cabinet.

A C-PEC may be further defined by its task or use and have other characteristics such as providing ISO 5 air quality in an engineering control used for sterile compounding. Such devices for use with HDs include, but may not be limited to, Class I BSCs (for non-sterile agents only), Class II BSCs, and compounding aseptic containment isolators (CACIs).

C-PECs used for sterile compounding should have ISO 5 air quality. C-PECs used for non-sterile compounding do not need to have ISO 5 air quality.

Containment Secondary Engineering Controls - The design and operation of the room in which the C-PEC is placed. Restricted access, barriers, special construction technique, ventilation and room pressurization are components of the secondary control strategy.

Containment Segregated Compounding Area (CSCA) - A segregated room that is restricted to preparing low-risk HD CSPs with a 12-hour or less BUD or a segregated room that is restricted to preparing non-sterile HDs. Such area should contain a Containment Primary Engineering Control that meets the specifications of USP <797>.

Containment Supplemental Engineering Control - Adjunct controls used in concurrence with Primary and Secondary Control Strategies. Supplemental controls offer additional levels of protection and may facilitate enhanced occupational protection as the HD is handled outside of the protective controls of primary and secondary control environments.

Containment Ventilated Enclosure (CVE) - A C-PEC used for manipulation of non-sterile HDs.

Controlled Environment Testing Association (CETA). CETA, the Controlled Environment Testing Association, is a non-profit trade association devoted to promoting and developing quality assurance within the controlled environment testing industry. http://cetainternational.org/.

Deactivation - Treatment of a hazardous drug with another chemical, heat, ultraviolet lights, or other agent to create a less hazardous agent.

D**econtamination** - Inactivation, neutralization, or removal of HDs, usually by chemical means.

Disinfectant - A chemical agent that destroys or inhibits the growth of microorganisms that cause disease.

Engineering Control - Primary, secondary, and supplemental devices designed to eliminate or reduce worker exposure to a

chemical, biological, radiological, ergonomic, or physical hazard. Examples include laboratory fume hoods, retracting syringe needles, sound-dampening materials to reduce noise levels, safety interlocks, and radiation shielding.

Entity - A pharmacy, hospital, physician office, clinic, veterinary office, or other location wherever HDs are procured, stored, prepared, dispensed, and distributed to a final user or healthcare personnel who will administer the HD.

Expiration date/expiry date -The expiration date identifies the time during which the article may be expected to meet the requirements of the compendia monograph, provided it is kept under the prescribed storage conditions (See USP 34, Labeling in General Notices and Requirements, Section 10.40.100).

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

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

Hazard Communication Standard (HCS) - A U.S. government regulation designed to ensure that the hazards of all chemicals produced or imported are classified, and that information concerning the classified hazards is transmitted to employers and employees [29 CFR 1910.1200(a)(1)].

Hazardous Drug (HD) - Any drug identified by at least one of the following six criteria:

- Carcinogenicity;
- Teratogenicity or developmental toxicity;
- Reproductive toxicity in humans;
- Organ toxicity at low doses in humans or animals;
- Genotoxicity; and
- New drugs that mimic existing HDs in structure or toxicity.

Laminar Air Flow Workbench (LAFW) - A primary engineering control designed for use for compounding non-HDs. A laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) should not be used for the compounding of an antineoplastic HD (USP 800, 2016).

Labeling - A term that designates all labels and other written, printed, or graphic matter on an immediate container of an article or preparation or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling on the immediate container [See General Notices and Requirements, 21 U.S.C. 321 (k) and (m)].

Negative Pressure Room - A room that is at a lower pressure than the adjacent spaces and, therefore, the net flow of air is into the room.

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

Pharmaceutical product - A commercially manufactured drug or nutrient that has been evaluated for safety and efficacy by the FDA. Products are accompanied by full prescribing information, which is commonly known as the FDA approved manufacturer's labeling or product package insert.

Positive Pressure Room - A room that is at a higher pressure than the adjacent spaces and, therefore, the net flow of air is out of the room.

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

Spill Kit - A container of supplies, warning signage, and related materials used to contain the spill of a HD.

Sterilization - A process that destroys or eliminates all forms of microbial life (including spores) and is carried out in healthcare facilities by physical or chemical methods. Steam under pressure, dry heat, ethylene oxide gas, hydrogen peroxide gas plasma, and liquid chemicals are the principal sterilizing agents used in healthcare facilities.

XI. RESOURCES

American College of Occupational and Environmental Medicine (ACOEM)

Task Force on Reproductive Toxicology. Reproductive and developmental hazard management guidance. April 26, 2011.

http://www.acoem.org/Reproductive_Developmental_Hazard_Management.aspx

American Society of Health-System Pharmacists (ASHP)

ASHP guidelines on handling hazardous drugs. In: Drug distribution and control: preparation and handling—guidelines. Bethesda, MD: ASHP; 2006. p. 95-114.

http://www.ashp.org/DocLibrary/BestPractices/PrepGdlHazDrugs.aspx

The Controlled Environment Testing Association (CETA) (http://www.cetainternational.org/)

CETA application guide for the use of surface decontaminants in biosafety cabinets CAG-004-2007. January 7, 2007.

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http://www.cetainternational.org/reference/CETACompoundingIsolatorTestingGuide2006.pdf.

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Centers for Disease Control

Centers for Disease Control and Prevention. Biosafety in microbiological and biomedical laboratories (BMBL) 5th edition. Department of Health and Human Services. December 2009.

Centers for Disease Control and Prevention. Hand hygiene in healthcare settings. Department of Health and Human Services. 2013.

Department of the Army

Occupational Health and Industrial Hygiene Guidance for the Management, Use and Disposal of Hazardous Drugs

http://armypubs.army.mil/med/DR_pubs/dr_a/pdf/tbmed515.pdf

Environmental Protection Agency (EPA)

EPA Inaction in Identifying Hazardous Pharmaceuticals May Result in Unsafe Disposal

Emerging EPA Regulations of Pharmaceuticals in the Environment

International Society of Oncology Pharmacy Practitioners Standards

International Society of Oncology Pharmacy Practitioners Standards Committee. ISOPP standards of practice. Safe handling of cytotoxics. J Oncol Pharm Practice 2007:13 Suppl:1-81.

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