USP <800>: Guidelines for Handling Hazardous Drugs

Faculty

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Disclosure

Christopher A. Fausel: Expert Witness — Dr. Reddy's Laboratory
Learning Objectives

• Describe the risk points for exposure to hazardous drugs in healthcare settings
• Explain the scope of USP <800> and resultant impact on healthcare facilities
• List engineering controls that are implemented to minimize exposure to hazardous drugs
• Describe strategies to employ proper use of PPE that can protect healthcare workers from exposure to hazardous drugs (HD)

PPE = personnel protective equipment.

Evolution of Recommendations

• 1990, 2006 ASHP® Guidelines on Handling Hazardous Drugs
  – ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs
    (Am J Hosp Pharm. 1990;47:1033-1049)
• 2004 NIOSH® Safety Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings
  – Posted September 2004
  – Updated every 2 years
• USP® Chapter <797>: Pharmaceutical Compounding-Sterile Preparations
  – Posted September 2015
  – Final chapter published: February 1, 2016
  – Official compliance date (enforceable): July 1, 2018

Evolution of Recommendations

• 2004 NIOSH® List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016
  – Posted September 2016
  – Updated every 2 years
• USP® Chapter <800>: Hazardous Drugs-Handling in Healthcare Settings
  – Final chapter published: February 1, 2016
  – Official compliance date (enforceable): July 1, 2018

ASHP = American Society of Health-System Pharmacists; NIOSH = National Institute for Occupational Safety and Health; USP = United States Pharmacopeia.

Definitions of Hazardous Drugs

<table>
<thead>
<tr>
<th>NIOSH</th>
<th>ASHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogenicity</td>
<td>Carcinogenicity in animal models, in the patient population, or both as reported by the International Agency for Research on Cancer</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Teratogenicity in animal studies or in treated patients</td>
</tr>
<tr>
<td>Reproductivity</td>
<td>Fertility impairment in animal studies or in treated patients</td>
</tr>
<tr>
<td>Organ toxicity at low doses</td>
<td>Evidence of serious organ or other toxicity at low doses in animal models or treated patients</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Genotoxicity (ie, mutagenicity and clastogenicity in short-term test systems)</td>
</tr>
<tr>
<td>Structure and toxicity profile of new drugs that mimic existing drugs determined hazardous by the above criteria</td>
<td></td>
</tr>
</tbody>
</table>

HD = hazardous drug
Consequences of Exposure to HDs

- **Short term**
  - Skin irritation/burning
  - Gastrointestinal toxicity
  - Flu-like symptoms
  - Ocular irritation
- **Long term**
  - Fertility impairment
  - Birth defects
  - Secondary cancers


Scope of USP Chapter <800>

- Standards apply to:
  - Areas where HDs are compounded, stored, transported, and administered
- Facilities:
  - Hospitals, pharmacies, physician offices, patient clinics, veterinarian’s offices
- Healthcare personnel include, but are not limited to:
  - Pharmacists and pharmacy technicians
  - Physicians and physician assistants
  - Nurses and home healthcare workers
  - Veterinarians and veterinary technicians

HD = hazardous drug.

Definitions in <800>

- **Must** = Compliance is mandatory effective July 1, 2018
- **Should** = Recommendations only – not requirements

Maintenance of HD List

- Cite NIOSH Hazardous Drug list
- Assess new drugs as they enter the marketplace
- Recategorize as new toxicologic data become available
- Consider investigational agents hazardous if the mechanism of action suggests HD
- Consider dosage form and whether dosage form will be altered/crushed/compounded
- Label all hazardous drugs


HD Exposure Risk Points

<table>
<thead>
<tr>
<th>Job Function</th>
<th>Risk Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt</td>
<td>Drug residue is present on outer packaging of HDs</td>
</tr>
<tr>
<td>Dispensing</td>
<td>Counting or splitting tablets or opening capsules</td>
</tr>
<tr>
<td>Patient-care activities</td>
<td>Handling body fluids or contaminated linens</td>
</tr>
<tr>
<td>Spills</td>
<td>Spill management and disposal</td>
</tr>
<tr>
<td>Transport</td>
<td>Moving HDs within a healthcare setting</td>
</tr>
<tr>
<td>Waste</td>
<td>Collection and disposal of hazardous waste</td>
</tr>
</tbody>
</table>


