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# Hazardous Drug Surface Contamination

Guidance Document

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## FOREWORD

The United States Pharmacopeia (USP) Chapter <800> is focused on the implementation of systems that ensure the protection of healthcare employees and their work environments where hazardous drugs (HDs) are handled. Prior to the publication of USP <800>, USP Chapter <797> included a small section dedicated to the preparation of HDs. USP <797> outlines the minimum standards for the preparation of compounded aseptic sterile preparations (CSPs) to minimize patient harm. All requirements outlined in USP <797> regarding the preparation of sterile products must also be followed when preparing HDs under USP <800>. Nonsterile compounding preparations of HDs must follow USP <795> and USP <800>. Patients are treated with HDs to effectively address their illness and improve their health outcomes. This can be done with minimal impact on other people or the environment.

The goal of USP <800> is to ensure that HDs are handled, stored, prepared, and administered to patients while controlling residual contamination of the environment and unintended personnel exposure. One of the primary focus areas of USP <800> stems from the complex nature of compounding HDs. Environmental sampling has widely been used to evaluate a variety of surfaces in occupational environments to identify unsafe conditions and implement administrative and engineering controls. In the context of USP <800>, HD surface sampling is a tool to evaluate the effectiveness of containment strategies and deactivation/decontamination processes as well as the presence of HD contamination in healthcare environments.

This guidance document aims to provide technical clarity and best practice approaches to effectively evaluate the potential for HD surface contamination in healthcare environments. The guidance document will also provide insights from primary literature to

help practitioners plan and execute an effective surface contamination sampling program and understanding sampling program results through the lens of risk assessment.

While surface sampling for HDs is a recommended (but not a required) element of USP <800>, it is a critical component of a comprehensive HD management program. It enables organizations to assess the effectiveness of their HD handling protocols, control systems and cleaning, conducting HD surface sampling is often met with confusion in determining where and how often to sample as well as how to interpret results. HD surface sampling is most effective in helping reduce environmental contamination when a strategy is followed consistent with the stated program goals.

HDs are handled throughout a healthcare organization and in several other settings, including independent compounding pharmacies, 503Bs, infusion centers, and potentially in delivery of home health. Professionals tasked with implementing a sampling program need to consider the following:

- Is there an acceptable surface limit (ASL) for comparison to determine if the contamination level is acceptable?
- Should sampling be conducted by a health and safety professional, or could this be accomplished by someone from pharmacy or nursing?
- What credentials or training are required to perform sampling and interpret sample results?
- Which HDs should be monitored?
- How will the sampling be conducted?



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- Is there a commercial analytical method available?
  - Are there multiple sampling kits available?
  - Which sampling kit and analytical method is appropriate for the needs of the organization?
  - Should the organization utilize both quantitative and qualitative assays? And if so, when should one be used over the other?
- A facility may handle many different types of HDs. Should they sample every type of HD or a strategic few?
- What locations and how many samples should be taken to provide the most value for a comprehensive program?
- What should be done with the results?

The Hazardous Drug project team (under the auspices of the Healthcare Working Group) developed these guidelines to provide answers to these questions for healthcare and compounding pharmacy organizations. Comments and questions should be directed to [infonet@aiha.org](mailto:infonet@aiha.org).



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HEALTHIER WORKPLACES | A HEALTHIER WORLD

Table of Contents

**Section 1. Introduction..... 10**

**Section 2. Rules and Regulations Overview ..... 12**

**Section 3. Hazard Characterization and Developing Acceptable Surface Levels (ASLs) ..... 15**

    Hazard Characterization ..... 15

    Development of ASLs..... 17

    Dermal Absorption Potential ..... 19

    Estradiol Example ..... 24

    Warfarin Example ..... 24

    5-Fluorouracil Example..... 25

**Section 4. Exposure Potential for Healthcare Workers – A Risk Assessment Approach..... 26**

    Risk Assessment - <800> Assessment of Risk..... 27

    HD Handling Tasks ..... 27

    HD Aerosolization and HD Surface Contamination ..... 29

    HD Surface Contamination and Dermal Exposure Potential ..... 29

    Control Systems - Hierarchy of Controls ..... 30

    Elimination ..... 30

    Substitution ..... 32

    Engineering Controls, Administrative Controls, and Personal Protective Equipment (PPE)..... 32

**Section 5. Sampling and Analysis of HDs in Healthcare Settings..... 34**

    Introduction..... 34

    HD Surface Sampling Methodologies ..... 34

    The Role of HD Surface Sampling in USP <800> and Healthcare Worker Safety ..... 35

    USP <800> Sample Collection ..... 35

    USP <800> Sample Quantitative Analysis..... 36

    Laboratory Services for USP <800> Quantitative Analysis ..... 36

**Section 6. HD Surface Levels – Data Interpretation – Large Dataset Research Findings..... 40**

    Health-Based Acceptable Surface Limits (ASLs) vs. Statistically-Based Hygiene Guidance Values (HGVs)..... 41

    Implementing a Continuous Improvement Plan Using HGVs or ASLs ..... 43

    Limitations of HD Surface Sampling ..... 44

**Section 7. A Comprehensive HD Surface Sampling Strategy ..... 46**

    Objectives of the HD Surface Sampling ..... 46

    Roles and Responsibilities..... 47

    HDs to be Analyzed ..... 48

    Selection of a HD Surface Limit or Method of Data Interpretation ..... 48

    Sampling and Analytical Methods ..... 48

    Where to Sample, How Many Samples, and When to Sample..... 49

    Interpretation ..... 49

    Documentation and Communication of Results.... 49

    Frequency of Surveillance Sampling ..... 49

**Appendix A. NIOSH Hazardous Drug Definition ..... 50**

**Appendix B. Glossary..... 52**

**Appendix C. Toxicology Principles..... 58**

    Route of Exposure ..... 58

    Worker Exposure ..... 59

**Appendix D. Hazards of Drugs – Potency, Adverse Effects, Identifying Mechanism/Indication/Category.. 61**

    Genotoxicity ..... 62

    Carcinogenicity ..... 63

    Developmental and Reproductive Toxicities (DART) ..... 63

    Other Hazards ..... 64

**References..... 65**



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## Background Hazardous Drug Program/USP <800> Standard

Despite being published in 2016 and first becoming official in 2019, USP <800> is now official and will become “compendially applicable and enforceable” on November 1, 2023. The previously official versions of USP chapters <797> and <795> were published in 2008 and 2014, respectively, and do not reference <800>. USP Chapter <797> outlines the minimum standards and requirements for compounding sterile preparations in all practice settings where sterile preparations for both human and animal use are prepared. USP Chapter <795> is focused on the minimum standards and requirements for compounding nonsterile preparations for both human and animal use. On November 1, 2022, revised chapters of <795> and <797> were published, which directly reference chapter <800>. On November 1, 2023, chapters <795> and <797> become official and enforceable,

USP chapter <800> will also become an enforceable standard. USP <800> is federally enforceable only to the extent to which USP <795> and <797> apply.

### USP <800> Hazardous Drug Program

#### Elements of a Hazardous Drug Program

Although this document focuses on HD surface sampling, that is only one component of a comprehensive HD management program. A comprehensive HD Management program, according to USP <800>, includes these minimum elements:

- A List of Hazardous Drugs (HDs)
- Facility and Engineering Controls
- Competent Personnel

## Timeline for USP Chapter <797> & <800> Revisions

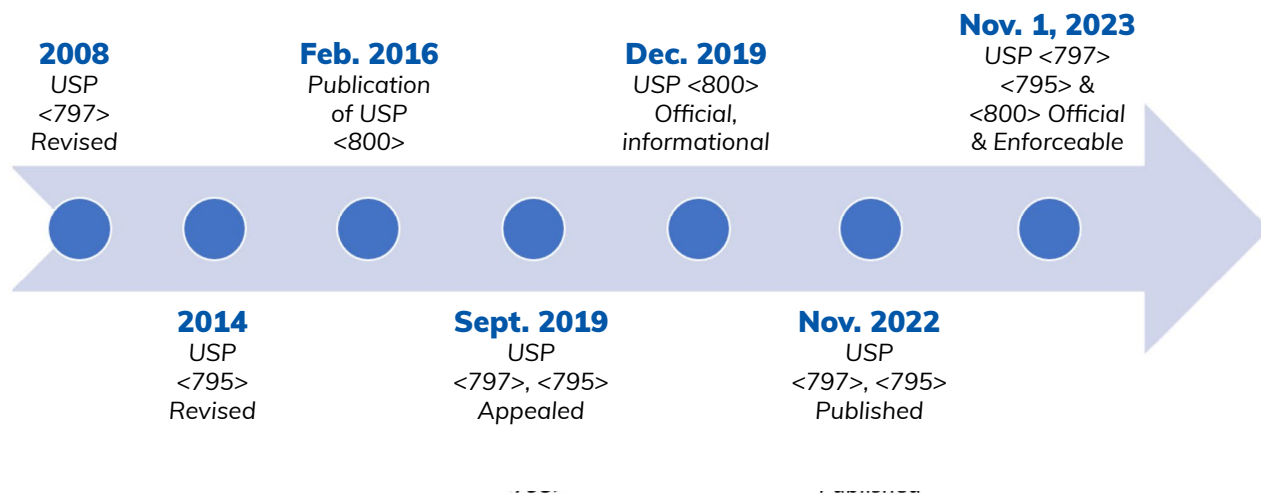


Figure 1. Timeline for USP Chapter Revisions by A. Snow and E. Strauss, 2023.



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- Safe Work Practices and Standard Operating Procedures
- Proper use of appropriate Personal Protective Equipment (PPE)
- Policies for HD waste segregation and disposal

Implementing all of these elements into an HD Management program can help effectively and safely deliver HDs to patients while minimizing worker exposure to HDs and maintaining the integrity of the drugs.

The Occupational Health and Safety Administration (OSHA) is responsible for protecting worker health and safety in nearly all private and public workplaces in the United States. Federal OSHA does not have a specific HD regulation. However, OSHA has developed a guidance document for HDs. Hazardous Drugs - Overview | Occupational Safety and Health Administration ([osha.gov](https://www.osha.gov)) OSHA does have the ability to cite under the General Duty Clause if able to demonstrate the presence of a recognized hazard and the potential for exposure, which could result in citations and/or monetary fines. Federal OSHA may also focus on the effectiveness of a hazard communication program (29 CFR 1910.1200) and personal protective equipment (PPE) program (29 CFR 1910.132) when addressing HDs in a workplace and pursue related citations. There are a few state plans with HD rules. For example, North Carolina NCGS 95-156 handling of dangerous antineoplastics- 13 NCAC 07G .0101 – handling of antineoplastic agents. However, even if there is a state OSHA rule, HD surface sampling is most likely a recommended rather than a required activity.

Engineering controls are one of the cornerstones of a HD management program. Operations and maintenance (O&M) facility engineering controls include collaboration with the facilities and engineering experts to ensure proper installation and maintenance of primary and secondary engineering controls and

that spaces have proper pressure differentials (e.g., negative pressure for HD compounding spaces). HD programs must also ensure that negative or neutral/normal pressure spaces are designed for the proper receipt and unpacking of HDs. Typically, storage of HDs requires a negative pressure environment to minimize the potential for inadvertent HD contamination. Some organizations may conduct an assessment of risk and exempt the negative pressure storage environment for some HDs that are not Active Pharmaceutical Ingredients of any HD on the NIOSH list or NIOSH Table 1 antineoplastics that will be manipulated. Implementing supplemental engineering controls, such as closed-system drug-transfer devices (CSTDs), requires collaboration with the drug manufacturer, CSTD manufacturer, pharmacy, and nursing personnel on the selection, use, and user training for each CSTD.

The development and review of administrative controls includes the development of Standard Operating Procedures (SOPs) for transport, receiving, storage, compounding, administration, labeling, deactivation/decontamination/cleaning/disinfection, disposal, PPE, and spill control. A facility should ensure proper evaluation, procurement, and implementation of PPE use. This includes providing gloves, gowns, eye, and face protection and in special cases when needed respiratory protection alongside monitoring proper use, especially during donning and doffing. A robust training program with initial and ongoing competencies is critical to ensure staff across all disciplines that may encounter HDs have the proper training and skills. All of these administrative controls work in conjunction to minimize HD surface contamination, which may lead to the potential for employee HD exposure. A comprehensive, well-designed HD surface sampling plan can help evaluate the effectiveness of controls and ensure that sampling is completed efficiently and effectively, meaning there is a high probability of detecting HD surface contamination where it truly exists (e.g., number and area of surfaces sam-



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**Hazardous Drug (HD) Surface Sampling Continuous Improvement (CI) Cycle -  
Evaluate and Reduce Exposure Potential throughout the HD path.**

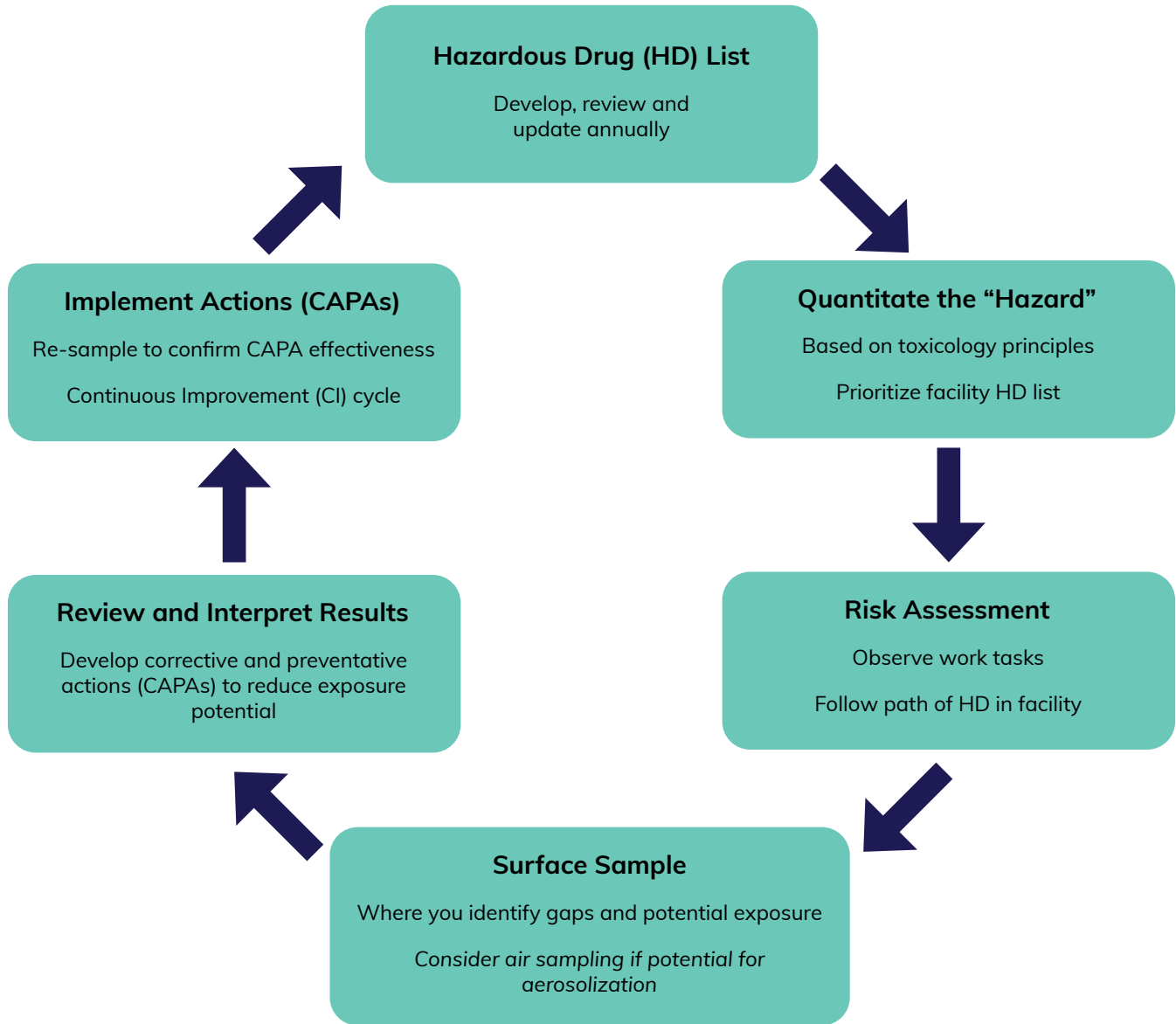


Figure 2. Strategy and Steps for an Effective USP <800> HD Surface Sampling Program by A. Snow, 2023.



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pled, frequency, and HD assessed). Recent research supports developing an HD surface sampling plan based on high-touch sentinel surfaces in pharmacy and administration areas and high throughput representative compounds. This approach builds a data set to help observe trends and identify gaps in program implementation (Jeronimo, Arnold et al., 2021).

An effective HD sampling program is developed when healthcare professionals have a keen understanding of toxicology and industrial hygiene standards, how and where to measure quantitatively, appropriate use of qualitative approaches and tools, HD surface level results, and how to interpret those results. Effective sampling strategies allow an organization to assess the performance of its HD program for identifying areas where systems need to be improved and where HD residue may be migrating outside of defined preparation, storage, and administration areas. HD sampling is used to assess work practices in healthcare environments and evaluate the effectiveness of primary, secondary, and supplemental engineering controls (e.g., closed-system drug-transfer devices CSTDs), SOPs, and administrative controls such as training programs and cleaning/deactivation procedures with regard to minimizing and eliminat-

ing unintended HD exposure throughout the facility. USP <800> states, “Healthcare settings should conduct environmental wipe sampling for HD surface residues routinely, initially as a benchmark, and then at least every six months.”

A variety of healthcare professionals may be tasked with implementing an HD surface sampling program at their facility. Typically, industrial hygienists (IH) and safety professionals are asked to evaluate HD surface contamination as part of USP <800> compliance activities within the healthcare environment. If a healthcare facility does not have an IH or safety professional, other healthcare team members, (such as pharmacy, nursing, occupational health, or risk management, or an external IH consulting company) may be considered for this role. This document will provide recommendations for the professionals looking to translate the regulatory guidance on HD environmental contamination (as measured by HD surface sampling) into best practice in their respective healthcare environments.

Figure 2. Strategy and Steps for an Effective USP <800> HD Surface Sampling Program will help guide you forward as you evaluate surfaces and potential risks in your healthcare environments.



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## Section 1. Introduction

Environmental HD contamination continues to be a far-reaching concern in healthcare environments and beyond. While all drugs are designed to impact a physiological response in the human body, the potency and the type of effect vary greatly. To address the most concerning drugs, NIOSH reviews drugs on the US market to determine whether they pose an occupational hazard to workers in a healthcare setting (NIOSH, 2023 and NIOSHa, 2023). Those meeting the criteria (further discussed in Section 3 and Appendix A) are included on the NIOSH HD list (available at <https://www.cdc.gov/niosh/topics/hazdrug/default.html>). The NIOSH list has been updated several times since it was first developed in 2004. When determining which drugs are considered hazardous, USP <800> deems at minimum any drug on the NIOSH list as hazardous. Organizations are required to define their facility specific HD list and review it at least annually.

It should be noted that not all drugs have been assessed for inclusion on the NIOSH list. Recently marketed drugs, experimental drugs being tested in clinical trials or drugs approved by FDA's Center for Biologics Evaluation and Research (CBER) or drugs only used in veterinary settings may meet the definition of hazardous; however, they are not on the NIOSH list, and it is up to the institution to determine if the drug meets the HD definition. The NIOSH definition serves as a guiding definition for organizations to review and incorporate new HDs into their organization's HD list. Each facility should consider the potential hazards of other treatments that may not meet the NIOSH definition but still pose an occupational hazard.

HDs are present in a variety of settings, including pharmacies, hospitals, clinics, home health settings, other healthcare institutions, and veterinarian offices. Industrial hygienists (IH), Environmental Health and Safety (EHS) professionals, and pharmacy staff that work with HDs are generally aware of the pharmacological aspects of a compound for treatment and related risks. However, they may not have as deep an understanding of the occupational health risks and inherent toxicity of these HDs. There are gaps in understanding potential occupational exposure risks and inherent toxicity in the wider healthcare and patient communities.

The following graphic (Figure 1) from the USP outlines the variety of possible occupational exposures to HDs. Clinical personnel with risks of direct occupational HD exposure through preparation or patient administration of HDs include nurses and home health personnel, pharmacists and pharmacy technicians, physicians, physician assistants, veterinarians, and veterinary technicians. Nonclinical healthcare personnel that may face possible downstream occupational HD exposure include environmental services (custodial), maintenance and facilities staff, and shipping and receiving staff. These nonclinical team members may have exposure through various mechanisms, including cleaning and spill management, laundry, transportation, maintenance, and others. Industrial Hygienists, Occupational and Environmental Health and Safety professionals, pharmacists, and other healthcare professionals are at the forefront of developing safety monitoring programs for their organizations to control HD surface contamination, which may lead to worker exposure and environmental impact.



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**Risk of Potential Exposure to Hazardous Drugs for Healthcare Workers.**  
 Follow the path of HDs throughout your whole facility.  
 Risk of potential exposure includes both your clinical and non-clinical workers.



*Risk assessment tools should be used for each type of worker and setting to assess the control systems (hierarchy of control) in place and the potential for exposure related to aerosolization or direct contact with hazardous drugs.*

**Figure 1.1. Risk of Potential Exposure to HDs for Healthcare Workers.**  
 Adapted from GC <800> Infographic (<https://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare>). Copyright 2020 by U.S. Pharmacopeia. Reprinted with permission.



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## Section 2. Rules and Regulations Overview

There are a myriad of rules, regulations, and guidelines surrounding the handling of HDs, yet few clearly and adequately address HD surface sampling. Of the agencies or guidelines that address HD surface sampling, it is unclear how or who enforces HD surface sampling. It is important to note that all documents that reference HD surface sampling use the term “should” when addressing HD surface sampling. There is currently no known direct requirement or regulation to conduct surface sampling, and this lack of regulatory authority governing the implementation of HD sampling programs has created confusion and inconsistent practices across the industry. Recommendations from the 2020 *Safe to Touch* Consensus Conference provide key consensus statements on the importance of implementing HD surface sampling programs. However, without consistent and streamlined regulations and guidelines, there may still be

perceived barriers to implementing HD sampling programs. An excellent resource on USP <800> HD program development and compliance is the Answer Book (Kienle, 2023) published by ASHP.

Table 2.1 below provides a brief overview of the various professional organizations and regulatory entities associated with handling HDs and their scope of enforcement as it relates to HDs. The primary entities that enforce HD surface sampling are the State Boards of Pharmacy, US Governments Centers for Medicare and Medicaid (CMS) Accreditation organizations such as The Joint Commission (TJC), DNV NIAHO®, Accreditation Commission for Health Care (ACHC) and The Center for Improvement in Healthcare Quality, OSHA and in some cases State Boards of Veterinary Medicine.

**Table 2.1. Overview of Professional Organizations and Regulatory Landscape**

Entity	Reference	Enforcement
American Society of Health-System Pharmacists (ASHP)	ASHP Guidelines on Handling Hazardous Drugs (ASHP, 2018)	Not enforceable unless specifically incorporated into a local or state regulation.
State Board of Pharmacy	Local or state pharmacy regulation. According to the NABP 2023 Survey, twenty state boards of pharmacy require compliance with or incorporate standards of USP <800>.	Not enforceable unless specifically incorporated into a local or state pharmacy regulation. In which case, failure to comply could result in citations, monetary fines, and, worst-case, loss of license.
NIOSH	NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016 ((NIOSH) September 2016) Proposed - DRAFT NIOSH List of Hazardous Drugs in Healthcare Settings, 2020 ((NIOSH) 2020) Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings (NIOSH, 2023) Managing Hazardous Drug Exposures: Information for Healthcare Settings (NIOSH, 2023)	Not enforceable unless specifically incorporated into a local or state regulation.



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Table 2.1. Overview of Professional Organizations and Regulatory Landscape (cont.)

Entity	Reference	Enforcement
Oncology Nursing Society (ONS)	Safe Handling of Hazardous Drugs, 3rd Edition (Polovich & Olsen, 2018) 4th edition anticipated in 2023	Not enforceable unless specifically incorporated into a local or state regulation.
OSHA, Federal	General Duty Clause (OSHA, 1970; OSHA, 2023)	HD surface sampling is not required. However, OSHA does have the ability to cite General Duty Clause if able to demonstrate the presence of hazard and exposure, which could result in citations and/or fines.
OSHA, Federal and 22 approved OSHA State Plans <i>(please review your local jurisdiction for hazardous drug rules)</i>	Example State Legislation North Carolina, Handling of Antineoplastic Agents, 13 NCAC 07G.0101 (6/13/2016) (Labor June 13, 2016.) Washington, Hazardous Drug Rule, WAC 296-62-500 (01/01/2015) (Industries December 18, 2018) California, Assembly Bill No. 1202 not implemented at the printing of these guidelines (10/19/2013) (Relations October 9, 2013)	HD surface sampling is not required by these rules adopted by state OSHA plans.
The Joint Commission (TJC) DNV NIAHO®, Accreditation Commission for Health Care (ACHC), and The Center for Improvement in Healthcare Quality	Medication Management Chapter, M.01.01.03: The hospital safely manages high-alert and hazardous medications (TJC, 2023) Environment of Care Chapter, EC.02.02.01 The hospital manages risk related to hazardous materials and waste. (TJC, 2023)	TJC tends to follow local rules and regulations. Failure to comply could jeopardize accreditation status.
United States Pharmacopeia (USP)	USP General Chapter <800>, Hazardous Drugs – Handling in Healthcare Settings (07/01/2020)	USP standards are recognized in the federal Food, Drug, and Cosmetics Act and laws, regulations, and policies implemented by states. These standards are enforced by the U.S. Food and Drug Administration. Compounded medications must be made in accordance with the USP national formulary standards.
U.S. Food and Drug Administration (FDA)	2013 Drug Quality and Security Act (DQSA) <a href="https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacy-compounding-human-drug-products-under-section-503a-federal-food-drug-and-cosmetic-act">https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacy-compounding-human-drug-products-under-section-503a-federal-food-drug-and-cosmetic-act</a>	Clarify FDA's authority over drug compounding and reaffirmed USP's role under Section 503A. Compounded preparations made by a licensed pharmacist or physician qualify for an exemption from requirements of a new drug application if they are compounded in compliance with the <a href="#">USP chapters on pharmacy compounding</a> using bulk drug substances and ingredients that comply with the standards of an applicable USP or NF monograph, if one exists.



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State boards of pharmacy would enforce HD surface sampling through licensure requirements when that state recognizes and adopts USP standards. Even then, HD surface sampling is considered a 'should' rather than a 'must' activity. At the time of printing these guidelines, some state boards of pharmacy have postponed enforcement of USP <800> until November 2023 to coincide with the recent updates to <795> and <797>. Notably, the 2018 Pew Charitable Trusts and National Association of Boards of Pharmacy (NABP) study assessed state conformance to the USP compounding standards. The study identified 32 states requiring full compliance with USP <797>. While the study did not specifically call out reference to compliance with USP <800>, the revised USP <797> directly references USP <800>. Since the Pew/NABP study was published, several states listed as requiring other compounding quality standards aside from USP (while not specifically requiring compliance with USP) have since promulgated draft or final compounding standards requiring full compliance with USP standards. In 2023, NABP published a survey of pharmacy law and reviewed

compliance status and minimum standards of practice with <795>, <797>, and <800> for all fifty state, DC, Guam, and Puerto Rico. This survey identifies 20 states that require compliance with or incorporate standards of USP <800>. Healthcare professionals should check with their local state boards of pharmacy for state-specific compounding requirements.

The Environment of Care and Medication Management Chapters of The Joint Commission (TJC) state that healthcare organizations seeking accreditation must have a plan to manage HDs. Each CMS recognized accreditation body, DNV NIAHO®, Accreditation Commission for Health Care (ACHC) and The Center for Improvement in Healthcare Quality will have requirements for management of HDs following USP and OSHA.

Facilities should work with their pharmacy, nursing, regulatory affairs, risk managers, and other professional stakeholders to ensure their program aligns with local, state, and federal regulatory requirements.



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### Section 3. Hazard Characterization and Developing Acceptable Surface Levels (ASLs)

Drugs are designed to impart a physiological response to the body at a specific dose. Therefore, the potential for them to cause unwanted pharmacological or adverse toxicological effects on the healthcare provider (workers) handling them must be examined carefully. The potential for exposure exists depending on the task required to prepare or administer the drug to the patient. Certain, more potent drugs have the potential to be a concern or cause an unwanted response under these conditions. These should be identified and focused on to reduce exposure to healthcare personnel. This section explains how to identify the more concerning HDs.

#### Hazard Characterization

While all drugs are designed to impart a physiological response to the human body, the potency and the types of effects vary greatly. In this case, USP <800> standard defines HDs as those listed on the NIOSH hazardous drug list or those meeting the NIOSH definition of HD. As such, these will be considered the most concerning compounds for impacting healthcare worker health and is the focus of the HD surface sampling component of USP <800>.



Figure 3.1. Professionals must consider hazard and exposure in the context of a risk assessment for employee safety in hospitals, pharmacies, and clinics by J. Gould, 2023.

The term **risk assessment**, or an **assessment of risk**, has been used by several organizations. How industrial hygiene professionals use the term “risk assessment” may differ depending on their professional background. For occupational health and safety professionals, the term “risk assessment” often means a **chemical risk assessment**, a process that examines and describes all the hazards related to certain chemical exposures, quantitates the probability of adverse outcomes related to those hazards, and calculates acceptable exposure levels to limit the risk related to exposure. However, the term “risk assessment” has also been used in some places to describe other processes. In USP <800>, an **assessment of risk** is a documentation of the formulations of a drug, how it is handled in a specific facility, and where workers can potentially be exposed. **This assessment of risk** is not related to specific adverse health outcomes and does not provide acceptable exposure levels, **but rather is more of a qualitative determination of the probability of potential exposure to a specific HD in a given facility based on the dosage form and specific activity**. Therefore the assessment of risk laid out in USP <800> does not require a site to perform all the requirements necessary for what some industrial hygienist may refer to as a **Risk Assessment**.

NIOSH defines a hazardous drug as a drug that is identified as a carcinogenic, developmental, reproductive, or genotoxic hazard or other health hazards by exhibiting one or more of these toxicity criteria in humans, animal models, or in vitro systems or a drug that the manufacturer specifies special handling information (Manufacturer Special Handling Information-MSHI) to protect workers handling the



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drug. One important additional criterion is an understanding of organ toxicity at low doses. While all drugs have toxic side effects, some exhibit toxicity at low doses. Generally, a daily therapeutic dose of <10 mg/day or a dose of <1 mg/kg/day in laboratory animals that produces serious toxicity has been associated with OELs <10 µg/m<sup>3</sup> and, therefore, would be considered an HD. The full NIOSH HD definition is in Appendix B. NIOSH has assessed many marketed drugs and created a list of HDs that meet this definition which is available at <https://www.cdc.gov/niosh/topics/hazdrug/default.html> and has been updated several times.

USP <800> considers drugs on this list to be HDs and requires that all organizations have a list of HDs updated at least annually. It should be noted that not all drugs have been assessed for inclusion on the NIOSH list, such as recently marketed drugs, biologicals, investigational drugs being tested in clinical trials, or drugs used only in veterinary settings. These very well could be hazardous, and it is up to the hospital, pharmacy, and clinic to determine if the drug meets the HD criteria through their risk assessment process.

The hazards (e.g., carcinogen, mutagen, etc.) are identified as part of the hazard characterization. The route of exposure and dose that cause these responses are also integral to determining the inherent hazard of the drug. First, the routes of exposure for the healthcare worker are considered. In the workplace, exposures to HDs may occur through inhalation, skin contact, ingestion, or injection. Inhalation and skin contact/absorption are the most likely routes of exposure. HD surface contamination also poses a risk to workers in the form of accidental ingestion. When contaminated surfaces are touched by workers, that contamination can be transferred to hands or mucous membranes (e.g., eye, nasal passages). Contamination on the hands may be transferred into the mouth if a worker then touches the area around their mouth or if they handle food or drink before

washing off the contamination. An accidental injection through a needle-stick or sharps injury is also possible. Additionally, the exposure scenarios that are relevant for healthcare workers handling HDs are not well understood or quantified. Healthcare worker exposures are generally different than patients', and they may face daily exposure repeatedly over their career. These doses in the workplace may occur from higher concentration from preparations in the pharmacy repeatedly during the day or low concentrations of the HD from various sources (e.g., pharmacy, patient room, contaminated common areas). These exposures are unintentional in that these are not prescribed by a physician and lack health benefit compared to a single daily or intermittent bolus dose received by the patient. The potential for the HD to enter the body by these routes and the frequency of exposure is included in the hazard characterization and protective exposure limits.

Not all HDs have equal potential to cause harm, with some drugs from NIOSH Table 2 and some more potent drugs that may not even be on the NIOSH List having increased potential risk of harm at low doses (Table 3.1). To focus and prioritize an HD program and exposure control strategy for the HDs with the greatest risk, the overall potency and innate hazards of a HD can be quantified in a numerical value: the occupational exposure limit (OEL). The OEL is a well-recognized tool that quantitates the health hazard typically by inhalation route in order to identify and prescribe risk mitigating and exposure control measures in proportion to the hazard, which then can be used to establish acceptable surface levels (ASL). An OEL is defined as an air concentration for a particular substance that a healthcare worker would not experience adverse effects (a No-Observed-Adverse-Effect Level [NOAEL] for workers) from handling an HD over an 8-hour workday, 5 days per week for a 40-year career. An acceptable surface limit (ASL) is the amount of a chemical or material found on workplace surfaces that is considered to be protective



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for workers to be exposed to via dermal contact (Kimmel, Sussman et al. 2011).

Numerous regulatory bodies and well-respected expert organizations<sup>1</sup> provide publicly available OELs. While some US government derived values exist, others have provided more recent evaluations and a greater number of chemical OEL values; however, few drugs have been evaluated. Because of the special nature of pharmaceutical chemicals (i.e., they are designed to alter human physiological function) and the fact that drug-related adverse effects have been observed in employees manufacturing those drugs [e.g., estradiol and gynecomastia (Harrington, Stein et al. 1978); penicillin and occupational asthma (Díaz Angulo, Szram et al. 2011); nitroglycerin and cardiac arrest (Ben-David 1989)], the pharmaceutical industry has taken it upon itself to set OELs for ensuring safe processing and handling in the laboratory and manufacturing settings (Lehman and Fitzhugh 1954, Sargent and Kirk 1988, Lewis, Lynch et al. 1990, Galer, Leung et al. 1992, Baird, Cohen et al. 1996, Dourson, Felter et al. 1996, Naumann and Sargent 1997, Dankovic, Naumann et al. 2015). The OEL determination consists of an analysis of relevant information on clinical and nonclinical pharmacology and toxicology to identify critical health effects extrapolating with adjustment factors to an estimated no effect level in workers. In general, these companies take advantage of proprietary data and expertise not necessarily available to external groups, and use methods consistent with those of expert OEL-setting committees. Additionally, as suggested by OSHA, these should be included on the Safety Data Sheet (SDS) and available to downstream users of the pharmaceutical materials.

## Development of ASLs

The OEL addresses the inhalation route of exposure and is provided as an air concentration, assuming a time-weighted average exposure over eight hours. Additionally, it is recognized by OSHA that the pharmaceutical industry commonly adjusts from the OEL air limit to a dermal ASL for surface contamination in the workplace (Occupational Safety and Health Administration [OSHA] 2014).

In the context of USP <800>, HD surface sampling has been identified as a key risk management tool of an HD program; however, they openly state that ASLs are not readily available for HDs and use the example for an extremely low ASL for cyclophosphamide of 1.00 ng/cm<sup>2</sup> without a clear, defensible, health-based rationale. The result of the USP <800> reference to this low surface limit for cyclophosphamide appears to indicate the need to control all HDs to the same very low level, which may result in diluting resources on the development of low detection limit analytical methods and excessive cleaning with an overall questionable improvement in worker safety. Development of ASLs would allow each entity to focus on those with the lowest limit as their most concerning HDs.

As stated above and as seen across the spectrum of HDs, potency (as well as the severity of toxicity) determines the potential for adverse effects. Generally, the most sensitive and apparent toxicity for HDs is related to the mechanism and pharmacological activity. As can be seen in Table 3.1, which provides a comparison of various HDs, not all drugs are equally potent or toxic. Due to many factors (e.g., receptor binding, pathway redundancy, capacity to repair the damage, etc.), there are multiple steps and a thresh-

<sup>1</sup>OEL setting committees and value name: Occupational Safety and Health Administration (OSHA) permissible exposure limits (PEL), American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLV), Occupational Alliance for Risk Assessment (OARS) Workplace Environmental Exposure Levels (WEEL), California OSHA (Cal/OSHA) PEL, European Union's Scientific Committee on Occupational Exposure Limits (SCOEL) Indicative Occupational Exposure Limit Values (IOELVs), German MAK value ("maximale Arbeitsplatz-Konzentration"; maximum workplace concentration)



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old for the onset of an adverse effect. With this basic toxicological principle of the dose-response relationship employed broadly to identify an acceptable exposure level (i.e., OEL), more stringent OELs are derived for more potent and toxic drugs. Because the potency and toxic potential have been accounted for in the OEL, following the concept of converting an OEL to an ASL would also incorporate these hazard understandings and dose response.

The OEL reflects an acceptable daily dose by the inhalation route ( $\mu\text{g}/\text{m}^3$ ) over a full workday, 5 days per week for a working lifetime and, upon conversion to an ASL, would be equivalent to an acceptable daily dose delivered by the dermal route ( $\mu\text{g}/\text{cm}^2$ ). **This can be accomplished by converting the inhalation air concentration value to a total daily dose or occupational acceptable daily exposure (OADE) (Equation 1);** the OEL is multiplied by the estimated air volume (V) an individual inhales ( $10 \text{ m}^3/\text{day}$ ) over an 8-hour day work shift at moderate activity for a 70-kg adult (Baird, Cohen et al. 1996, EPA 2011, Occupational Safety and Health Administration [OSHA] 2014). The basic assumption for the OEL is that 100% of the drug is absorbed upon inhalation (Figure 3.2).

**Equation 1:**

$$\text{OADE } (\mu\text{g}/\text{day}) = \text{OEL } (\mu\text{g}/\text{m}^3) \times V (10 \text{ m}^3/\text{day})$$

The OADE is then converted to a concentration on a surface that may be absorbed to a dermal dose that would not be expected to cause adverse effects (Equation 2). The assumption in developing an ASL from an OEL is that the entire amount (in milligrams of drug) present on a specified surface area transfers to the exact surface area of the skin and is completely absorbed systemically, equivalent to after inhalation exposure. The assumed surface area (SA) of one adult male hand is  $100 \text{ cm}^2$ .

**Equation 2:**

$$\text{ASL } (\mu\text{g}/\text{cm}^2) = \text{OADE } (\mu\text{g}/\text{day}) \div \text{SA } (100 \text{ cm}^2)$$

The dermal assessment incorporates several assumptions about the total dose, including the amount of surface area that contacts the skin, the number of touches to the surface, the amount that transfers from the surface to the skin, and absorption through the skin, all of which are included in a route-to-route adjustment (Figure 3.2).

**Table 3.1 Example of Drug Associated Toxicities and Their Therapeutic Doses**

Drug	Indication	Toxicity	Therapeutic Dose
Hydroxyurea	Cancer	Genotoxicity	1000 mg (15 mg/kg*)
Cyclophosphamide	Cancer	Genotoxicity, carcinogenicity	70 -350 mg (1-5 mg/kg*)
Digoxin	Heart failure	Cardiac toxicity, lethality	0.56 – 0.84 mg (0.008-0.012 mg/kg*)
Warfarin	Anticoagulant	Bleeding, lethality	0.5 – 10 mg
Colchicine	Gout	Genotoxicity, low dose lethality	0.6 mg
Fentanyl	Analgesia	Life threatening respiratory depression	0.14 – 1.4 mg (0.002-0.02 mg/kg*)

† Drug information available in the FDA Full Prescribing information available at: <https://dailymed.nlm.nih.gov/dailymed/>

\*Dose stated in mg/kg and converted to an mg dose for a 70 kg individual



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## Dermal Absorption Potential

Many factors can affect the actual internal exposure for different drugs: the physical form of a drug, such as coated vs. not coated tablet, a higher concentration of HD in the tablet, liquid compared to powder, the impact of excipients, solvents, intact vs. crushing/compounding impacts dusting, and the concentration on surfaces. Different formulations can enter the body in various ways. Some drugs may need to be resuspended in solvents that are highly hydrophobic. These solvents may serve to carry drugs through the skin barrier when normally they would not be able to. In addition, the concentration of the drug product can reduce the amount of API in contact with the body. While many are dilute, some formulations may be high [ $>50\%$ ; i.e., 83.33% hydroxyurea in HYDREA<sup>®</sup> (hydroxyurea) Capsules, 500 mg] (BMS, 2013). Dermal absorption is affected by various physical and chemical properties, including physical state, molecular weight, lipophilicity, solvent carriers, skin type, the integrity of the skin, skin contact time, and dose over an area to the skin ( $\text{mg}/\text{cm}^2$ ) (Law, Ngo et al. 2020).