Pharmacy Staff Risk Points

<table>
<thead>
<tr>
<th>Activity</th>
<th>Risk Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounding and other manipulations</td>
<td>Crushing/spitting tablets or opening capsules</td>
</tr>
<tr>
<td></td>
<td>Transferring oral or topical liquids between containers</td>
</tr>
<tr>
<td></td>
<td>Weighing or mixing components</td>
</tr>
<tr>
<td></td>
<td>Reconstituting powdered or lyophilized HDs and/or withdrawing or diluting injectable HDs from stock containers</td>
</tr>
<tr>
<td></td>
<td>Expelling air or HDs from syringes</td>
</tr>
<tr>
<td></td>
<td>Contacting HD residue present on PPE or other garments</td>
</tr>
<tr>
<td></td>
<td>Cleaning activities on surfaces containing HD residue</td>
</tr>
<tr>
<td></td>
<td>Maintenance activity on potentially contaminated equipment</td>
</tr>
</tbody>
</table>

### Potential HD Exposure Risk Points

<table>
<thead>
<tr>
<th>Activity</th>
<th>Potential Opportunity for Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Generating aerosols during administration by various routes (eg, injection, irrigation, oral, inhalation, topical)</td>
</tr>
<tr>
<td></td>
<td>Performing certain specialized procedures (eg, intraoperative or intraperitoneal injection or bladder instillation)</td>
</tr>
<tr>
<td></td>
<td>Priming an IV set</td>
</tr>
<tr>
<td>Patient-care activities</td>
<td>Handling body fluids (eg, urine, feces, sweat, or vomit) or body-fluid contaminated clothing, dressing, linens, or other materials</td>
</tr>
</tbody>
</table>

**IV** = intravenous.

**API** = active pharmaceutical ingredient.

**ACPH** = air changes per hour.

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### Receipt of HDs

- Antineoplastic HDs and all HD APIs must be unpacked (ie, removed from external shipping containers) in areas that are **neutral** or **negative** pressure relative to surrounding areas.
- HDs must **not** be unpacked from their external shipping containers in sterile compounding areas or in positive-pressure areas.

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### Storage of HDs

- HDs must be stored to prevent spillage/breakage if the container falls; no storage on the floor.
  - **Storage of antineoplastic HDs** not in a final dosage form must be segregated from non-hazardous inventory in an externally ventilated negative-pressure environment with ≥12 ACPHs.
  - Sterile and non-sterile HDs may be stored together.
  - **Refrigerated HDs** must be stored in a dedicated unit in a negative-pressure room with ≥12 ACPHs.
  - Reproductive risk only HD and final dosage forms of antineoplastic HDs may be stored with other inventory.

**ACPH** = air changes per hour.
Personnel Protective Equipment

- PPE provides worker protection to reduce exposure to HD aerosols and drug residue
- Gowns, gloves, head, hair, and shoe covers are required for compounding sterile and non-sterile HDs
- Gloves and gowns are required when administering injectable HDs
- Institutions must develop SOPs for PPE based on risk of exposure and activities performed

SOP = standard operating procedure.


Use of Gloves with HD Handling

- Two pairs of gloves are required for compounding and administering HDs
  - Use sterile gloves for outer pair for sterile compounding
- Gloves must meet standards set by the American Society for Testing and Materials (ASTM)
- Chemotherapy gloves must be powder free
- Inspect gloves for defects before using
  - Do not use defective gloves
- Change gloves every 30 minutes or when torn, punctured, or contaminated


Use of Gowns with HD Handling

- Gowns must be tested to resist permeability by HDs
  - Polyethylene-coated polypropylene or other laminate materials preferred
- Gowns must close in the back and have no seams/closures to allow HDs to pass through
- Gowns changed per manufacturer’s recommendations or every 2 to 3 hours and after any spills/splashes
- Clothing, laboratory coats, and scrubs can retain HDs

Other Recommended PPE

- Head/hair covers (including those for beard/moustaches) are required
- Second pair of shoe covers must be donned when compounding sterile HDs
  - Remove when exiting buffer room
- Eye and face protection must be used when there is a risk of spills/splashes
- Use NIOSH-certified N95 respirator masks for respiratory protection for spills, cleaning activities, or potential airborne exposure
- Disposal
  - Consider all PPE worn when handling HDs as being contaminated with trace quantities of HDs
  - Place PPE in an appropriate waste container and disposed of per regulations

HD Compounding and Engineering Controls

- Engineering controls are required to prevent cross- and microbial contamination using three controls:
  1. Containment primary engineering control (C-PEC): A ventilated device for direct handling of HDs
  2. Containment secondary engineering control (C-SEC): The room in which the C-PEC is placed
  3. Supplemental engineering controls: Closed-system transfer devices (CSTDs)

Engineering Controls for Sterile HD Compounding

<table>
<thead>
<tr>
<th>Configuration</th>
<th>C-PEC</th>
<th>C-SEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO class 7 buffer room with an ISO class 7 ante-room</td>
<td>Externally vented Example: Class II BSC or CACI</td>
<td>Externally vented 30 ACPH Negative pressure between 0.01 inch and 0.03 inch of water column relative to the adjacent areas</td>
</tr>
<tr>
<td>Unclassified C-SCA</td>
<td>Externally vented Example: Class II BSC or CACI</td>
<td>Externally vented 12 ACPH Negative pressure between 0.01 inch and 0.03 inch of water column relative to adjacent areas</td>
</tr>
</tbody>
</table>

Notes: LAFW or CAI must not be used for compounding HDs. Segregate non-sterile and sterile compounding C-PECs; C-PEC shall operate continually.
**Recommended Configurations for Sterile HD Compounding**

- BSC or CACI
- BSC or CACI
- LAFW or CAI

Ante-room:
Minimum positive pressure of 0.02 inch of water column to adjacent spaces; at least 0.01 inch of water column to HD buffer room; 30 ACPH; hand-washing sink.