**Surface Area and Skin Contact:** The first assumption in the ASL calculation is the contaminated surface area touched. The concentration per area of skin is important in the rate and total absorption of a drug. The selection of the area exposed to the surface impacts the total dose delivered to the skin. The  $100\text{ cm}^2$  value approximates the surface area of a worker's palm, giving rise to the customary size of the surface area to be wiped being  $10\text{ cm} \times 10\text{ cm}$  square, or  $100\text{ cm}^2$  (EPA, 2011; OSHA, 2014). Gloves are worn in most work areas (e.g., pharmacy, laboratories). Outside of these areas (i.e., in more public places), the palm of the hand is the most likely body part to touch benchtops, doorknobs, or other surfaces in the workplace. The full hand touching a door handle, light switch, or downstream contami-

nation from floors would result in decreased surface level or lack of a full  $100\text{ cm}^2$  area, thus an overestimation. Furthermore, in one study, a single-hand contact resulted in  $<16\%$  percent of the total surface of the palm of the hand being exposed to a contaminant, whereas after 12 contacts, this was increased to about 40 percent (Brouwer, Kroese et al. 1999), indicating that even multiple touches to a surface does not result in 100% of the available skin surface making contact. It should be noted that by using the surface of a palm, the ASL does not address direct skin contact with powder or liquid encountered while conducting a work task (e.g., sticking one's hand in a container of HD or direct contact with the skin from the air).

The second assumption is that all of the HD on the surface transfers to a worker's hand upon contact (OSHA, 2014). This also is expected to be an overestimation of dermal exposure due to a single hand-surface contact in the workplace. Depending on chemical properties, the efficiency of transfer was  $\leq 2\%$  of the contamination of the surface, although in this study, the result was still  $1.07\text{ }\mu\text{g}/\text{cm}^2$  after 12 contacts (Brouwer et al., 1999). In another study, average dermal transfer efficiencies of methamphetamine ranged from 11% for dry hands to 26% for wet hands (Van Dyke et al., 2014), indicating that surface properties play a role in the transfer. Additionally, certain chemicals can remain on surfaces for prolonged periods and be a source of surface contamination that may transfer to the skin. Contaminated gloves also have been shown to efficiently transfer the chemical to the skin (Van Dyke et al., 2014; Andreu et al, 2012; Sahmel et al., 2012). While the amount that transfers from the surface to the skin is overestimated at 100% in this simple ASL derivation, this allows for the possible scenario of the palm of the hand touching multiple other contaminated areas on the same day.



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**Physical State:** Chemicals can penetrate the skin in both solution and powder states, although chemicals in solution are more effectively absorbed than powders (WHO, 2006).

**Molecular Weight:** Molecular weight (MW) is used as a proxy for molecular size. Permeation of chemicals through the skin decreases exponentially with increases in MW (Potts and Guy 1992, Magnusson, Anissimov et al. 2004). A general rule of thumb is that compounds with a MW of less than 500 Daltons are more likely to permeate the skin, while compounds with a MW of greater than 1000 Daltons are less likely to permeate the skin (Hostýnek and Magee, 1997 and Bos and Meinardi, 2000). Many traditional antineoplastics have relatively low molecular weights, such as cyclophosphamide with a MW of 261 Daltons. In contrast, monoclonal antibodies such as trastuzumab have molecular weights of approximately 150,000 Daltons.

**Lipophilicity:** Log octanol/water partition coefficients ( $\log_{PO/W}$ ) are a common way of expressing the lipophilicity (i.e., the ability of a compound to migrate into fats) of a compound.  $\log_{PO/W}$  is often used as a qualitative measure of skin permeability. Compounds with  $\log P_{O/W}$  between -1 and 5 are more likely to permeate through lipid membranes, including skin (Schuhmacher-Wolz, Kalberlah et al., 2003). On its own, the octanol/water partition coefficient is not the sole indicator of significant dermal absorption (WHO, 2006).

**Solvent Carriers:** Many solvents, such as dimethyl sulfoxide, (DMSO), isopropyl alcohol and ethanol, can act as skin penetration enhancers and may facilitate the transdermal absorption of compounds (Lachenmeier, 2008). Ethanol is regularly used in healthcare as the primary component of alcohol-based hand rubs. Isopropyl alcohol is used regularly in compounding pharmacies for the sanitization of surfaces.

**Chemical Stability:** Some drugs can remain on surfaces for extended periods of time. Workers who routinely come in contact with the same contaminated surfaces may be exposed repeatedly. Other drugs may breakdown more quickly on surfaces decreasing the potential for exposures. This breakdown could also increase the potential exposure to hazardous breakdown products, such as the very toxic components of an antibody drug conjugate therapeutic agent.

**Skin parameters:** Depending on the drug's molecular properties, the HD can pass through the skin's barrier layer and enter the systemic circulation. Small molecules and very hydrophobic molecules have a greater ability to be absorbed. Some solvents can carry drugs through the skin. Another concern is damaging the skin in situations where workers are wearing gloves frequently or are washing their hands often. Damaged skin compromises the protective skin layers, and the systemic level of HD following dermal exposure in this situation can be higher than if the skin was intact.

The precise amount of the drug absorbed into the human body is difficult to quantify and can depend upon the following personal factors: occlusive application, contact time on the skin, skin age and condition, the location on the body, race, and sex. In some cases where frequent handwashing can damage the skin, increased drug penetration may occur. However, handwashing also has the benefit of removing HD that is on the hands. In addition to systemic hazards posed by skin exposure, the skin itself can be a target for some hazards of drug exposure.

We see that many factors can affect the exposure to HDs. Some, such as healthcare workers repeatedly washing their hands and handling HDs in certain solvents, both of which could damage the skin, enhancing penetration, can increase potential internal exposures. Multiple touches to contaminated sur-



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faces throughout the day and exposure to several different drugs with similar, additive, or synergistic hazards can also increase the hazards the workers contend with. However, there are substantial factors such as the slow rate of absorption of the skin, that may also decrease the potential for an internal exposure. Additionally, frequent hand washing, which can remove the drug, and proper PPE use decreases the total amount of exposure. The inhalation OEL which can serve as the basis of an ASL, is also conservative in its overestimation of systemic dose as well as addressing other pharmacokinetic factors like accumulation from repeated daily exposures. With these assumptions about the potential absorption of a drug through the skin built in, the HD surface exposure at an ASL would not likely equal a harmful systemic dose for concerning adverse

effects or result in a dermal exposure that would cause local effects on the skin.

**For the ASL determination, it is assumed that 100% of a drug is absorbed dermally. As described above, there are many factors that influence and limit dermal absorption.** Even for those molecules with higher dermal penetration capability, the absorption occurs over an extended period of time to obtain the maximum dose compared to other routes, which indicates that the amount of drug on the skin does not necessarily become absorbed immediately or at all. Administrative controls, such as handwashing, can reduce dermal absorption.

Furthermore, no additional adjustment for route-to-route is needed other than the inhaled air volume and skin surface area included in Equation 1 and 2.

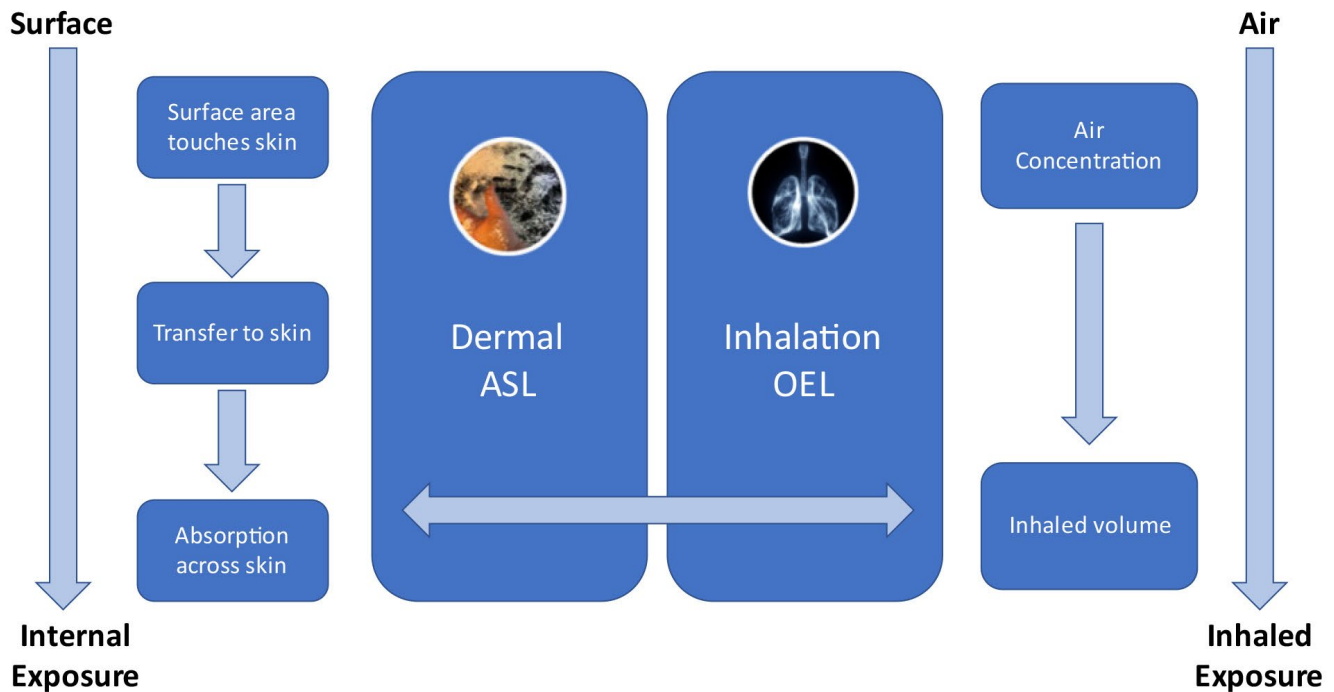


Figure 3.2. The route-to-route comparison of the OEL and the ASL.



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The data to develop the inhalation OEL is derived from clinical and preclinical studies conducted primarily by intravenous or oral administration, and a route-to-route adjustment factor was likely applied if dosing by the study routes does not expect the same internal exposure as by the inhalation route (OEL). Dermal exposure would be expected to be less than by the inhalation route (i.e., if inhalation has low bioavailability, dermal bioavailability would also be low). Even in situations where workers may have an increased skin permeability, due perhaps to increased hand washing or other skin damage, that internal exposure is still expected to be less than the inhalation route. **Together, the cautious assumptions regarding bioavailability in the development of the OEL along with the default of 100% dermal absorption contribute to the protective nature of this simple drug-specific ASL determination.** While not directly related, a conservative ASL is also desired since healthcare workers prepare and administer multiple HDs on any given day, and there could be additive or synergistic responses. This hazard characterization in the form of the ASL, as suggested in the OSHA Technical Manual, is consistent with the pharmaceutical industry standard.

To use the above equation to develop ASLs, OELs must first be available for the HD of concern. Many pharmaceutical companies have internal commitments to derive OELs for all drugs, including HDs. It is standard pharmaceutical industry practice to generate these values and include them on drug product safety data sheets (SDS), as required per OSHA's Hazard Communication standard (1910.1200 Appendix D) to list not only the relevant OSHA PEL but also any other exposure limit used or recommended by the chemical manufacturer, importer, or employer preparing the SDS. These documents, which are required to be provided upon shipment of the drug from the drug supplier, must contain the manufacturer's OEL and thus should be present and available to the hospital, pharmacy, or clinic.

For many drugs, a robust health-based OEL may not be available due to limited data (e.g., those in clinical trials), and an occupational exposure band (OEB) or occupational hazard categorization (OHC) may be provided instead. These risk assessment tools are an established practice widely used across the pharmaceutical industry to address limited data compounds and are based on in-depth experience in setting pharmaceutical OELs. An OEB (or OHC) is a range of concentrations (e.g., 1-10  $\mu\text{g}/\text{m}^3$ ) that defines performance-based handling practices in the form of engineering controls, administrative measures, and PPE. Exposure controls are targeted below a concentration within the band, generally the bottom (e.g., 1  $\mu\text{g}/\text{m}^3$  for a band range of 1-10  $\mu\text{g}/\text{m}^3$ ) (Naumann, Sargent et al., 1996). This exposure control target can then be equated to an OEL for purposes of determining an OADE and finally an ASL. The OEB is assigned based on the expected potency and toxicity, and it is generally considered conservative because of the limited or lack of robust review of the data (Naumann, Sargent et al. 1996; NIOSH, 2019). NIOSH has developed a banding system for industrial chemicals (Table 3.2), and several banding systems have been developed for pharmaceuticals (Naumann, Sargent et al., 1996; Gould and Taylor, 2011; Graham, Hillegass et al., 2020). Take caution in interpreting the band since different names and different band ranges exist across companies. An occupational health professional should ensure an understanding of the band range, in  $\mu\text{g}/\text{m}^3$ , assigned to an HD to inform downstream actions. An example used by two companies of band ranges, exposure control target, and corresponding ASL is presented in Table 3.3 (Naumann, Sargent et al., 1996; Gould and Taylor, 2011). Additionally, Table 3.2 provides an extrapolated ASL associated with the NIOSH bands. While OEBs or OHCs are not reliably presented on a drug's SDS, be sure to ask the drug manufacturer for this safety information.



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**Table 3.2. Airborne Concentration Ranges (mg/m<sup>3</sup>) Associated with NIOSH Occupational Exposure Bands (NIOSH, 2019) Converted ASLs according to Equation 1 and 2 (NIOSH, 2019).**

Occupational Exposure Band	Airborne target range (mg/m <sup>3</sup> )	Surface target range (mg/cm <sup>2</sup> )	Surface control target ASL (mg/cm <sup>2</sup> )
A	>10	>1	1
B	>1 to 10	>0.1 to 1	0.1
C	>0.1 to 1	>0.01 to 10	0.01
D	>0.01 to 0.1	>0.001 to 1	0.001
E	≤0.01	≤0.001	See below

**Table 3.3. OEB Air Concentration Ranges (µg/cm<sup>3</sup>) for HDs and Their Associated Surface Target Range Utilizing Equation 1 and 2 (Naumann, Sargent et al. 1996, Gould and Taylor, 2011).**

OEB Airborne target range (µg/m <sup>3</sup> )	Surface target range (µg/cm <sup>2</sup> )	Surface control target ASL (µg/cm <sup>2</sup> )
>1 to 10	>0.1 to 1	0.1
>0.1 to 1	>0.01 to 10	0.01
>0.01 to 0.1	>0.001 to 1	0.001
≤0.01	<0.001	<0.001

For most drugs, the above strategy for assigning an ASL from an OEL or OEB will result in an actionable, conservative, protective limit. However, not all HDs are on the NIOSH list. Drugs in early clinical trials may be both unassessed (therefore not appearing on the HD list) as well as have too limited data to derive an OEL. In this case, utilizing the bottom concentration of an OEB range is a reasonable approach to derive an ASL. Additionally, the cautious nature of the ASL is expected to be protective when healthcare personnel may work with multiple HDs simultaneously.

Direct dermal hazards would not necessarily be considered in the OEL determination. Topical therapeutic agents, dermal sensitizers, or irritants should be considered separately from systemic pharmacolog-

ical activity in determining an ASL. Dose as a concentration in a formulation per skin area is critical to the production of these types of responses. Thus, an occupational toxicologist can evaluate the information and take the effect-dose per surface area and apply adjustment factors to directly derive an ASL is recommended instead of the above method. This has been described as an effective approach with dermal sensitizers in consumer product formulations or in the banding and ASL determination in pharmaceutical manufacturing (Kimber et al., 2008; Gould et al., 2011; Naumann & Arnold, 2019). While dermal sensitization or allergy is not listed in the definition or results in an assignment to the NIOSH HD list, there have been reports in pharmacies and hospitals where staff displayed contact dermatitis (Cetinkaya et al., 2007; Kim et al., 2012; Classen & Fuchs, 2015). Dermal irritants generally act by direct nonspecific mechanisms such as pH extremes, reactivity, or interaction with membranes at the site of contact NIOSH. These generally occur at higher concentrations per unit area than an ASL that would be required for a HD. Overall, avoiding dermal contact is important to reduce skin irritation, sensitization, or direct dermal pharmacological responses.

Some HDs may have acute toxic responses that have resulted in the assignment of a short-term exposure limit (STEL; 15-minute exposure) or “not to exceed” ceiling limits. These limits have different



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considerations than the 8-hour OEL, and it is not recommended to use the STEL or ceiling limit for the ASL determination unless examined carefully by an occupational toxicologist.

Presented here is a method to derive a reasonable and conservative ASL from an OEL or OEB that is expected to be available on the pharmaceutical manufacturer's SDS. In some cases, the conservative nature or questions may arise regarding the simple ASL assumptions, and as such, a robust compound-specific assessment by a trained toxicologist may be implemented.

Several HD ASL derivation examples (estradiol, warfarin, and 5-fluorouracil) are presented below, including the health hazard information on an HD, a summary of the drug properties, a publicly available OEL, and the ASL derived utilizing Equation 1 and 2.

### Estradiol Example

Estradiol is a naturally occurring hormone circulating endogenously and is considered the primary female reproductive hormone. It is commercially available in several hormone therapy products for managing conditions associated with reduced estrogen, such as vulvovaginal atrophy and hot flashes. Some available forms of estradiol include oral tablets, injections, vaginal rings, transdermal patches, sprays, gels, and creams (DrugBank, 2023). The most commonly reported adverse effects following the administration of estradiol include edema, application site irritation, chloasma (brown patches on the face), hirsutism (abnormal hair growth), loss of scalp hair, persistent erythema of the skin, pruritus, weight increased, abdominal pain, bloating, headache, breast tenderness, swelling and pain, menstrual abnormalities, vaginal discomfort, withdrawal bleeding, upper respiratory infection and pain (Amneal, 2021; Millicent, 2021). More severe and less commonly reported adverse effects include heart disease, myocardial infarction,

hypercalcemia, disorder of gallbladder, deep venous thrombosis, venous thromboembolism, cerebrovascular accident, dementia, and angioedema (Amneal, 2021; Millicent, 2021). Occupational exposure to synthetic estrogen is known to produce feminizing effects in males and menstrual disorders in females (Harrington, 1982). Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver (Amneal, 2021).

An occupational exposure limit (OEL) 8-hour time weighted average (TWA) Of  $0.2 \text{ mg/m}^3$  has been reported for estradiol by one manufacturer (10).

#### ASL calculation: Estradiol:

$$\text{OADE } (\mu\text{g/day}) = \text{OEL } (\mu\text{g/m}^3) \times V \text{ (10 m}^3\text{/day)}$$

$$2 \mu\text{g/day} = 0.2 \mu\text{g/m}^3 \times 10 \text{ m}^3\text{/day}$$

$$\text{ASL } (\mu\text{g/cm}^2) = \text{OADE } (\mu\text{g/day}) \div \text{SA (100 cm}^2\text{)}$$

$$0.02 \mu\text{g/cm}^2 = 2 \mu\text{g/day} \div 100 \text{ (cm}^2\text{)}$$

### Warfarin Example

Warfarin is an anticoagulant drug normally used to prevent blood clot formation as well as migration. Although originally marketed as a pesticide (d-Con, Rodex, among others), warfarin became the most frequently prescribed oral anticoagulant in North America (Lim, 2017). Warfarin has several properties that should be noted when used medicinally, including its ability to cross the placental barrier during pregnancy (Aphena, 2012). Warfarin can cause fetal harm when administered to a pregnant woman. Warfarin exposure during pregnancy causes a recognized pattern of major congenital malformations known as warfarin embryopathy and fetotoxicity, fatal fetal hemorrhage, and an increased risk of spontaneous abortion and fetal mortality. Additional adverse effects such as necrosis, purple toe syn-



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drome, osteoporosis, valve and artery calcification, and drug interactions have also been documented with warfarin use (DrugBank, 2023). Considering the low therapeutic dose and the narrow therapeutic index, the OEL of warfarin has been established by the manufacturer at  $2 \mu\text{g}/\text{m}^3$  (BMS, 2022; DrugBank, 2023). Currently, the ACGIH TLV is  $10 \mu\text{g}/\text{m}^3$  and the OSHA PEL and NIOSH REL are listed as  $0.1 \text{ mg}/\text{m}^3$  while the immediately dangerous to life (IDLH) has been established at  $100 \text{ mg}/\text{m}^3$  (NIOSH, 2019; ACGIH, 2023; OSHA, 2023). The use of the OSHA PEL and the NIOSH REL may pose an unacceptable risk to occupationally exposed individuals since the OADE may be considered a therapeutic dose in some sensitive individuals. To be conservative, the lowest OEL is selected to calculate the ASL in this example.

#### ASL calculation: Warfarin:

$$\text{OADE } (\mu\text{g}/\text{day}) = \text{OEL } (\mu\text{g}/\text{m}^3) \times V \text{ (10 m}^3/\text{day)}$$

$$20 \mu\text{g}/\text{day} = 2 \mu\text{g}/\text{m}^3 \times 10 \text{ m}^3/\text{day}$$

$$\text{ASL } (\mu\text{g}/\text{cm}^2) = \text{OADE } (\mu\text{g}/\text{day}) \div \text{SA (100 cm}^2)$$

$$0.2 \mu\text{g}/\text{cm}^2 = 20 \mu\text{g}/\text{day} \div 100 \text{ (cm}^2)$$

#### 5-Fluorouracil Example

Fluorouracil (also known as 5-fluorouracil [5-FU]) is an antimetabolite fluoropyrimidine analog of the nucleoside pyrimidine with antineoplastic activity. It is indicated for the treatment of actinic keratosis and various cancers (breast, colorectal, gastric, pancreatic, and superficial basal cell carcinoma) (Spectrum, 2016; AHFS, 2021). Fluorouracil is available as a solution for intravenous (IV) administration and as a solution, cream, and ointment for topical administration. There are two mechanisms of action of fluorouracil that result in cytotoxic effects. One is the competitive inhibition of thymidylate synthetase, the enzyme catalyzing the methylation of deoxyuridylic acid to thymidylic acid. The consequent thymidine deficiency results in the inhibition of deoxyribonu-

cleic acid (DNA) synthesis, thus inducing cell death. The second mechanism of action is evidenced by the moderate inhibition of ribonucleic acid (RNA) and the incorporation of fluorouracil into RNA. The predominant mechanism of antitumor action appears to be dependent, at least in part, on individual tumor intracellular metabolism. The effects of DNA and RNA deprivation are most significant on those cells which are most rapidly proliferating (Spectrum, 2016; AHFS, 2021). The most commonly reported adverse effects following the administration of fluorouracil include infections, myelosuppression (leukopenia, pancytopenia, and thrombocytopenia), agranulocytosis, anemia, febrile neutropenia, bronchospasm, increased risk of infection, electrocardiogram (ECG) changes, chest pain, diarrhea, nausea, vomiting, anorexia, inflammation of the gastrointestinal tract, alopecia, malaise, and weakness. An occupational exposure band (OEB) of 5 (control exposure to  $<1 \mu\text{g}/\text{m}^3$ ) has been reported for fluorouracil by the manufacturer (Pfizer 2012). In cases where the OEB has a  $<1 \mu\text{g}/\text{m}^3$ , an approach used in pharmaceutical companies is to assume an exposure control target of 10-fold below, at  $0.1 \mu\text{g}/\text{m}^3$ ; however, for very potent, concerning drugs, an occupational toxicologist can advise on a control target.

#### ASL calculation: 5-Fluorouracil:

$$\text{OADE } (\mu\text{g}/\text{day}) = \text{OEL } (\mu\text{g}/\text{m}^3) \times V \text{ (10 m}^3/\text{day)}$$

$$1 \mu\text{g}/\text{day} = 0.1 \mu\text{g}/\text{m}^3 \times 10 \text{ m}^3/\text{day}$$

$$\text{ASL } (\mu\text{g}/\text{cm}^2) = \text{OADE } (\mu\text{g}/\text{day}) \div \text{SA (100 cm}^2)$$

$$0.01 \mu\text{g}/\text{cm}^2 = 1 \mu\text{g}/\text{day} \div 100 \text{ cm}^2$$

These examples demonstrate the determination of ASLs from an OEL or OEB for three HDs. These are expected to be sufficiently conservative in that if this concentration were found on a workplace surface, no deleterious effect would be expected in the healthcare staff.



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## Section 4. Exposure Potential for Healthcare Workers – A Risk Assessment Approach

A key concept to understanding worker health risk related to HDs is whether there is potential for exposure.

This risk assessment aka “the <800> assessment of risk” (2020) approach encompasses the following:

- HD handling task being performed,
- the route of exposure,
- physical form of the drug,
- general facility location (pharmacy, administration, patient care, storage/receiving), and
- control systems in place to prevent exposure potential.

Each of these elements will be discussed in more detail below.

The **route of exposure** is important for determining the risk. In this document, the focus is on circumstances that lead to HD surface contamination and

potential exposures from HDs remaining on HD surfaces. It is important to recognize that HD surface contamination is a *lagging indicator* of HD handling that was not fully contained or controlled and resulted in the contamination of surfaces. **It is especially important to conduct risk assessments, as the work tasks are actively conducted, qualitatively and quantitatively, observing and measuring potential exposure risk.**

The AIHA ARECC model provides an outline of the risk assessment (aka “assessment of risk”) and risk management continuous improvement cycle for OEHS programs. A HD program and the related HD surface sampling strategy should follow this risk assessment (aka assessment of risk) approach and the risk management actions and behaviors to minimize risk and improve control systems following the hierarchy of control.

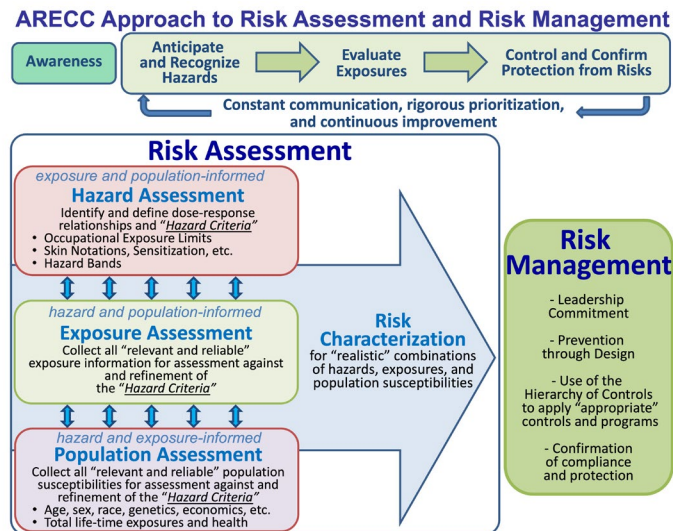


Figure 4.1. Illustration of the ARECC approach to risk assessment and risk management as shown in the AIHA Competency Framework: Understanding and Applying ARECC to Occupational and Environmental Health and Safety (2022). Please see more information [here](#).



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### Risk Assessment - <800> Assessment of Risk

- **Hazard Identification** - Identify which drugs are a potential hazard.
- **Determine which HDs to sample** based on factors such as:
  - Volume/through put,
  - Particular hazard, and
  - Acceptable surface limit (ASL).
- **Potential Exposure Identification** - Identify potential sources for exposure in workflow:
  - Consider spill/release of HD during handling,
  - Consider formulation of HD (liquid, tablet, capsule, aerosolized),
  - Consider handling techniques (human compounding, robotic/automated compounding, tablet crushing/cutting, transport through facility), and
  - Consider potential contamination sources (potentially contaminated packaging, contaminated PPE, etc.)
- **Assess the Risk of Exposure** - actual potential for exposure of workers with consideration for control systems in place (see Table 5.1 for common sampling locations)
- **Identify the best surfaces for sampling (consider sentinel surfaces).**
- **Conduct HD surface sampling.**
- **Review and interpret results.**
  - When surface contamination is identified by HD surface sampling, an IH must address contamination sources where there is a high probability of direct contact by workers without a control system in place (engineering, administrative and personal protective equipment (PPE)).
- **Address the contamination sources**
  - cleaning, to remove contamination, and

- conducting a root cause analysis (RCA) to identify root cause and identify and implement corrective and preventative actions (CAPAs) to prevent future failures and related HD surface contamination. Root cause analysis should include careful observations of work tasks in the area where contamination was identified, and ideally the RCA team should include a cross functional diverse team (front line workers, leaders, quality and EHS staff member).

### Review and repeat

- Risk Assessments aka <800> Assessment of Risk on an appropriate schedule based on changes and/or previous results.

### HD Handling Tasks

#### Drug Aerosolization and Inhalation Exposure Potential

Some forms of administration (e.g., tablet crushing, nebulization) can also lead to airborne drugs that can be inhaled. Automation and tablet counting operations should be carefully evaluated for the potential to generate dust exposure in the environment. In day-to-day operation, these units are designed to provide containment of particulate and aerosols; however, in periods of loading, unloading, cleaning, and maintenance, there is an increased risk of particulate and aerosol exposure. In this respect, aerosol (which can be particulate or liquid) exposure potential to workers should be fully evaluated by industrial hygiene air sampling (see Table 4.1 IH Measurements - Air Sampling vs Surface Sampling). In cases where there is not a validated analytical industrial hygiene method available for an HD, surrogate compounds can be used to evaluate control systems. The use of surrogate compounds to confirm containment performance is a common practice in the pharmaceutical industry following ISPE guidance for containment verification, Good Practice Guide: Assessing Particulate Containment,



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2nd Edition, May 2012. The ISPE GPG: <https://ispe.org/publications/guidance-documents/assessing-particulate-containment-performance>

Vapors are rare with most drugs having extremely low vapor pressures. Surface sampling requirements in USP <800> do not adequately address potential exposure risk through respiratory routes. Consult with the relevant EHS or IH resource for your workplace to obtain more guidance on the assessment of risk for a respiratory route of exposure.

**Examples of tasks that may result in the aerosolization of drugs and potential inhalation exposure:**

- Administration of a nebulized drug

- Aerosolization of HD particulate may occur when working on contaminated surfaces in areas where drugs are compounded or administered
- Crushing HD tablets by various methods (e.g., in baggies in the nursing unit or veterinary clinic)
- Crushing tablets in administration areas or compounding powders could lead to dust spread
- Manipulating uncoated tablets or opening the bottles of uncoated tablets can release HD particulate
- Opening an ampule or making connections (e.g., starting a line or priming tubing) for may release pressure and create aerosol droplets
- Maintenance and cleaning activities for automation/robotics or tablet counting devices

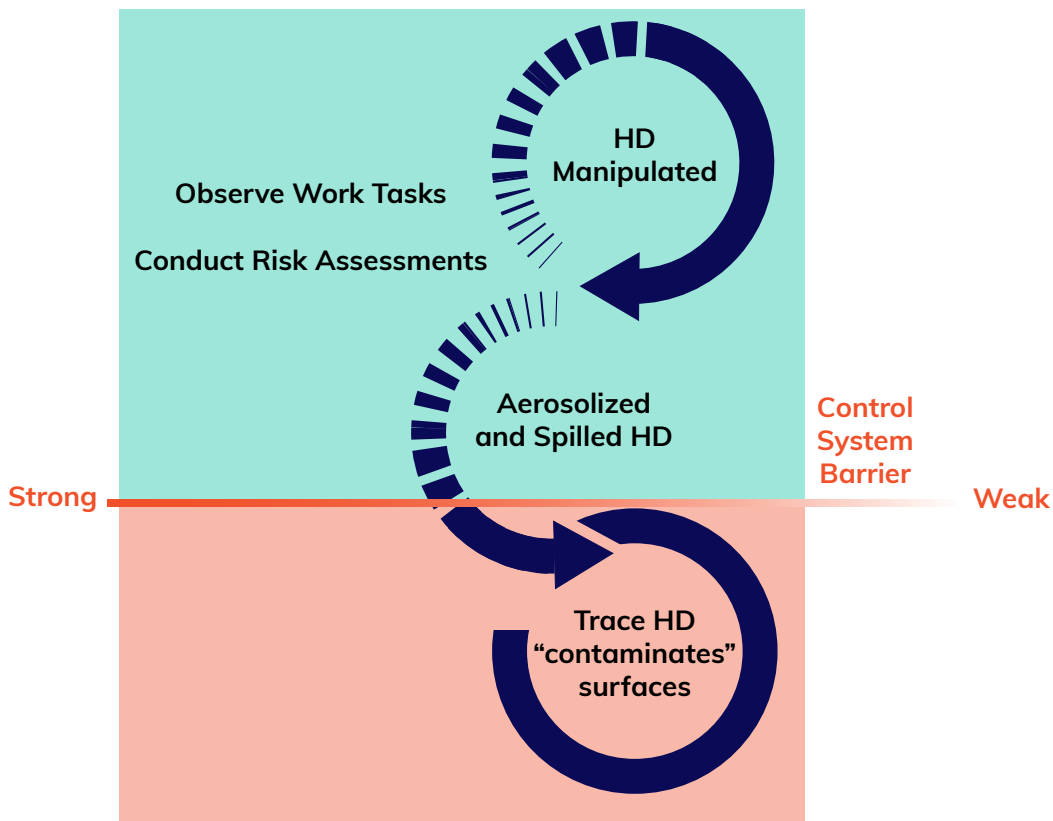


Figure 4.2. Control System Barrier - Strong -> Weak by A. Snow, 2023.



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- Unpacking shipping totes of HDs without proper PPE
- Post-administration – emesis (vomiting) or excrement aerosolization in patient care and patient restrooms can create aerosolization of unmetabolized drugs or metabolites of a drug
- HD spill clean up

### HD Aerosolization and HD Surface Contamination

Often the work surfaces in areas where HDs are compounded or administered can become contaminated with drugs. Drug administration or handling conditions (such as nebulizer use or vigorous manipulations) may lead to airborne droplets and particulates. HDs, once in the air, can land on surfaces in the vicinity and migrate beyond the source. There have been industrial hygiene studies that have noted drug contamination in areas where drugs had been administered to patients via inhalation using a nebulizer. Aerosols and particulate settle on surfaces in areas surrounding workspaces (Eain et al., 2022). It should be noted that for HDs, hazardous levels of surface contamination and the corresponding ASL will often be invisible to the unaided eye with particulate levels at 1–5 µg/cm<sup>2</sup> (OSHA, 2014).

### HD Surface Contamination and Dermal Exposure Potential

One common route of HD exposure potential for healthcare workers is contact with contaminated surfaces by the skin. As discussed above, when working with HDs, some materials can become airborne, which then settle on nearby surfaces. HD surface contamination can also be from other contaminated surfaces (drug vials, gloves, bottom of containers). Administration areas can be contaminated by bottles placed on counters. All of these potentially contaminated surfaces offer a chance for skin to come in contact with HDs.

Sources of HD surface Contamination:
Handling and processing tablets, capsules, powders, and liquids outside of containment (C-PEC and CSTDs)
External drug packaging and container contamination from the drug manufacturer or pharmacy
Accidental spills
Transferring HD from contaminated gloves or containers and touching contaminated surfaces in common areas
Powder or liquid aerosol droplets settling from the air, resulting from: <ul style="list-style-type: none"> <li>• Spill</li> <li>• Working with powder or liquid aerosols</li> <li>• Dried liquid on a surface</li> </ul>
Maintenance and cleaning activities for automation/robotics or tablet counting devices
Patient emesis and excrement in patient care areas

Patients receiving HDs can themselves be sources of contamination as body fluids are a potential source of exposure. Depending on the HD, excretion can occur through urine, feces, sweat, and vomitus. Surfaces associated with patient urinary excretion, such as bathroom floors, have been consistently shown to have high levels of HD surface contamination loads (Hedmer & Wohlfart, 2012; Eisenberg et al., 2021; Cai et al., 2022). HD contamination of toilet handles and bathroom door handles has also been reported (Jeronimo, Arnold et al., 2021). Monitoring these surfaces for contamination is important for developing evidence-based hazard awareness training, determining appropriate PPE use, and evaluating the adequacy of housekeeping measures.



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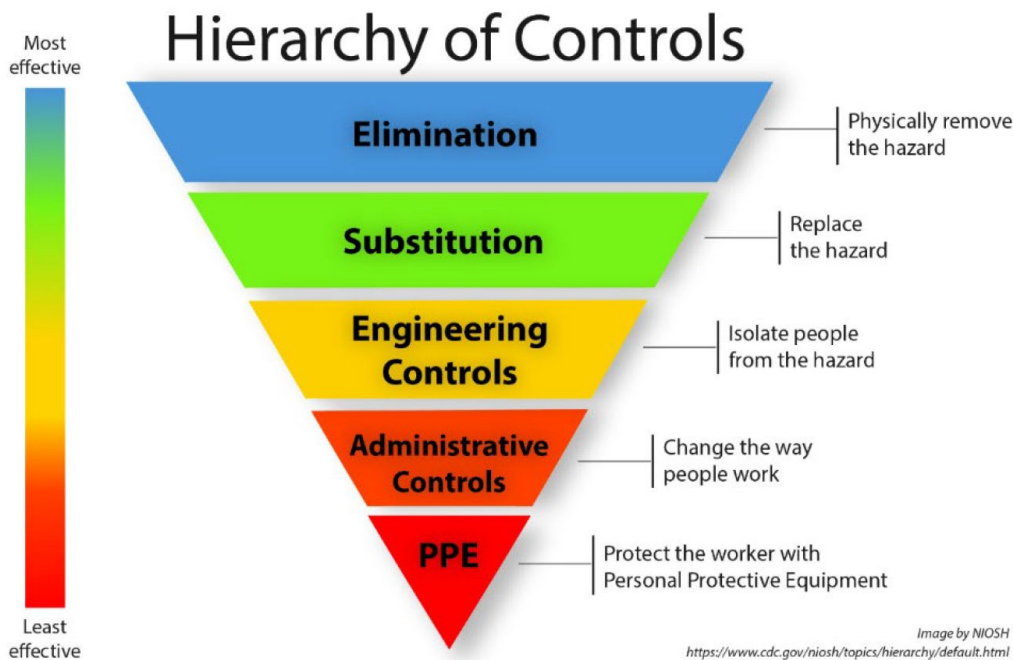
Nurses' work practices associated with patient administration of HD vary more widely within and between institutions compared with the more tightly regulated compounding pharmacy practices (Arnold & Kaup, 2019). Nurses' focus on providing the highest quality patient care and ensuring patient safety in a complex and dynamic work environment can lead to both perceived and real barriers to consistent and appropriate PPE use. Nurses may frequently touch IV bags, lines, pumps, patient ports, and computer workstation surfaces in a multi-center observational study (Arnold & Kaup, 2019), and these surfaces have been reported to have surface HD contamination. In this same study, both gloved and ungloved hands touched some of these same surfaces, potentially leading to the transfer of contamination with contact between contaminated surfaces and unprotected skin.

**Control Systems - Hierarchy of Controls**

Control systems following the hierarchy of controls (see figure 4.3) help healthcare systems build layers of protection for their staff members when handling HDs throughout their lifecycles. **A control system's strength improves with the layering of controls, and this helps minimize both surface contamination and exposure potential (Figure 4.4).** Each layer of the hierarchy of controls and how it can be implemented in healthcare systems is discussed below.

**Elimination**

Recent advances in the automation of compounding have eliminated some manual compounding tasks that were formerly conducted by pharmacists or pharmacy technicians. Please note that healthcare workers operating, maintaining, and cleaning automated



**Figure 4.3. Hierarchy of Controls (NIOSH) The strength of a control system is improved with the layering of controls which helps minimize HD surface contamination and reduce exposure potential.**



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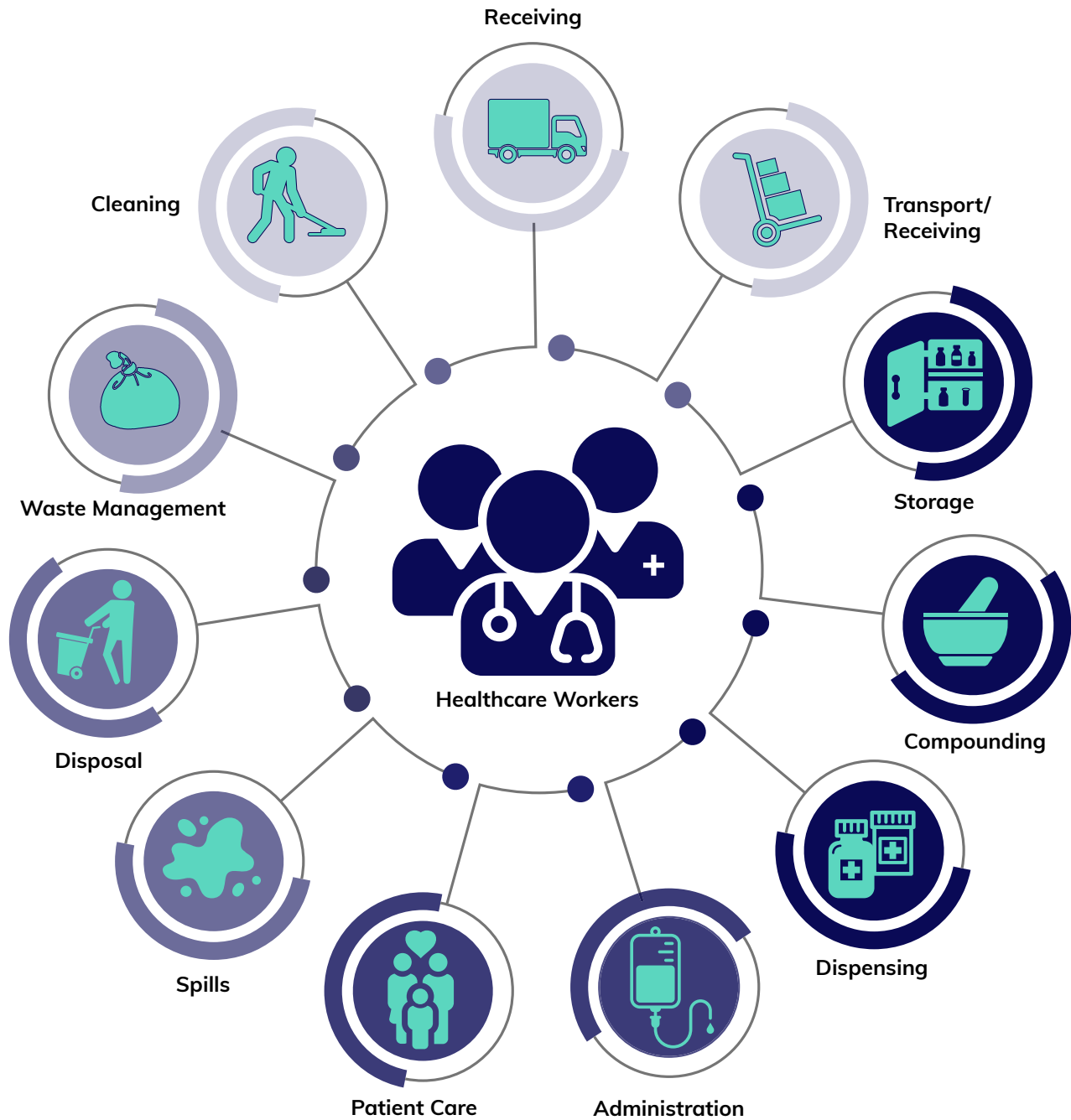


Figure 4.4. Strength of Control Systems for the HD Path in the Healthcare Setting. All drugs can be hazardous, but the potential exposure to those hazards and the relative risk of having an adverse effect can be differentiated. The lighter shading reflects less control measures in place. Adapted from GC <800> Infographic (<https://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare>). Copyright 2020 by U.S. Pharmacopeia. Reprinted with permission.