**Supplemental Engineering Controls**

- Some CSTDs shown to limit potential for generating hazardous aerosols during sterile compounding
- No universal performance standard exists by which CSTDs are evaluated for containment
- CSTD must not be used as a substitute for C-PEC when compounding
- CSTDs should be used when compounding HDs when the dosage form allows
- CSTDs must be used when administering HDs when the dosage form allows

**Environmental Quality Control: Wipe Studies**

- Environmental wipe studies for HDs should be performed routinely at least every 6 months
- Surface wipe sampling should include:
  - Interior of C-PEC and equipment contained in it
  - Staging or work areas near C-PEC/pass-through
  - Areas adjacent to C-PECs (eg, nearby flooring)
  - Areas outside of buffer room and patient administration areas
- Currently, no studies exist demonstrating the effectiveness of a specific number of wipe samples in determining levels of HD contamination
Labeling/Packaging/Transport

- **Labeling**: HDs must be labeled as such at all times during their transport
- **Packaging**: Compounding personnel must select and use packaging containers to maintain physical integrity, stability, and sterility during transport
  - Packaging must protect from damage, leakage, contamination, and degradation
- **Transport**: HDs must be transported in containers that minimize the risk of breakage/leakage
  - Pneumatic tubes must **never** be used to transport liquid or antineoplastic HDs

Compounding

- Institutions compounding HDs must be compliant with USP <795> (non-sterile) and USP <797> (sterile)
  - Use plastic-backed preparation mat on the work surface of the C-PEC
  - Change regularly during use and following spills
  - Disposable or clean equipment dedicated only to HD compounding
  - Bulk containers of liquid and API HDs must be handled in C-PEC to prevent worker exposure

Administration

- HDs must be administered safely by using protective medical devices and techniques (eg, priming IV tubing with non-HD solution in a C-PEC)
- Appropriate PPE to be worn when administering HDs and disposed of properly thereafter
- CSTDs must be used for administration of antineoplastic HDs when the dosage form allows
- Avoid manipulating HD dosage forms (eg, crushing tablets, opening capsules) when possible
  - If necessary, use appropriate PPE
### Cleaning Procedures

<table>
<thead>
<tr>
<th>Cleaning Step</th>
<th>Purpose</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deactivation</td>
<td>Render compound inert or inactive</td>
<td>EPA-registered oxidizers (e.g., peroxide formulations, sodium hypochlorite)</td>
</tr>
<tr>
<td>Decontamination</td>
<td>Remove HD residue</td>
<td>Alcohol, water, peroxide or sodium hypochlorite, or other materials validated to be effective for HD decontamination</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Remove organic or inorganic material</td>
<td>Germicidal detergent</td>
</tr>
<tr>
<td>Disinfection</td>
<td>Destroy microorganisms</td>
<td>Sterile alcohol or EPA-registered disinfectant</td>
</tr>
</tbody>
</table>

### Spill Control

- Train personnel about proper spill kit use
- Ensure SOPs are in effect
  - Required for spill prevention, clean-up procedures, and use of PPE and respirators
- Document circumstances of spill
- Provide immediate medical evaluation to potentially exposed personnel
  - Non-employees exposed to HD should report to designated emergency service for evaluation

### Medical Surveillance

- Institutions should develop a surveillance program for workers handling HDs
- Purpose: To minimize adverse health effects in personnel potentially exposed to HDs
- Secondary prevention tool for early detection
- Program involves:
  - Assessment and documentation of symptom complaints, physical and/or laboratory findings
  - Comparison of health variables over time in populations of workers
Conclusions

USP <800> is an enforceable standard that changes compliance and workflow for pharmacy practice

• Compliance
  – A single published standard exists for defining requirements for HD handling

• Facilities
  – Updating existing buffer rooms: All HD compounding to be done in negative-pressure C-SEC in externally vented C-PEC
  – Proper “de-boxing” areas for receiving HDs

• Personnel
  – Designated person for overseeing compliance with HD handling is best suited for a trained oncology pharmacist

• Work procedures
  – Chain of custody of HDs
  – PPE
  – Cleaning methodology for HD handling areas
  – Surveillance

Questions?