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compounding equipment may have some work tasks with potential exposure to HDs. Healthcare systems are encouraged to complete risk assessments, qualitative and quantitative, for automated compounding work activities with particular attention to maintenance and cleaning activities.

### Substitution

Substitution is unlikely to be an effective control in healthcare environments with HDs. Patients must receive medication as prescribed. In some cases, providers may consider different formulations or dose forms per patient treatment needs.

### Engineering Controls, Administrative Controls, and Personal Protective Equipment (PPE)

Engineering controls (C-PEC and CSTDs), administrative controls, work practices using Standard Operating Procedures (SOPs), and personal protective equipment (PPE) are all helpful controls that minimize exposure risk for staff. PPE is the lowest tier of the hierarchy of control and is the least effective protection for workers, especially if PPE is the only control in place. In the compounding pharmacy, it is common for each of these layers to be in place and provide a strong overall control system for staff. However, as the HD lifecycle progresses beyond the pharmacy into nursing administration and patient care areas, the layers of control systems often decrease. In patient care areas post-administration, staff members that care for patients and clean these areas may not benefit from any control system. The amount of HDs present is likely diminished; however, studies have shown that there are residues of HDs in these patient care areas (patient rooms and restrooms).

It is important to consider HD surface sampling throughout the HD lifecycle, particularly in areas where the strength of the overall control system may be weaker with only the PPE layer in place. The figure below shows the relative strength of the overall control system throughout the HD lifecycle. Where

CSTDs have been shown to reduce surface contamination of HD on surfaces. (Sessink, Trahan et al., 2013) In a recently conducted study of nine cancer centers in Alberta, Canada, and Minnesota, USA, all six centers in Alberta used CSTDs, while the three centers in Minnesota had not yet transitioned to using these devices. Wipe sampling was conducted monthly over 12 months in pharmacy and patient administration areas. There was a significantly higher percentage of samples above the LOD in the Minnesota-based clinics (2-4x, depending on the HD) compared to the Alberta-based clinics. There was a smaller but notable difference in the 90th percentile levels of contamination, with higher levels of surface contamination observed in the Minnesota-based centers. While other factors that were not specifically captured, such as staff-to-patient ratios, staff workload, and differences in employment models, vary between the two health systems, the use of CSTDs in the Alberta clinics likely contributed to this difference (Jeronimo, Arnold et al., 2012). Another well-designed study by Bartel et al. (2018) supports CSTDs effective reduction of HD surface contamination.

the strength of the control system is lower, it is important to confirm that there is also low exposure potential through qualitative or quantitative risk assessment.

As indicated in the above sections, when evaluating HD surface contamination and the risks posed to workers and patients, it is important to understand the following:

- The potential hazards of the drug substance (as discussed in Section 3),
- How a drug may become aerosolized or spilled through handling,
- The routes of exposure,



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- How the drug compounds may be transferred to and from surfaces, and
- What controls are available or have been implemented to eliminate or reduce exposure

The routes of exposure depend on many of the factors mentioned above and require careful evaluation

by a qualified person. **Once the hazard of the drug substance and the routes of potential exposure have been determined, a risk assessment can be performed to determine the appropriate level of controls (following the hierarchy of controls) to reduce the potential exposure risk to an acceptable level.**

**Table 4.1. Industrial Hygiene Measurements - Air Sampling vs. Surface Sampling**

	Air Sampling	Surface Sampling
<b>Methods</b>	Use validated methods and AIHA-accredited labs	Use validated methods and AIHA-accredited labs
<b>Why</b>	Are employees over-exposed > OEL	Is there contamination in the environment > ASL
<b>Target Levels</b>	<b>OEL</b> = Occupational Exposure Levels (ug/m <sup>3</sup> )	<b>ASLs</b> = Acceptable Surface Levels (ug/cm <sup>2</sup> ) Note: derived from OELs and conservative assumptions by Occupational Toxicologists <b>HGVs</b> = statistically derived health guidance values
<b>Matrix</b>	Air	Hard cleanable surfaces Tile, glass, countertops, door handles, keyboards, IV bags/ poles, keypads, etc.
<b>Exposure Pathway</b>	<b>Personal Breathing Zone (PBZ)</b> Established IH assumptions that if measured in the PBZ, then an employee will directly inhale Employee considered “exposed” based on the results (ug/m <sup>3</sup> )	<b>Multiple Paths and Steps</b> Surface contact with bare skin Re-aerosolized from surface Environmental contamination may lead to “exposure” but not a direct relationship from presence on a surface to “exposure”



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## Section 5. Sampling and Analysis of HDs in Healthcare Settings

### Introduction

There are several ways data are generated to assess occupational HD exposure and exposure risk. While HD surface residuals are considered a significant source of employee exposure to HDs in healthcare settings, all potential exposure routes (i.e., inhalation, transdermal, ocular, oral, and needle stick) should be considered. The most comprehensive means for measuring HD exposures is directly through biological monitoring by analyzing body fluids for the drugs, drug metabolites, or other biological endpoints, but these techniques are typically employed in research settings and not for routine monitoring of healthcare workers. When inhalation is the primary route of exposure, such as in drug manufacturing, industrial hygienists perform exposure assessments indirectly by air sampling with HD-specific sampling and analytical methods available from industrial hygiene laboratories. Due to the noted correlation between HD surface residuals and HD exposures in healthcare environments, industrial hygienists must consider HD surface contamination when assessing the potential of worker exposure.

### HD Surface Sampling Methodologies

There are two general types of sampling methods: (1) qualitative methods yielding a simple “positive” (detected) or “negative” (not detected) result, and (2) quantitative methods that generate numeric values, indicating how much of a drug is collected from a given surface and surface area at a given point in time. Sampling for both method types are typically performed using wet surface swabs or wipes.

Qualitative methods often employ immunoassay technologies, which limit an individual swab/wipe to typically one, or possibly a very small number of specific drugs per sample, and for which assays are available for a relatively modest number of HDs. The

Professionals must note that HD surface sampling measures potential exposures and is not a direct measure of exposure to HDs. HD surface sampling, as recommended in USP <800>, is the most commonly available data source for evaluating and controlling HD exposure risk in healthcare settings.

techniques most commonly used for qualitative testing are enzyme-linked immunosorbent assay (ELISA) and lateral flow immunoassay (LFIA) (Connor & Smith, 2016). These qualitative methods are cost-effective and typically do not require submission to a laboratory for analysis, which makes them particularly useful for activities requiring immediate results, such as spill scenarios to determine the extent of contamination or efficacy of the cleanup. An example of a widely used qualitative sampling method would be BD HD Check. Limitations of these techniques are they have been developed for a relatively small number of HDs (examples: cyclophosphamide, methotrexate, and doxorubicin) and the assessment of only a single drug at a time, which may underestimate the level of total HD contamination (Hon et al. 2014.).

Quantitative methods are generally preferred for routine HD surface sampling as they offer the capability for analyzing multiple HDs simultaneously without requiring individual samples for each drug, provide information for assessing relative levels of contamination, and offer the availability for a larger number of HD analysis options. This is despite a higher relative cost and longer turnaround time for results compared to the qualitative methods. There are a variety of analytical technologies employed by different laboratories for quantitative methods with various levels of sensitivity and specificity. The most common qualitative technologies used in USP <800>



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HD surface sample analysis are High-performance Liquid Chromatography (HPLC) and Mass Spectroscopy Coupled Liquid Chromatography (LC/MS and LC/MS/MS). Regardless of the analytical technology employed, if collected from a measured HD surface area, the sample results allow expressing HD surface concentration in addition to a mass-per-sample result.

### **The Role of HD Surface Sampling in USP <800> and Healthcare Worker Safety**

USP <800> recommends collecting HD surface samples for three distinct reasons. **The first is to confirm that the HD management program and all related procedures are working effectively to prevent or minimize HD surface contamination, and if not, to identify where gaps exist and present opportunities for improvement.** This type of sampling helps to ensure that the work practices surrounding the full life cycle of HD handling from receipt to disposal (but with a particular focus on preparation [counting, compounding, etc.] and administration) minimizes the potential for HD surface contamination. **The second reason for HD surface sampling is to establish a baseline of environmental contamination.** Without a regulatory or USP <800> standard for an acceptable level of HD surface contamination, this baseline serves both as a starting point for improvement and as a measure for assessing future sampling. **The third reason for HD surface sampling is to assess and validate the cleaning procedures.** When compared with the baseline surveillance, this verification can determine the effectiveness of the cleaning procedure and if improvements are needed.

HD surface sampling results also have value in understanding the potential for worker exposure from a health-based ASL approach. A complete review of all the locations that may house or have the potential to come into contact with HDs must be performed. These areas include but are not limited to: compounding pharmacies, dispensing pharmacies,

areas adjacent to these pharmacies (break rooms, office spaces), and patient administration areas (including laundry and waste handling [receiving, IV pump service]). Because the number of locations can be large and resources and budget are usually limited, a comprehensive sampling strategy should be developed to ensure all critical locations within the facility are surveyed at least semi-annually (as recommended by USP <800>) and that every sample collected provides value. If unable to articulate an actionable insight corresponding to a sampling outcome, consider sampling in an alternate sample location where data will provide actionable insights.

See the **Comprehensive Strategy** section of this document for further information and guidance on selecting what and where to sample. In addition, Table 5.1 is provided to assist with selecting common sampling locations, identifying possible gaps associated with corresponding positive sampling results, and proposing potential mitigation actions to close any gaps and reduce employee HD exposure risk.

### **USP <800> Sample Collection**

The procedures for physically collecting USP <800> samples are similar to any other IH surface sampling: using sampling templates with a defined surface area for regular flat surfaces, wipes or swabs wetted with a collection solvent, and sample tubes or vials. NIOSH has developed a resource for guidance for industrial hygiene surface sampling titled “Surface Sampling Guidance, Considerations, and Methods in Occupational Hygiene”. [https://www.cdc.gov/niosh/nmam/pdf/nmam\\_chap\\_sg-508.pdf](https://www.cdc.gov/niosh/nmam/pdf/nmam_chap_sg-508.pdf) The analytical laboratory selected will provide detailed sampling and submission instructions specific to their methods, as well as the sampling media (swabs or wipes) and any tools or materials necessary to complete the sampling task. In the case of qualitative field methods and kits, the supplier or manufacturer will provide materials and instructions for sampling and reading the result.



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## USP <800> Sample Quantitative Analysis

For quantitative laboratory methods, the analysis technique will be as specified by the laboratory performing the analysis. There are a variety of analytical technologies employed in quantitative methods for HDs, each with various levels of corresponding sensitivity and specificity. The most common techniques include High-Performance Liquid Chromatography (HPLC), Ultra-High Performance Liquid Chromatography (UPLC), Mass Spectroscopy Coupled Liquid Chromatography (LC/MS), and Tandem LC/MS (LC/MS/MS). Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis for total platinum is used in some laboratory methods as an indicator of undifferentiated platinum-containing drugs. These techniques (LC/MS/MS in particular) provide the necessary selectivity and sensitivity to accurately quantify HDs in complex matrices at nanogram to picogram mass/sample levels.

## Laboratory Services for USP <800> Quantitative Analysis

There are a number of commercial laboratories offering testing kits and services tailored to USP <800> HD sampling. Selecting a laboratory with demonstrable experience analyzing HDs from surface swabs/wipes as well as methods and capabilities matching the sampling plan is highly recommended. Laboratories should have recognized accreditation for HD sample analysis, such as AIHA lab accreditation. A list of AIHA-accredited laboratories with HD capabilities is available on the AIHA website: <https://online.aihaaccreditedlabs.org/lapssa/f?p=AIHAS-SA:117800>

Below is a list of items to assess and consider when selecting a laboratory for USP <800> sampling and analysis.

- **Does the lab offer analysis for the particular drug(s) you are interested in sampling?** Note that labs often have applications for drugs which are

not included on standard kit lists, so it is a good idea to inquire with the lab if they have a method for sampling a particular HD.

- **Does the reporting limit provide adequate sensitivity to meet the limit (ASL) or targets?** The most meaningful comparative assessment is the reporting limit (RL) in terms of absolute mass per swab or sample, but also consider the RL in terms of mass per surface area based upon recommended sampling area.
- **How are the samples collected and returned for analysis?** What type of swabs or wipes and solvent or wetting solution are used for collection? Swabs may be preferred because they do not require contact with the collection portion of the media, thus limiting cross-contamination risk, while wipes can be easier to use on irregular surfaces such as IV poles or fixtures. For flat regular sampling surfaces such as floors, counters, and work surfaces, sampling templates are commonly provided for consistency in the surface area sampled. A standard 100 cm<sup>2</sup> area is common in industrial hygiene swab sampling as it represents the approximate area of a typical “man hand.” Larger areas are sometimes preferred because they can provide a more representative sample while also improving sensitivity when assessed as mass/area. It is recommended to inquire with the laboratory to confirm that collection efficiency determinations of dried residues of each drug material have been performed from “typical” USP <800> sampling HD surfaces using the technique defined for sampling to verify that the swab/solvent and sampling area/procedures are efficient in quantitatively collecting the samples. Similarly, the laboratory should have defined shipping and storage requirements based upon empirical assessments of each drug, performed on the wetted media under controlled and stress conditions for defined time intervals.



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- **What is the turnaround time from submission to analysis?** Inquire about standard services and whether expedited services are available.
- **Training and guidance in support of the analytical services?** Inquire about live or virtual onboarding training with Q&A, training materials, instruction, and technical resource availability for guidance or questions.
- **Cost of services?** It makes sense to compare pricing from more than one laboratory. Generally, it is most cost effective to collect multiple HDs for analysis from a single sample, assuming that matches the sampling plan. Sampling of sentinel surfaces for representative drugs rather than trying to sample many surfaces for every drug used is a good strategy to manage resources and get the best value from sampling.

**Table 5.1. Risk Assessment Rationale for HD Surface Sampling Locations**

HD Sampling Location	Potential for HD Surface Contamination	Potential for Skin Contact	Possible HD Surface Contamination Source	Recommended Intervention/Action
Upstream contamination areas (exterior packaging of HD vials; exterior of com-pounded sterile product)	Moderate (unknown)	High	Manufacturer/ Supplier contamination on outside of HD primary container Shipping (broken vials, upset conditions) (HD identified)	Feedback to Supply Chain Alternative Suppliers SOPs (best practice to wipe down with decontamination wipe) and PPE
HD Storage Areas	Moderate	Moderate	See above	See above
HD Prep Area (buffer room C-SEC)	Moderate	Low	Variable work habits including non-compliance with SOPs and guidance	Ensure compliance with SOPs and training
Interior of C-PEC and equipment	High	Low	Inadequate cleaning techniques	Regular cleaning; Disposable surfaces; Careful removal of materials from C-PEC; Doffing procedure in C-PEC
HD sterile Parenteral Preparation within C-PEC	High	Low	Noncompliance with administrative controls; Inappropriate PPE; Inadequate cleaning techniques;	Robust cleaning procedures and PPE requirements in administrative procedures
HD non-sterile manipulation within C-PEC/CVE (crushing cyclo-phosphamide)	High	Moderate	Poor handling practices during preparation, inadequate cleaning techniques; lack of PPE	
HD non-sterile manipulation outside of CPEC (counting cyclophosphamide tablets)	Moderate	Moderate	Poor handling practices during preparation, inadequate cleaning techniques; lack of PPE	



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Table 5.1. Risk Assessment Rationale for HD Surface Sampling Locations (cont.)

HD Sampling Location	Potential for HD Surface Contamination	Potential for Skin Contact	Possible HD Surface Contamination Source	Recommended Intervention/Action
Pass-through Chambers	High	Moderate	Potential contamination from: 1. exterior packaging of HD vials 2. exterior of compounded sterile product 3. inadequate cleaning of compounded sterile preparation (CSP) or CSTD is contaminated leaving the prep area	Primary Engineering Control Improve handling practices upstream; Administrative controls and SOP
HD Buffer Room/C-SEC HD surfaces in Staging or Work Areas near C-PEC	High	Moderate	Contamination on HD packaging shipping or as prepared	Procedures; Improve handling practices upstream; Administrative controls and SOP Secondary packaging systems
Areas adjacent to C- PEC (floors directly under C-PEC, staging and dispensing area)	Moderate	Low (floors) Moderate (high touch areas)	Non-conformance with procedures Spills, tracking	Procedures Secondary packaging systems
Areas immediately out-side the HD buffer room or C-SCA	Low	Moderate	Non-conformance with procedures; gowning Spills, tracking	Procedures Gowning
Automation/Robotic equipment High touch areas (HMI - human – machine interface)	Low	High	Non-routine activities/trouble-shooting Interaction/ engagement with interior of equipment without glove change or hand washing	Procedures Strict policies for glove use, glove change and hand washing
Automation/Robotic equipment Loading/Unloading	High	High	High volume/quantity of HD	Engineered systems for closed container loading/unloading Thorough IH evaluation to quantitate potential exposure risk with high volume/quantity of HDs
Automation/Robotic equipment Cleaning	High	High	High volume/quantity of HD	Engineered systems for clean in place Thorough IH evaluation to quantitate potential exposure risk with high volume/quantity of HD



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Table 5.1. Risk Assessment Rationale for HD Surface Sampling Locations (cont.)

HD Sampling Location	Potential for HD Surface Contamination	Potential for Skin Contact	Possible HD Surface Contamination Source	Recommended Intervention/Action
Patient Administration Areas (bed, infusion chair, IV pump, operating room, procedural areas)	High	High	1) Release during administration or 2) Patient related loss (excreta, body fluid)	Administration procedures Gowning/gloves cleaning protocols
Nursing administration cart high touch areas Keyboard, scanner, mouse, handles	High	Moderate	System requirements not aligned to gowning/PPE doff and don	Procedures that consider medication accountability system and healthcare worker protection
Downstream contamination areas such as (housekeeping, cleaning cart, elevator buttons) and patient care surfaces (patient toilets, bed pans, linens etc)	High	High (high touch)	HD tracking through facility Unanticipated contamination on public areas and patient care surfaces; exposure to ancillary, non-clinical staff members (maintenance staff without robust training)	Administration procedures cleaning protocols
Locations where IV pumps are cleaned and serviced	High	High	There are surfaces with high probability of direct contact with HDs	Closed cleaning systems, clean in place (CIP) solutions
Common areas (hallways, family waiting areas, elevators, stairwells)	Low	High	Migration due to HD handling	Cleaning protocols

Note: This information is base on standard controls and assumes SOPs are followed. This table is not intended to be a comprehensive list of surface controls.



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## Section 6. HD Surface Levels – Data Interpretation – Large Dataset Research Findings

Interpreting results depends on the sampling objectives and the surveillance strategy that is used. Sampling may be conducted to demonstrate compliance with guidelines such as USP <800> or it may be conducted as part of a comprehensive HD surface contamination assessment program. How the results are interpreted will also depend on how the analytical lab reports the results. Some labs will report results as 'negative' or 'non-detect (ND).' Results could also be reported as 'quantitative Limit of Quantitation (LOQ).' Conversely, detectable levels of contamination may be reported as 'positive,' or they may be reported quantitatively. Since different HD surface areas may have been sampled, quantitative results should be normalized. For example, ng/cm<sup>2</sup> or pg/cm<sup>2</sup> are commonly reported. Objects such as doorknobs or pens have much less HD surface area than a 10 cm x 10 cm flat HD surface, and reported values can be distorted because of this difference.

A negative result below the decision target, such as ASL, HGV or other actionable level, indicates that on the day that sampling was conducted, the HD surface where the sample was collected did not have levels of that HD above the defined threshold suggesting work practices and hygiene are effective. It provides a HD surface-specific snapshot-in-time perspective.

With a more comprehensive strategy using a sentinel surfaces approach, where key HD surfaces are selected to represent surfaces with a higher likelihood of potential contamination, a negative result suggests that existing controls and work practices are adequate for that surface. If all sample results were negative, the results suggest that existing controls and work practices in that area are working as they should. Greater confidence in worker protection may be given to results that are compared to an ASL

rather than an analytical LOQ, which will vary due to a number of factors.

Results that are above the ASL action level for a particular HD should be investigated further. Thorough root cause analysis (RCA) should be conducted, including observing work activities in the area that may contribute to the HD surface contamination. Consider assessing the location of the surface where the contamination was detected. Is it a surface where contamination is expected, such as a BSC, or is it in an area where surface contamination is unexpected, such as a table in the breakroom or an area with public access? In the latter cases, the presence of HD on these surfaces would require special attention with timely investigation of the source of contamination and ensuring adequate removal and cleaning was conducted. In these unexpected areas, people are less likely to be wearing the appropriate PPE or even be aware of the risk, and there may not be established cleaning protocols. While contamination in the BSC would still require deactivation and decontamination, the source of contamination in the BSC is better understood, not surprising, and procedures are more likely to be in place for addressing it.

Are there multiple surfaces on which the same HD was detected? Multiple contaminated surfaces involving the same HD within a localized area can be indicative of an unplanned event (such as a spill) for which controls, work practices, cleaning, and decontamination did not sufficiently remove the drug. A report showing more than one HD on multiple surfaces suggests existing controls and work practices are not adequate. In these cases, a systematic review of controls and work practices including the use of PPE may be needed. Training or retraining may be necessary to ensure staff are familiar with how and when to use engineering controls and PPE.



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Table 6.1. Reported Hygiene Guidance Values for Various Hazardous Drugs by Country

Hazardous Drug	Country	HGV-1 pg/cm <sup>2</sup>	HGV-2 pg/cm <sup>2</sup>	Source
Platinum (Pt)	Germany	0.6	4	Schierl et al. (2009)
5-Fluorouracil (FU)	Germany	5	30	Schierl et al. (2009)
Cyclophosphamide (CP)	Germany, CAN/USA, Italy	1	5-360	Quartucci et al. (2022); Arnold et al (2022); Sottani et al. (2017)
Ifosfamide (IF)	Germany	1	5	Quartucci et al. (2022)
Gemcitabine (GEM)	Germany, CAN/USA, Italy	1	5-7	Quartucci et al. (2022); Arnold et al (2022); Chaucat et al. (2019)
Methotrexate (MTX)	Germany	2	10	Quartucci et al. (2022)
Docetaxel (DOC)	Germany	3	15	Quartucci et al. (2022)
Paclitaxel (PAC)	Germany CAN/USA	3	15	Quartucci et al. (2022) Arnold et al (2022);
Universal HGV	Germany	100		Kiffmeyer et al. (2013)

Note: HD levels below HGV-1 work practices represented good working practices, whereas levels at or above HGV-2 indicated the need for improving handling practices among pharmacy workers. HGV-1 and HGV-2 values represent the median and 75th percentile contaminant levels for the specific AD.

One component of a comprehensive strategy may be a continuous improvement process, in which HD surface contamination levels can be shown to be going down over time. Here, the benchmark is a non-health-based Hygienic Guidance Value (HGV). HD-specific HGVs are based on upper percentile values of a distribution of results and are typically derived from large-scale surveillance studies. HGVs may be tiered, HD-specific, and associated with specific outcomes and actions, such as the Threshold Guidance Values proposed by Schierl et al. (Schierl, Böhlandt et al., 2009). Universal HGVs that are not HD-specific have also been proposed. Results that are below HD-specific HGVs can be used as evidence of effective controls, work practices, and housekeeping. The use of HGVs in this context requires fairly large data sets and is therefore best suited to larger facilities and more mature programs that have the capacity to collect and analyze a sufficient number of samples.

The collection of HD surface samples, as laid out by USP <800>, generates data to provide insights for assessment and subsequent action to limit the potential for personnel exposure to HDs. This provides a target to maintain exposure at a level “as low as reasonably achievable” (ALARA). ALARA is a principle used within the radiation safety and health physics community to control agents known or suspected to have adverse health effects (e.g., mutagenic, carcinogenic, teratogenic properties, etc.) but lacks defined exposure or control limits.

**Health-Based Acceptable Surface Limits (ASLs) vs. Statistically-Based Hygiene Guidance Values (HGVs)**

Unlike HD inhalation Occupational Exposure Limits (OELs) which are indirectly related to exposure and associated health risk, HD surface limits are indicative of the potential and risk for exposure. This potential



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exposure is related to the possibility of worker skin contact with contaminated HD surfaces in the work environment. In contrast, inhalation exposure limits are based on airborne containment levels in the work environment and the strong probability that employees will inhale the air and contaminant in the work environment, which is generally equated with exposure (see figure of inhalation-dermal slide). There are different types of HD surface limits and that are complementary, but they address different objectives. We briefly describe here two types of HD surface limits, their application, and their limitations.

Ideally, an ASL exists and serves as an objective benchmark for assessing controls and housekeeping. Where there is no ASL, a couple of approaches

can be considered:

**Banding** –ASLs and HGVs as representative compounds/HDs

**Health-based Acceptable Surface Limits (ASLs)**

Health-based ASLs consider the dose-response of a toxicant and are conceptually comparable to inhalation health-based Occupational Exposure Limits (OELs). They represent the top of the hierarchy of OELs, (Figure 6.1)(Laszcz-Davis 2014), reflecting OELs that are set using robust data. Just as HD surface sampling results do not indicate exposure to a particular drug, comparison of a sample result to the ASL is not indicative of internal exposure. The

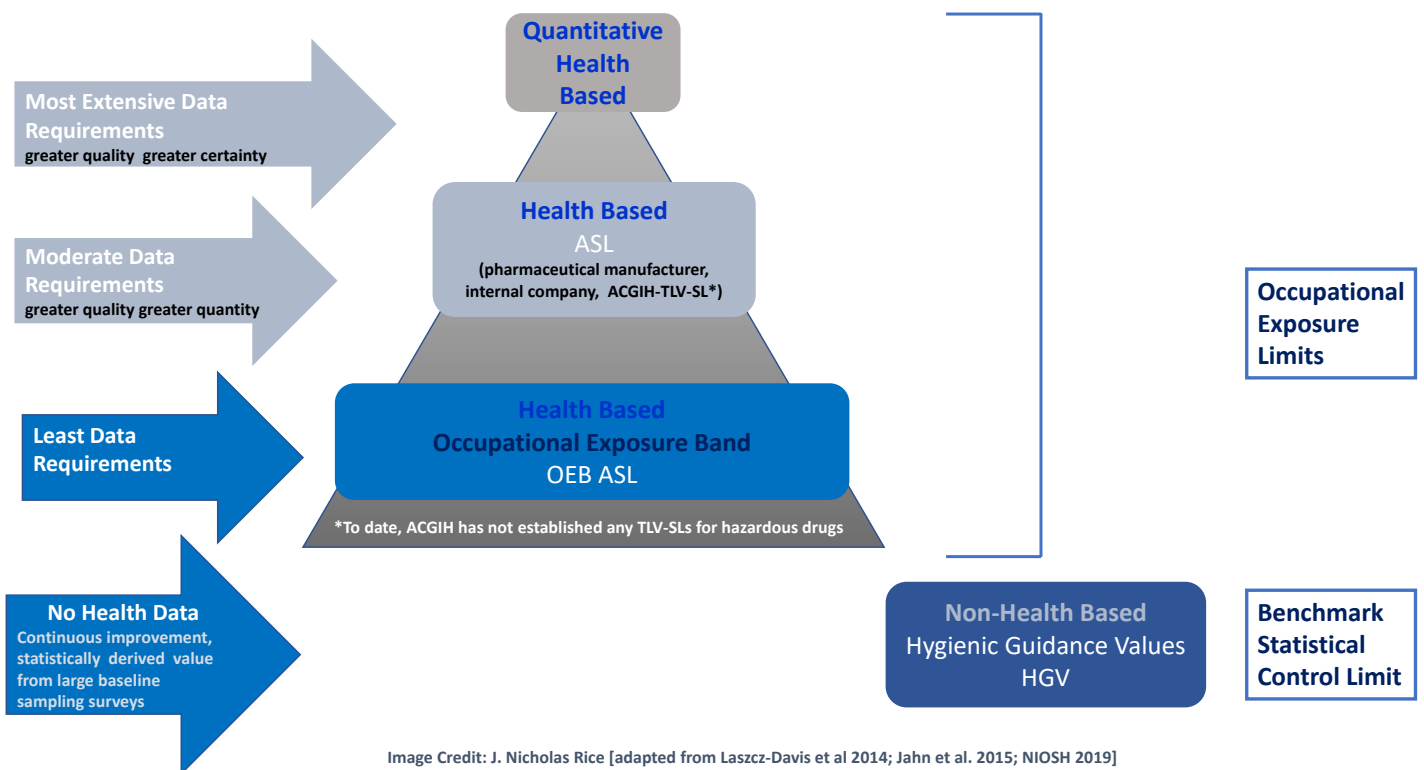


Image Credit: J. Nicholas Rice [adapted from Laszcz-Davis et al 2014; Jahn et al. 2015; NIOSH 2019]

Figure 6.1. A hierarchy of risk-based occupational exposure benchmarks. As more toxicological and epidemiological data become available, one moves up the hierarchy. Adapted from a version of the hierarchy developed by Laszcz-Davis et al. (2014)©AIHA. Reproduced by permission of AIHA. Permission to reuse must be obtained from the rightsholder.



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relationship between a HD surface limit value and its associated health risk is complicated due to the complex and sometimes convoluted pathway from a contaminant on a surface to skin contact, absorption, and adverse health outcome. Typically, a series of conservative assumptions are made to account for this complexity when deriving an ASL. The specific ASL value will reflect its potency and severity of potential adverse health effects such that the more potent and toxic drugs will have lower ASLs. ASLs are useful benchmarks for comparing engineering controls, adherence to work practices, and adequacy of housekeeping measures. The differences in ASLs according to drug potency and toxicity are helpful in prioritizing engineering, work practice control, housekeeping resources, and promoting efficient use of these measures. ASLs can be used to verify a surface has been cleaned adequately following a spill and providing context to wipe sample results for risk communication. They are typically set by toxicologists who interpret toxicological studies of the HD. While they are drug specific, ASLs are conservative to account for additive or synergistic effects associated with exposure to multiple, concurrent exposures. Additionally, an ASL can be adjusted for the class of drug (e.g., estrogens) such that total daily potential exposure of that specific class of drugs be compared to the class of drug's ASL.

### Hygienic Guidance Values (HGVs)

Hygienic guidance values are not health-based. They are performance-based, statistical benchmarks that are estimated from robust data sets of HD surface sampling data. A 90th percentile HGV, for example, reflects the level below which 90 percent of the HD surface sampling results lie. The HGV will trend downward over time if engineering controls, work practices, and housekeeping practices are working effectively. In the absence of health based ASLs for HDs that are especially concerning (e.g., mutagens, carcinogens, reproductive or developmental toxicants, especially if

potent), HGVs can be useful in demonstrating continuous improvement towards the goal of reducing the overall level of HD surface contamination and potential for dermal, inhalation, and oral exposure. HGVs can also be used to verify a surface has been cleaned adequately following a spill and providing context to wipe sample results during risk communication.

**HGVs are typically also drug-specific and therefore require a large enough data set of drug-specific surface sample results to calculate a value that adequately captures the overall magnitude and variability of surface contamination. These values can be calculated by the industrial hygienist or any individual with appropriate statistical training.** The resources and cost to generate such a large data set may be a barrier for smaller organizations or organizations that are just establishing HD surface sampling programs. HGVs developed from other centers could be useful in that case, especially when they represent similar facilities, working environments, and cultures.

Where ASLs exist, this same approach could be used as a best practice to evaluate continuous improvement, substituting a health-based ASL for the statistically-based HGV. Using this approach and following industrial hygiene conventions, targets such as an “action limit” at one-half or one-tenth of the ASL could be used. For this practice to be feasible and become widely adopted, more ASLs must be set with clear documentation showing the basis for the ASL.

### Implementing a Continuous Improvement Plan Using HGVs or ASLs

A three-phase process can be considered for those who select a continuous improvement approach using HGVs or ASLs. The practices presented here are focused on continuously reducing the potential for exposure to HD and HD residues, thereby demonstrating that the potential for exposure is minimized by following a multi-phased approach. The drugs that are referenced from previous surveillance stud-



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ies are among a subset of candidate HDs that can be used to apply this strategy. In this context, they serve as surrogates. Using a panel of HDs efficiently and effectively provides insight into the adequacy of the overall control program.

**Phase I:** Conduct a baseline survey to identify contaminated HD surfaces and quantify contamination levels. This first phase focuses on identifying contaminated HD surfaces associated with routine conditions, work practices, and housekeeping to establish a baseline level of contamination. The strategy is designed to maximize the likelihood of detecting HD surface contamination in HD preparation and patient administration areas.

- Use Hygienic Guidance Values (HGVs) or ASLs as benchmarks for follow up.
  - Use the HGV as a ‘cleaning criteria level’ that when exceeded will trigger an escalating series of housekeeping practices, follow-up testing and re-training.
  - Having an objective quantitative threshold and communicating it before sampling is conducted allows for a more systematic and effective approach to reducing contamination. Transparency in advance while communicating the actions associated with exceeding the level builds trust and confidence in the surveillance program.
  - When the predefined proportion of samples are below the HGV move to Phase II.

**Phase II:** Conduct routine surveillance, and augment with ad hoc sampling. This second phase focuses on identifying contamination that may be due to non-routine events and conditions, e.g. spills, leakage, or breakages of containers containing HD and allows for a more comprehensive evaluation of controls, work practices and housekeeping.

- Sample at least five HD surfaces where you do not expect to find AD residues and assess the same multi-HD panel.

- Select five HD surfaces in area of previously reported unplanned events and sample for multiple HD (select HDs reported in unplanned events and supplement panel with HDs that persist in environment and are routinely used in the clinic).

**Phase III:** Assuring continuous improvement through ongoing surveillance.

- Sample five HD surfaces (‘clean’ areas, e.g., snack area, observation windows, nurses’ station, etc.) selecting a combination of sentinel and non-sentinel HD surfaces.
- When sampling results are all below their respective HGVs or ASLs, consider reducing the HGVs (as the analytical sensitivity allows).

### Limitations of HD Surface Sampling

While the collection, analysis, and interpretation of HD surface sample data may provide useful information to improve worker health and safety, it is not without limitations. Some of the limitations of surface sampling for HDs include:

- Sensitive analytical methods may be costly to develop or unavailable. Without a standard analytical method, limits of detection and limits of quantitation vary, sometimes by orders of magnitude. This variability makes it difficult to compare results across sites where different methods or laboratories have been used, which in turn makes it more challenging to identify trends.
- Some drugs may not be stable in the environment or on the sampling materials, making it more difficult to detect them. Further, analysis has to date focused on the parent compound, so the presence of breakdown products that may be equally or more toxic (e.g., prodrugs such as antibody-drug conjugates) could go undetected.
- It may be difficult to correlate elevated HD surface levels with specific sources of contamination. The lag time between sampling and receiving lab



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results makes it difficult to link contamination to events, work practices, or control-related issues. Documenting contextual details related to the sample collection is critically important! This can help to understand unexpected results. Consulting with staff working in the areas during sampling can provide important insights about working conditions, practices, or events that might influence the sampling results.

- High variability in HD surface sampling technique (pressure, surface area, number of swipes) may lead to inconsistent results. Differences in surface area wiped impacts the reported limit of detection and can also influence the likelihood of capturing contamination on surfaces. Using trained staff to collect samples and ensuring consistency in ap-

proaches is important. If a change is made in the analytical lab processing the samples, the sampling method and media should be carefully reviewed and documented since these changes can lead to differences in sampling results.

- The results from HD surface sampling are not an indication of occupational exposure but may be indicative of the potential for exposure if a surface is found to be contaminated. The potential may be higher for surfaces that are frequently touched by unprotected skin. Multiple HDs are frequently detected on surfaces so the possibility of additive or synergistic effects should be considered. HD surface sampling results provide insight into the adequacy of controls, workplace practices, and house-keeping.



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## Section 7. A Comprehensive HD Surface Sampling Strategy

An HD surface sampling plan should be established up front and define several parameters:

- 1) Objective of HD surface sampling,
- 2) Roles and responsibilities,
- 3) HDs to be analyzed,
- 4) Selection of a HD surface limit (examples ASL, HGV, RL) or method of data interpretation,
- 5) Sampling and analytical methods including surface area (cm<sup>2</sup>) to be sampled,
- 6) Where to sample and how many samples, and when to sample,
- 7) Interpretation,
- 8) Documentation and communication of results, and
- 9) Frequency of surveillance sampling.

### Objectives of the HD Surface Sampling

While the overall intent of a comprehensive HD program is to protect worker health, the objectives of a sampling plan can differ.

All routes of exposure should be considered – skin contact, inhalation, ingestion, and injection. Many postulate that skin contact is the primary route of exposure in healthcare delivery environments (Connor & McDiarmid, 2006; Fransman et al., 2007; Hama et al., 2011; Hon et al., 2011; Hon et al., 2015; Sottani et al., 2010; Suspiro & Prista, 2011). Inhalation can be a significant route of exposure when HD powders are handled, when HD aerosols are generated such as nebulized medications, or when high vapor pressure compounds are encountered such as nitrogen mustard. While inhalation and other routes of exposure should be considered, the focus of this guidance is on HD surface contamination.

Ideally, the objective is for the HD surface sampling to inform the assessment of risk, i.e., the exposure piece of a thorough occupational risk assessment. HD surface sampling is also useful to determine that the engineering and administrative controls are effectively controlling exposure potential. A risk-based approach assesses potential exposure against a hazard criterion such as a health-based ASL. For pharmacy preparation and healthcare delivery, a risk-based approach is complicated by the sheer number of HDs that can be handled and the historic lack of access to HD ASLs. Guidance toward developing an efficient and effective sampling strategy to overcome some of these barriers is provided below and throughout this document.

An alternate, continuous improvement approach aligned with the ALARA principle has been proposed where HD surface levels are compared against HGVs, which are non-health-based limits statistically derived from baseline HD surface sampling surveys. The HGV approach leads to continuous reduction of environmental contamination and associated potential exposure. The HGV approach is a new concept in the United States but has been used in several European countries (Arnold et al., 2022; Hedmer & Wohlfart, 2012; Kiffmeyer et al., 2013; Quartucci et al., 2023; Schierl et al., 2009; Sottani et al., 2017). A limitation of the HGV approach is that it may continue to drive control to very low HD surface levels that can be overly conservative with diminishing returns for worker health protections.

Sampling objectives can also be targeted at specific scenarios (Connor et al., 2016), such as:

- Verification of cleanliness following a spill,
- Verification of cleanliness when decommissioning equipment or rooms (e.g., BSCs, CACIs, or CVEs), and



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- Evaluating or comparing effectiveness of cleaning, decontamination, and deactivation processes.

### **Roles and Responsibilities**

Ideally, a multidisciplinary team establishes the comprehensive HD program while including the sampling strategy. Team roles should be defined, including who will contribute to the sampling plan, who is qualified to collect samples, who is qualified to interpret samples, and who will report results (this includes reporting results to potentially exposed workers). Primary team members should consist of pharmacists, pharmacy technicians, nurses, and an industrial hygienist. Support from a toxicologist can be especially valuable in developing acceptable HD surface limits and interpreting data. Other supporting team members may include the industrial hygiene laboratory, facilities maintenance, custodial services, toxicologist, and certifiers such as CETA Registered Cleanroom Certification Professionals for Sterile Compounding Facilities (RCCP-SCF).

Outside of the United States, industrial hygienists are referred to as occupational hygienists. Many industrial hygienists do not work in heavy industry, and the industrial reference can be a misnomer. The core role of industrial hygiene is protecting worker health. Industrial hygienists are exposure scientists with specialized training in chemistry, toxicology, epidemiology, and ventilation controls. Most industrial hygienists have a graduate degree. The gold standard in the United States is professional certification as a CIH (Certified Industrial Hygienist). In Canada, the Canadian Registration Board for Occupational Hygienists issues the credential of ROH (Registered Occupational Hygienist). The International Occupational Hygiene Association (IOHA) organizes a National Accreditation Recognition scheme that evaluates and recognizes certification programs against the IOHA Model Certification Program.

Industrial hygienists are exposure scientists, problem solvers, and solution focused. They are highly skilled at taking exposure measurements and understanding the best methods for the collection and determination of contaminants in the environment. Industrial Hygienists are also highly skilled at risk assessment - observing worker behavior and identifying gaps and opportunities to improve the overall control system. Hygienists should be a part of the USP <800> Hazardous Drug team to help you measure effectively, interpret your results, and provide recommendations for improvements in your control systems including - engineering, administrative/SOP/work practices, and personal protective equipment (PPE).

Occupational toxicologists are instrumental in establishing occupational exposure limits including acceptable surface limits. The American Board of Toxicology issues the certification of Diplomate of the American Board of Toxicology (DABT). In pharmaceutical manufacturing, toxicologists are routinely involved in exposure limit setting.

Industrial hygienists and toxicologists partner across disciplines to effectively address occupational exposure control, especially in situations with limited information, where the hazard characterization is incomplete and where there are no accessible exposure limits or acceptable surface limits. Industrial hygienists routinely interface with specialized analytical laboratories and are accustomed to the nuances of collecting HD surface samples and interpreting results. For pharmacies or healthcare institutions that do not have access to internal industrial hygiene resources, AIHA and ACGIH publish consultant directories. If consulting industrial hygienists are used, those with experience in healthcare or pharmaceutical manufacturing can bring specialized insight to the HD program. Considering the analytical cost associated with HD surface sampling, having a professional industrial hygienist support the HD program is a beneficial investment in protecting worker health.



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Industrial hygienists and toxicologists are employed in a wide range of industries, including the pharmaceutical industry where HDs are developed and manufactured. In the pharmaceutical industry the commonly used terminology for potent compounds is potent active pharmaceutical ingredients (API) and highly potent API (HPAPI); in most cases potent API and HPAPI would be defined as HDs under the NIOSH definition. There are well-established hygiene principles, control systems, and ways of working in the pharmaceutical industry with potent API and HPAPI, designed to provide containment and minimize potential exposure to workers in the environment. Healthcare environments and USP <800> HD programs have unique challenges in patient administration areas. However, there are lessons learned from the pharmaceutical industry that can be translated to healthcare environments.

### HDs to be Analyzed

Depending on the pharmacy and drug administration nuances of the healthcare facility, the specific type and number of HDs handled can vary. For example, a specialized compounding pharmacy preparing non-sterile hormones will differ from a retail pharmacy that prepares a handful of oral HD preparations, a physician-based oncology infusion center, or a large academic research hospital. A good starting point for selecting the most appropriate HDs to sample is the USP <800> mandated HD list specific to the facility. It is also useful to identify the top HDs by volume prepared and administered. Further, special cases where HD surface contamination potential is high or where containment controls are not ideal should be considered in selecting HDs to sample. Such special cases may include HDs not compatible with CSTDs, HDs in ampules, API in powder form, preparation with many manipulations, opening of capsules, crushing of tablets, oral and topical preparation, interoperative intraperitoneal chemotherapy, bladder installation, and ophthalmologic injection.

Consider potency and environmental stability when selecting HDs. Some HDs are more difficult to clean and may persist on surfaces longer compared to other HDs. Several laboratories and published studies have suggested HD panels, which tend to focus on antineoplastics that may be encountered in oncology-focused centers; these panels may not be representative of HDs used at a particular pharmacy or facility. In these cases, customized panels may be more useful.

It is typically not feasible to sample for all HDs handled and representative drugs must be selected. Sampling for a minimum of three HDs is recommended. In simulation studies, sampling for three antineoplastic HDs versus only one antineoplastic HD demonstrated a higher probability of detecting contamination on truly contaminated HD surfaces (Arnold et al., 2022, Figure 2). For a large or complex pharmacy and administration scenario selecting five or ten representative drugs may be more appropriate.

### Selection of a HD Surface Limit or Method of Data Interpretation

Section 6 covers HD surface limits and data interpretation in detail. HD surface limits and the method of data interpretation should be established prior to sampling. Depending on objectives, sample results may be compared to health-based ASLs or continuous improvement HGVs. Some may choose to use an ALARA approach. In addition, sample results can be trended over time and between similar facilities

### Sampling and Analytical Methods

Section 5 provides a review of sampling and analysis. A practical limitation of HDs selected for analysis can be the analytical offerings of commercial industrial hygiene laboratories. Cross-reference the short list of HDs of most interest against analytical offerings. Industrial hygiene laboratories with pharmaceutical manufacturers as clients will have more HDs offerings and validated methods. Methods with reporting limits



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(RLs) in the low ng or pg level offer the best chance of detecting HDs. The RLs for the analytical method selected need to be sensitive enough to support the sampling plan objective and associated ASL or HGV.

### **Where to Sample, How Many Samples, and When to Sample**

In selecting where to sample, HD workflow needs to be considered – receiving, preparation, administration, through disposal. See Figure ? graphic for potential areas of HD surface contamination. Both surfaces with a high likelihood of contamination and high-touch surfaces can be considered.

For an oncology infusion scenario, sample a minimum of five locations from HD preparation and patient administration areas; consider more sampling locations. Five Sentinel surfaces, typically high risk for contact or contamination, are defined as surfaces that are most likely to be contaminated, and are identified from previous in-house sampling, reported staff concerns, or highly suspected to be contaminated based on published literature. Compared to a random sampling strategy, sampling from sentinel surfaces showed a greater likelihood of finding contamination with fewer samples (Arnold et al., 2022).

Consider when to sample related to drug preparation and administration in the sampling plan. Sampling is ideally conducted within 48 hours of HD preparation or administration. In a surveillance study, antineoplastic HDs compounded within the past 48 hours were significantly associated with detection and contamination (Jeronimo et al., 2021; Arnold et al., 2022).

Sampling time related to routine cleaning and decontamination/deactivation activities is also a con-

sideration. Depending on your sampling plan objectives, sampling at the end of the compounding or administration day but before cleaning may provide a better representation of the potential for exposure during the day. Sampling before and after cleaning activities would address an objective related to the thoroughness and validation of cleaning.

### **Interpretation**

Section 6 covers data interpretation in detail. Sampling results are compared to the selected limit (ASL, HGV, RL, etc). If limits are exceeded, controls and work practices are reevaluated, and corrective actions confirmed with further sampling.

### **Documentation and Communication of Results**

Document the site-specific sampling plan results, interpretation, and corrective action. Including a site map and digital photos for future reference is highly recommended as it helps with recalling where sampling occurred when reporting, communicating results, and for any subsequent work practice training. OSHA requires that employee exposure records and associated SDSs be maintained for at least thirty years (OSHA). Results should be communicated to both management and staff.

### **Frequency of Surveillance Sampling**

Repeating wipe sampling at least twice per year as indicated in USP <800> is advised. Simulations showed an increase in the likelihood of detecting HD on contaminated HD surfaces with semi-annual sampling compared to annual sampling, but quarterly and monthly sampling showed only trivial increase in likelihood compared with semi-annual sampling (Arnold et al., 2022).



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## Appendix A. NIOSH Hazardous Drug Definition

Below is the HD definition as stated in Part IV of the NIOSH Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings, Effective: April 2023.

The NIOSH definition of a “hazardous” drug is a drug that is

- A. Approved for use in humans<sup>11</sup> by the Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER),<sup>12</sup>
- B. Not otherwise regulated by the U.S. Nuclear Regulatory Commission,<sup>13</sup> and
- C. Either
  1. Is accompanied by prescribing information in the “package insert”<sup>14</sup> that includes a manufacturer’s special handling information (MSHI),<sup>15</sup> or
  2. Is determined to be a carcinogenic hazard, developmental hazard, reproductive hazard, genotoxic hazard, or other health hazard by exhibiting one or more of the following toxicity criteria in humans, animal models, or in vitro systems:
    - Carcinogenicity,
    - Developmental toxicity (including teratogenicity),
    - Reproductive toxicity,
    - Genotoxicity,
    - Organ toxicity at low doses,<sup>16</sup> or a
    - Structure and toxicity profile that mimics existing drugs determined hazardous by exhibiting any one of the previous five toxicity types.<sup>6</sup>

However, if a drug also exhibits a molecular property<sup>17</sup> that may limit the potential for adverse health effects from exposure to the drug in healthcare workers, it may be determined it is not a hazard.

<sup>11</sup>Although only drugs approved by FDA for use in humans are included in the definition of hazardous drug, some of those drugs may be used in veterinary settings for treatment of animals and may be a hazard for veterinary care workers.

<sup>12</sup>Although biological products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, recombinant therapeutic proteins, are included in FDA definition of a drug, they are not included in the drugs that NIOSH evaluates for potential inclusion on the List because they are approved for use by FDA’s Center for Biologics Evaluation and Research (CBER), not by FDA’s CDER. This provision makes clear NIOSH’s long-standing practice of only considering drugs approved by FDA CDER.

<sup>13</sup>10 CFR Parts 19, 20, and 35. See <https://www.nrc.gov/materials/miau/med-use.html>. Drugs regulated by the Nuclear Regulatory Commission are not included on the List.



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<sup>14</sup>See Drug Advertising: A Glossary of Terms at <https://www.fda.gov/drugs/resourcesforyou/consumers/prescriptiondrugadvertising/ucm072025.htm>. "Prescribing information is also called product information, product labeling, or the package insert ("the PI"). It is generally drafted by the drug company and approved by FDA. This information travels with a drug as it moves from the company to the pharmacist. It includes the details and directions healthcare providers need to prescribe the drug properly. It is also the basis for how the drug company can advertise its drug. The prescribing information includes such details about the drug as: its chemical description; how it works; how it interacts with other drugs, supplements, foods, and beverages; what condition(s) or disease(s) it treats; who should not use the drug; serious side effects, even if they occur rarely; commonly occurring side effects, even if they are not serious; effects on specific groups of patients, such as children, pregnant women, or older adults and how to use it in these populations."

<sup>15</sup>MSHI includes language that informs those handling the drug of the need to follow heightened handling and disposal procedures. For example, language such as "follow special handling and disposal procedures" or "procedures for proper handling and disposal of anticancer drugs should be considered" is frequently used in package inserts. However, NIOSH does not consider language pertaining to packaging and temperature controls as MSHI.

<sup>16</sup>All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 milligrams per day (mg/day) or a dose of 1 milligram per kilogram (mg/kg) per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) after applying appropriate uncertainty factors. See Naumann BD, Sargent EV [1997]. Setting occupational exposure limits for pharmaceuticals. *Occup Med* 12(1):67–80; Sargent EV, Kirk GD [1988]. Establishing airborne exposure control limits in the pharmaceutical industry airborne exposure control limits in the pharmaceutical industry. *Am Ind Hyg Assoc J* 49(6):309–313; Sargent EV, Naumann BD, Dolan DG, Faria EC, Schulman L [2002]. The importance of human data in the establishment of occupational exposure limits. *Hum Ecol Risk Assess* 8(4):805–822. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry.

<sup>17</sup>Properties of a drug molecule that may limit adverse effects in healthcare workers are typically chemical, physical, and structural properties that affect its absorption (ability to enter the cells of the body), e.g., chemical structure, molecular weight, or mass. See Clementi F, Fumagalli G [2015]. *Molecular pharmacology*. Hoboken, NJ: Wiley & Sons; Di L, Kerns EH [2016]. *Drug-like properties: concepts, structure, design, and methods*. Oxford, UK: Elsevier; Mattson P, Kihlberg J [2017]. How big is too big for cell permeability? *J Med Chem* 60(5):1662–1664, <https://doi.org/10.1021/acs.jmedchem.7b00237>.



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## Appendix B. Glossary

\* - Definitions come from USP <800>

\*\* - Definitions come from the WHO

**Acceptable surface limit (ASL):** The concentration on workplace surfaces that is intended to protect workers from developing adverse systemic effects resulting from direct skin-to-surface contact.

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

**Active Pharmaceutical Ingredient (API)\*\*:** Any substance or combination of substances used in a finished pharmaceutical product (FPP) intended to furnish pharmacological activity or to otherwise have a direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to have direct effect in restoring, correcting, or modifying physiological functions in human beings.

**Ante-room\*:** An ISO Class 7 or cleaner room where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The ISO 7 ante-room is directly connected to a negative pressure buffer room where compounding of HDs occurs. Note: Can be ISO 8 if it opens only into positive space.

**Assessment of Risk\*:** An evaluation of risk to determine alternative containment strategies and/or work practices.

Note: Assessment of risk of exposure is typically a qualitative evaluation of risk, for potential worker exposure to determine alternative containment strategies and/or work practices.

**Beyond-use date (BUD)\*:** The date or time beyond which a compounded preparation cannot be used and must be discarded (see <795> and <797>). The date or time is determined from the date or time when the preparation was compounded. BUD is based on factors that affect sterility such as the conditions of the environment where CSP is prepared, sterility of starting components, and storage conditions.

**Biological safety cabinet (BSC)\*:** A ventilated cabinet often used for the preparation of HDs. These cabinets are divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, Type B2, Type C1). See Appendix 3 of USP <800> for more details.

**Buffer room\*:** an ISO Class 7 or better room in which PECs are placed for the creation of compounded sterile preparations (CSPs). They may either be positive pressure in relation to an adjoining ante or buffer room, suitable only for the preparation of nonhazardous CSPs, or negative pressure, suitable for the preparation of hazardous CSPs. If the latter, the adjoining ante room must contain ISO Class 7 or better air.

**Certified Industrial Hygienist (CIH):** The industrial hygiene board certification issued by the Board for Global EHS Credentialing. CIHs protect the health and safety of workers and the public by anticipating, recognizing, evaluating, and controlling chemical, physical, ergonomic, or biological hazards. A CIH must meet the minimum requirements for education and experience and, through examination, demonstrate a minimum level of knowledge and skills in areas including air sampling & instrumentation, analytical chemistry, biostatistics & epidemiology, community exposure, engineering controls/ventilation, ergonomics, health risk analysis & hazard communication, non-engineering controls, and toxicology.



HEALTHIER WORKPLACES | A HEALTHIER WORLD



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

**Chemotherapy gown:** A protective gown meeting design and performance standards for the prevention of exposure to liquid chemotherapy and other liquid HDs. ASTM F3267-22 establishes permeation resistance criteria for protective clothing used for HDs.

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

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

**Closed-system drug-transfer device (CSTD)\*:** A drug-transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD outside the system.

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

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

**Compounding aseptic isolator (CAI)\*:** A compounding isolator specifically designed for compounding

sterile, non-hazardous pharmaceutical ingredients or preparations. The CAI is designed to maintain an aseptic compounding environment throughout the compounding and material transfer processes.

**Compounding personnel\*:** Individuals who participate in the compounding process.

**Containment primary engineering control (C-PEC)\*:** A ventilated device designed and operated to minimize worker and environmental exposures to HDs by controlling emissions of airborne contaminants through the following:

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

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

**Containment segregated compounding area (C-SCA)\*:** A designated, unclassified room with fixed walls, HEPA-filtered supply air, a negative pressure between 0.010 and 0.030, and a minimum of 12 air changes per hour (ACPH). A hand-washing sink must be placed at least 1 meter from C-PEC and may be either inside the C-SCA or directly outside the C-SCA. It has a perimeter that contains a PEC and is suitable for the preparation of Category 1 CSPs only with BUDs described in <797> for CSPs prepared in SCA.



HEALTHIER WORKPLACES | A HEALTHIER WORLD

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

**Deactivation\*:** Treatment of an HD contaminant on surfaces with a chemical, heat, ultraviolet light, or another agent to transform the HD into a less hazardous agent.

**Decontamination\*:** Inactivation, neutralization, or removal of HD contaminants on surfaces, usually by chemical means.

**Disinfection\*:** The process of inhibiting or destroying microorganisms.

**Doff\*:** To remove PPE.

**Don\*:** To put on PPE.

**Engineering control\*:** Primary, secondary, and supplemental devices designed to eliminate or reduce worker exposure to HDs.

**EPA-registered disinfectant\*:** Antimicrobial products registered with the Environmental Protection Agency (EPA) for healthcare use against pathogens specified in the product labeling.

**Externally vented\*:** Exhausted to the outside.

**Final dosage form\*:** Any form of medication that requires no further manipulation before administration.

#### FDA – approved Prescribing Information

**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 covers the eyes, eye sockets, and facial area that immediately surrounds the eyes. Goggles provide

protection from impact, dust, and splashes. Some goggles fit over corrective lenses.

**Hazard\*:** The potential for harm (physical or mental). In practical terms, a hazard often is associated with a condition or activity that, if left uncontrolled, can result in an injury or illness.

**Hazardous drugs (HDs)\*:** Any drug identified by at least one of the following criteria:

- Carcinogenicity, teratogenicity, or developmental toxicity
- Reproductive toxicity in humans
- Organ toxicity at low dose in humans or animals
- Genotoxicity or new drugs that mimic existing HDs in structure or toxicity

*Note: HDs may be recognized as a hazard as defined by Globally Harmonized System (GHS) and implemented by OSHA for classification and labeling to communicate workplace hazards (GHS, 2019) may also indicate a drug is a hazard, but it is important to consider that these classifications have a broader scope and do not necessarily indicate a HD as described by NIOSH or USP <800>.*

#### See Appendix A. NIOSH Definition of Hazardous Drugs (2023)

NIOSH has formalized the methodology NIOSH uses to guide the addition of drugs to or removal of drugs from the List in a document entitled Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings (Procedures). The NIOSH procedure takes time and the NIOSH definition may not be inclusive enough for all facilities. Some facilities may need to consider what is in their formularies and if some of the treatments they have are not evaluated by NIOSH or are not yet evaluated by NIOSH. Things such as new drugs, investigational drugs, drugs approved



HEALTHIER WORKPLACES | A HEALTHIER WORLD

under emergency use applications, or biological treatments approved by CBER (vaccines, infectious agents, BCG) may not have been evaluated for placement on the NIOSH List. 1 As stated in the Procedures (See Appendix A. NIOSH Definition of Hazardous Drugs (2023)).

**Healthcare settings:** A setting that provides health-care across a continuum of care, including hospitals, doctor's offices, nursing homes, office-based surgery centers, laboratories, behavioral health treatment facilities, providers of home care services, and veterinary facilities.

**Hierarchy of Controls:** The preferred order of control processes to decrease the risk of worker exposures based on effectiveness. Arranged from the most to least effective and include: elimination, substitution, engineering controls, administrative controls, and personal protective equipment (see page 45 for figure *Hierarchy of Controls*).

**High-efficiency particulate air (HEPA) filtration\*:** An extended-medium, dry-type filter in a rigid frame, having a minimum particle collection efficiency of 99.97% for particles with a mass median diameter of 0.3  $\mu\text{m}$  when tested at a rated airflow in accordance with MIL STD 282 using IEST Recommended Standard RP-CC001.5.

**Hygienic guidance values (HGVs):** HGVs are non-health-based but practical, achievable levels that are generally set at an upper percentile, e.g. 90th percentile of the available monitoring results. They serve as a benchmark for healthcare workers of their own surface loads as an indicator of dermal exposure. Exceedances don't necessarily indicate that there is a health risk but they do suggest that the potential exposure from surface contamination that has not been adequately controlled.

**Industrial hygienists (IHS):** Professional scientists and/or engineers committed to protecting people's health and safety in the workplace and the community. See also *Certified Industrial Hygienist (CIH)*.

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

**National Institute for Occupational Safety and Health (NIOSH):** The United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.

**Occupational Exposure Limit (OEL):** the level of exposure established as the highest level of airborne exposure an employee may be exposed to without incurring the risk of adverse health effects. (OSHA PEL - <https://www.osha.gov/laws-regs/standardinterpretations/1995-10-06-3>)

**Occupational Exposure Band (OEB):** When OELs are not available, defines the range of air concentrations expected to be protective of worker health aligned with risk management decisions. Based on a chemical substance's toxicity. (NIOSH - <https://www.cdc.gov/niosh/docs/2019-132/>)

**Occupational Safety and Health Administration (OSHA):** A large regulatory agency of the United States Department of Labor that has the power to inspect and examine workplaces and enforce regulations. 29CFR

**Pass-through chamber\*:** An enclosure with interlocking doors that is positioned between two spaces for the purpose of reducing particulate transfer while moving materials from one space to another. A pass-through chamber serving negative-pressure rooms needs to be equipped with sealed doors.



HEALTHIER WORKPLACES | A HEALTHIER WORLD

**Permissible exposure limit (PEL):** The level of exposure established as the highest level of exposure an employee may be exposed to without incurring the risk of adverse health effects. (OSHA PEL definition <https://www.osha.gov/laws-regs/standardinterpretations/1995-10-06-3> The employee's average airborne exposure in any 8-hour work shift of a 40-hour work week which shall not be exceeded.)

**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.

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

**Prescribing information (PI):** A document containing the Food and Drug Administration (FDA) findings on safety and efficacy of the human prescription drug under the labeled conditions of use. The PI is written for healthcare professionals and contains specific details regarding the summary of scientific information for the drug.

**Recommended exposure limit (REL):** An occupational exposure limit (OEL) put forth by NIOSH.

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

**Reporting limit (RL):** The reporting limit (more precisely, the "lower reporting limit") refers to the lowest absolute mass or concentration reported by an analytical test method or laboratory as a positive result. Reporting limit is often confused with Detection Limit, which is the minimum level at which an analyte (HD) can be qualitatively detected from background noise. The limit of quantitation (LOQ, or more precisely, the lower limit of quantitation) is the minimum level at which an analyte (HD) can be reliably reported to a specified degree

of accuracy and precision. The reporting limit for quantitative analysis will empirically be demonstrated by a laboratory at or higher than the method LOQ.

**Representative drug:** An HD that is selected by an organization as a part of their surface sampling strategy, based on factors that may include: high volume use and handling throughout the facility, availability of analytical methods, and availability of recognized targets such as health based acceptable surface limits (ASLs) or health guidance values (HGVs).

**Risk:** The probability that an adverse event (such as an exposure, injury, or a loss) will happen.

**Risk assessment:** A process to identify potential hazards, related severity of the hazard, and the probability that an exposure to the hazard occurs. Risk = hazard X exposure probability.

**Root cause analysis (RCA):** A process, method, or procedure that helps discover and understand the initiating fundamental reason for the occurrence of a problem (Medgate).

**Root cause:** The fundamental reason for the occurrence of a problem (The Collins English Dictionary)

**Safety data sheet (SDS)\*:** An informational document that provides written or printed material concerning a hazardous chemical. The SDS is prepared in accordance with OSHA's Hazard Communication Standard (HCS) [previously known as a Material Safety Data Sheet (MSDS)].

**Sentinel surface:** A surface that is more likely to be contaminated with HD residues based on the frequency of detection in published surveillance data, previous in-house monitoring, or reported staff concerns. Several sentinel surfaces, such as HD prep area, pass-through chambers, and surfaces in patient administration areas (e.g., IV poles) are included in USP <800> guidance.



HEALTHIER WORKPLACES | A HEALTHIER WORLD

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

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

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

**Threshold Limit Value (TLV®):** The concentration in air that may be breathed in without harmful effects for five consecutive eight-hour working days. The OELs developed by the American Conference of Governmental Industrial Hygienists (ACGIH).

**Threshold Limit Value Surface Limit (TLV-SL®):** The concentration on workplace equipment and facility surfaces that is not likely to result in adverse effects following direct or indirect contact. Developed by the American Conference of Governmental Industrial Hygienists (ACGIH).

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

**USP\*:** United States Pharmacopeia is an independent, scientific nonprofit organization with a mission to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.



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## Appendix C. Toxicology Principles

### Route of Exposure

Exposures to HDs may occur through inhalation, skin contact, skin absorption, ingestion, or injection. Inhalation and skin contact/absorption are the most likely routes of exposure, but unintentional ingestion from hand to mouth contact and unintentional injection through a needle-stick or sharps injury are also possible (Murff, 2012). When considering the hazards associated with any drug exposure, it is important to note the route of exposure. The route of exposure is the specific way that the chemical enters or contacts the body. The primary routes of exposure are intravenous (IV), where chemicals are injected directly into the blood stream; orally, where chemicals are ingested and pass through the GI tract to enter the body; respiratory exposure, where airborne chemicals pass through the respiratory tract to enter the body; and dermal exposure, where chemicals come in contact with the skin. There are other, less common routes of exposure as well, such as contact with the eye which can lead to absorption into the body or subcutaneous injection which leads to exposures that are different than either external dermal exposure or IV injection. In general, the most common exposures to chemicals are respiratory exposure, oral exposure, dermal exposures, and IV exposures.

The route of exposure is important for determining the hazard. Some routes of exposure have specific hazards associated with them. Drugs may have effects directly on the tissues of the initial route of exposure or may face different metabolic fates through different routes of exposure. IV injection bypasses first-pass metabolism while inhalation may cause irritation and damage directly to the respiratory tract that would not happen via other exposure routes.

When patients are treated with drugs the exposure routes depend on the drug. Drugs are commonly ad-

ministered via IV injection, subcutaneous injection, and orally. Less commonly drugs can be administered dermally through transdermal patches, inhaled using mechanisms like nebulizers and inhalers, or even applied directly to the eye. The routes of exposure that are relevant for workers handling drugs in healthcare settings are different. Healthcare workers may be exposed repeatedly over a long time to low concentrations of multiple drugs via the common routes above. Surface contamination in areas where drugs are compounded or administered can lead to exposure on workers' skin. External contamination on drug packaging and containers can lead to surface contamination. Surface contamination can lead to accidental ingestion through hand-to-oral transfer. Drug administration or handling conditions, such as nebulizer use or vigorous handling outside of appropriate garbing and primary engineering controls, that may lead to aerosolization can lead to workers receiving repeated inhalation exposure. Worker exposures may be smaller on an acute basis; but workers may be repeatedly exposed to multiple potential HDs via multiple routes over a working lifetime.

Lots of factors can affect how workers are exposed to different drugs. Different formulations can enter the body differently. Some drugs may be shipped in tablets or in coated capsules. When handling uncoated tablets or opening bottles of uncoated tablets, there will be potential exposure to dust. This dust may result in inhalation or dermal exposure if handled without gloves. Some drugs may need to be resuspended in solvents that are highly hydrophobic. These solvents may serve to carry drugs through the skin barrier when normally they would not be able to. Handling activities that create dust may pose a risk of inhalation or cross-contamination with that dust. Crushing tablets in administration areas or compounding powders could lead to dust spread.



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Unpacking shipping totes of intravenous drugs without proper PPE could also lead to HD exposure.

## Worker Exposure

### Dermal Exposure

Perhaps the most common exposure risk for health-care workers is HD exposure to the skin. The most obvious source for skin exposure may occur from the handling of HD containing pills, powders, and liquids without appropriate gloves. Accidental spills also pose a clear risk of skin exposure. However, the most common source of dermal exposure to HDs is likely through contact with contaminated surfaces. When working with HDs some materials can become airborne, which then settle on nearby surfaces. Aerosols and dust settle on surfaces in surrounding HD handling activities. The exterior of drug containers can be contaminated by the production facility and mechanically transferred throughout the health care facility. Administration areas can be contaminated from drips or spills during disconnection of IV lines. Bed linen, bed pans and urinals, and patient toilets can be contaminated with body fluids. All potentially contaminated surfaces offer a chance for skin to come in contact with HDs.

The skin itself can be a target for some hazards of drug exposure. For example, genotoxic damage can accumulate in the cells of the skin after repeated exposure to genotoxic drugs. Depending on the drug's molecular properties, it can pass through the skin's barrier layer and enter systemic circulation. Small molecules and hydrophobic molecules can pass through the skin. Some solvents can carry drugs through the skin into the body. Another concern is, in situations where workers are wearing gloves a lot or are washing their hands often, the skin can become damaged. Damaged skin does not provide as good of a protective layer and the systemic level of HDs following dermal exposure can be higher than if the skin was intact.

While the potential dermal exposure is the amount of HD deposited on the skin, the absorbed dermal dose (internal exposure) is the amount of HD absorbed through the skin and into the body. Dermal absorption is affected by various physical and chemical properties, including physical state, molecular weight, lipophilicity, and solvent carriers.

**Physical State:** Chemicals can penetrate skin in both solution and powder states, although chemicals in solution may be more effectively absorbed than powders (WHO, 2006).

**Molecular Weight:** Molecular weight (MW) is used as a proxy for molecular size. Permeation of chemicals through the skin decreases exponentially with MW (Potts and Guy, 1992; Magnusson, et al., 2004). A general rule of thumb is that compounds with a MW of less than 500 Daltons are more likely to permeate the skin and greater than 1,000 Daltons less likely to permeate the skin (Hostýnek & Magee, 1997; Bos & Meinardi, 2000). Many traditional antineoplastics have relatively low molecular weights such as cyclophosphamide with a MW of 261 Daltons. In contrast, monoclonal antibodies, such as Trastuzumab, have molecular weights of approximately 150,000 Daltons.

**Lipophilicity:** Octanol/water partition coefficients are a common way of expressing the lipophilicity of a compound. Octanol/water partition coefficients ( $P_{O/W}$ ) are often used as a qualitative measure of skin permeability. Compounds with log octanol/water partition coefficients ( $\log P_{O/W}$ ) between -1 and 5 are more likely to permeate through lipid membranes including skin. Skin permeation is reported to be very low and is often assumed to be <10% when the  $\log P_{O/W} \leq -1$  or  $>5$  (Schuhmacher-Wolz, 2003). It is suggested that a compound with a log PO/W between 1 and 2 is the most favorable for dermal absorption (Kimmel, Sussman, et al. 2011). On its own, the octanol/water partition coefficient is not a reliable indicator of significant dermal absorption (WHO, 2006).



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**Solvent Carriers:** Many solvents, such as isopropyl alcohol and ethanol, can act as skin penetration enhancers and may facilitate the transdermal absorption of compounds (Lachenmeier, 2008). Ethanol is regularly used in healthcare as the primary component of alcohol-based hand rubs. Isopropyl alcohol is used regularly in compounding pharmacies for disinfection of surfaces.

The amount of the drug actually absorbed into the human body is difficult to quantify and can depend upon the following personal factors: occlusive contact, contact time on skin, skin age and condition, skin health, location on the body, race and sex. Drugs that do manage to pass through the skin don't face first-pass metabolism. This means drugs will enter the bloodstream in the form they pass through the skin. For some drugs, this may mean that the body will see greater levels of the hazardous version of the drug in its initial form, while for others it may slow the exposure to the hazardous metabolites.

### Inhalation

Particulate and droplet aerosols are primary inhalation hazards. The risk of a significant HD vapor component for inhalation exposure is expected to be negligible for nearly all of the HDs due to the very low vapor pressures of nearly all of the commonly used HDs (i.e., cyclophosphamide vapor pressure = 0.0000445 mmHg; 0.006 Pa at 25°C (calculated) (NCBI, 2023). When handling drugs shipped as powders there is the potential for powders to become airborne and be inhaled. Some forms of administration can also lead to airborne drugs that can be inhaled. There have been studies that have noted drug contamination in areas where drugs had been administered to patients via inhalation using a nebulizer, which could lead to inhalation exposure for the healthcare workers administering those treatments (Gurusamy et al., 2018).

Inhalation exposure potential may be limited for some types of drugs, such as HDs of low dustiness

which don't create aerosols when handled, HDs in solutions, or HDs with limited systemic availability via the inhalation route. While some large molecule drugs may have low bioavailability via inhalation, some studies have found that some large molecules, proteins, and monoclonal antibodies do appear to have some limited bioavailability via inhalation exposures. There can be hazards associated with inhalation exposures which may not require systemic bioavailability. Tissue insult may occur at the location of entry. Toxicity to the epithelium lining the airways or to other cells (immune) after constant repeat exposure to some chemicals can lead to damage to these specific tissues and/or increased susceptibility to infections.

### Oral Exposure and Ingestion

Ingestion of drugs in healthcare workplaces is often overlooked. While incidents of healthcare workers directly ingesting treatments in the workplace are rare, ingestion of HD surface contamination transferred from hand contamination may be more common. Often, the work surfaces in areas where HDs are compounded or administered can become contaminated with drugs. When these surfaces are touched by workers, that contamination can be transferred to hands which then makes it into the mouth. Hand-to-oral transfer is an often unexpected source of ingestion. While the amounts ingested may be low, consistent HD surface contamination and inattention to safe handling can lead to repeat exposures.

The level of systemic exposure caused by oral exposures can be limited by some factors. Some drugs may be broken down by the enzymes and conditions in the gastrointestinal tract. Some drugs may not be easily absorbed into the body via the oral route. Drugs that pass through oral exposure will be metabolized by first-pass metabolism. This may activate a drug's hazard, or help to decrease the hazard, depending on the drug.



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## Appendix D. Hazards of Drugs - Potency, Adverse Effects, Identifying Mechanism/Indication/Category

The first step in assigning a compound to a hazard category is a comprehensive evaluation of all available data on the compound, most of which is generated during the normal course of drug discovery and development. Data is evaluated for number of factors regarding the inherent hazardous properties of the substance and include the potency of the drug, the possible adverse effects, the acute warning symptoms, the acute as well as chronic toxicity, the cumulative effects, and the possible irreversible effects, among others (2).

The focus of the occupational toxicologist in the pharmaceutical industry is to identify potential adverse effects that are a result of occupational exposure to drug substances that may be handled during research and development (R&D), manufacturing and packaging activities, and during the drug dispensing activities in the hospital or the community settings. One of the challenges is to define what represents an adverse effect for an agent that is designed to modify biological function. **Whilst many of the effects observed are considered desirable in a patient population being treated under medical supervision, they are not acceptable as a result of occupational exposure (3).**

To evaluate the potential acute effects of the drug substance, both the activity and potency of the drug are evaluated. The type of pharmacological effects expected, the mechanism of action, and the dosage required to produce these pharmacological effects are important considerations. The severity of acute effects is assessed qualitatively to determine the likelihood that the anticipated pharmacological or toxicological effects may result in serious effects or death. An integral part of the evaluation is also related to the determination of whether medical intervention might be required if an overexposure occurs,

and how rapid the intervention must be. It is also of great importance to know about the availability of a specific antidote and if the adverse effects are treatable (2).

The compound may or may not have acute warning properties such as odor, irritancy, or rapidly occurring nonserious pharmacological effects that might alert an individual to the presence of the drug or potential exposure. Collectively, the more subtle the warning signs are, the higher the hazard category or the control banding category should be. The timing of the onset of action of the overexposure relative to the appearance of the more serious effects is also an important consideration (2).

Results of the acute toxicity in animals can also provide information on the ability of the substance to produce immediate adverse effects or death. Acute toxicity values may be available for various routes of exposure. They may include the median lethal dose ( $LD_{50}$ ), the approximate lethal dose, the median lethal concentration ( $LC_{50}$ ), and the maximum tolerated dose (MTD). Substances with a high order of acute toxicity and poor or delayed warning properties are of greatest concern. Skin sensitization studies are commonly performed in guinea pigs to evaluate the potential for a material to produce delayed skin hypersensitivity. The dosage required to induce sensitization or to elicit an allergic response in previously sensitized animals is considered. The results of patch tests in humans are also considered, when available (2).

A determination is also made on the likelihood and severity of possible chronic effects. This assessment is performed using the results of genotoxicity assays, *in vitro* experiments, and preclinical and clinical studies to determine the potential for the drug



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to produce target organ effects, reproductive or developmental toxicity, cancer, or other severe chronic adverse effects like cardiac toxicity or hepatotoxicity (2). **A crucial piece of information in evaluating the chronic toxicity studies is the dosage required to produce these effects, more specifically the overall no observed adverse effect level (NOAEL) and its relation to the maximum recommended human dose (MRHD) or anticipated exposure.**

An important key factor in assessing a control banding category is also dependent on the pharmacokinetics of the drug per the route(s) of exposure. The bioavailability of the drugs concerning the different exposure scenarios is taken into consideration as well as the potential for the drug to accumulate, more specifically defined as the elimination half-life ( $T_{1/2}$ ).

Finally, the reversibility of the effects, both from chronic and acute exposure are evaluated, as well as the potential for the exposure to cause an impact on an individual's lifestyle and quality of life (2).

Additional hazards that are of concern for occupational exposure are often distinct from the primary pharmacological effects. This is illustrated by the case of penicillin and cephalosporins which are designed for antimicrobial activity, but are also known to induce allergic contact dermatitis and asthma in occupationally exposed individuals (3).

When considering the hazard posed by exposure to an HD you must consider the nature of the hazard. In some cases, the hazard is linked directly to the pharmaceutical activity of the drug, in others it may be related to an adverse effect of the drug or other biological activity of the drug. **It is important to remember that what is a beneficial effect on a patient could be considered an unwanted adverse effect on workers.** There are several different mechanisms through which adverse events can happen when workers are exposed to potentially HDs.

## Genotoxicity

Genotoxicity is the ability of a chemical to damage the DNA in cells. This can lead to the death of the cells, changes within the cell that can lead to the development of cancer, or, if it occurs in germ cells or the cells of developing offspring, it can cause developmental and reproductive issues. Many drugs used as chemotherapies in the treatment of cancer have been genotoxic. Because cancer cells rapidly copy their DNA and divide, genotoxic drugs are often more likely to damage cancer cells and when enough damage is produced, the cells die. However, exposure to genotoxic drugs can lead to cancer and developmental and reproductive effects.

Genotoxicity is cumulative. As workers are exposed to more genotoxic hazards, they accumulate more damage. Over time, the amount of potentially damaging mutations increases and the risk that adverse effects will occur increases as well. Low levels of exposure over a long timeframe can lead significant and potentially harmful DNA damage, and minimizing exposure can be protective against effects that might not be evident for years after the exposure.

In the past, a great number of cancer treatments (treatments that have been called as a group of antineoplastics) were in large part genotoxic compounds. Now, drugs to treat cancer have been developed that target cell growth in other ways. Some antineoplastic drugs, meaning they are used to treat cancer, may not be genotoxic. They may be also used to treat other diseases and disorders. Some may be a potential hazard in ways that aren't genotoxic, and some may not pose a hazard to workers at all. Where in the past there might have been a generalization that cancer drugs were hazardous genotoxic compounds, that is not necessarily the case anymore. Some antineoplastic drugs may be genotoxic, some may carry other hazards and warnings unrelated to genotoxicity, and some may not be hazardous at all. While in the past



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many antineoplastic cancer treatments caused DNA damage, many drugs that today are classified in the AHFS Drug Information as “10:00:00 antineoplastic” are not genotoxic and may have other indications aside from cancer treatment.

### Carcinogenicity

Carcinogenicity is the ability to contribute to causing or promoting the development of cancer. Cancer is abnormal cell growth and reproduction. Abnormal cellular growth can be caused in a few different ways. The most common ways are through damaging DNA, leading to mutations that cause the mechanisms of cellular growth regulation to be broken down, and through cell signaling mechanisms that encourage irregular cellular division.

For carcinogenicity via genotoxicity, or DNA damage, often many mutations are required. In situations where hazardous carcinogenic compounds are consistently present in the environment, the risk can increase with each exposure as the damage is cumulative. Through this mechanism of action exposure to genotoxic compounds, like many antineoplastic drugs, can increase the risk of cancer over time.

There is evidence that some hormones, such as estrogens and progesterone, can promote abnormal cell growth as well. The mechanism that this happens though is likely not directly related to genotoxicity. These hormones are often regulators of normal cell growth, telling specific cells when to (or not to) divide and reproduce at normal times as needed. If workers are exposed to these kinds of signaling molecules some cells that shouldn't be dividing may get the message that they should, leading to abnormal cellular reproduction. This hormonal dysregulation may be reversible, such that if a worker who is regularly exposed to a hormone or hormone-like chemical stops being exposed, some or all of the effects of exposure may be resolved.

However, the effects of hormonal dysregulation can be further complicated by mutations. Cells that are rapidly dividing have increased chances of making a mistake when copying their DNA. Additionally, exposure to genotoxic compounds may lead to mutations that can make cells either more or less sensitive to hormonal messages. In these ways, hormonal promotion of cancer can lead to DNA damage, and DNA damage can make cells more sensitive to hormonal dysregulation.

### Developmental and Reproductive Toxicities (DART)

Developmental and reproductive hazards can affect a worker's ability to conceive a child, it could affect the ability of a worker to carry a child to term, or it could cause changes to the development of the conceived offspring. Many mechanisms can lead to this wide range of effects. Genotoxicity can lead to DNA damage and mutations in the gamete cells, causing them to be unable to form viable offspring or causing developmental changes in the offspring. Hormonal dysregulation can lead to changes in estrus or in the development of gametes or sex organs that can make conception difficult. Some drugs may block or compete with important nutrients or hormonal signals that control fetal development. All of these different mechanisms of action can cause drugs to be a DART hazard.

DART hazards can be broken down into those that affect reproduction or those that affect development. Reproductive hazards make it difficult to have offspring by damaging gamete production, somehow impeding conception, or making it difficult to carry an offspring to term. Developmental hazards can harm the normal growth and development of the offspring in utero or after birth. Developmental hazards may also lead to spontaneous abortions, congenital malformations during development (teratogenicity), or other issues with normal offspring development. Some developmental hazards are only a hazard at



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a specific time, perhaps increasing the risk of early labor in late pregnancy or altering the development of the nervous system in early pregnancy. For those, the timing of exposure can be critical for determining the hazard.

### **Other Hazards**

HDs can damage other organs and tissues in exposed workers as well. Some drugs may cause effects in neurons or the brain. Some drugs may cause adverse effects on the liver or the kidneys. Some

drugs may have specific intended effects in patients, that can be considered adverse in workers. A drug that is intended to regulate or slow heart rhythms may cause irregular heart rhythms or dangerously altered blood pressures in healthy patients. Some drugs may have acute effects, which are corrected after exposure. Some may cause immediate damage that may never be repaired. Still, others may cause damage that won't be manifested until years after the exposure.



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**We are experts in what we do.** We use our knowledge to better protect people and the environment.

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