"Hazardous Drugs: Managing them from Cradle to Grave"

Sponsored by: Pharmacy OneSource, May 5, 2010
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“Although I am a member of the USP Sterile Compounding Expert Committee, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.”
Objectives

- Why is addressing the issue of hazardous drug handling so important?
- Where do hazardous drugs and hazardous pharmaceutical wastes interface?
- What are the regulatory and environmental reasons for managing pharmaceutical waste more stringently?
- How do common pharmaceutical waste disposal practices need to be modified?
- What do compliant pharmaceutical waste disposal practices look like?
“I want to demythologize the idea that we have taken care of this problem,” stressed presenter Melissa McDiarmid, MD, MPH, DABT, professor of medicine and director of the University of Maryland School of Medicine’s Occupational Health Program, in Baltimore.

Some of these drugs, she noted, “came out of chemical/biological warfare from World War I. If that doesn’t get our respect, I don’t know what does.”

Cytotoxic Drug Residues Still Lurking in Health Care Facilities 75% of wipe samples from several hospitals deemed contaminated with at least one chemotherapeutic agent. Pharmacy Practice News, Hem/Onc Pharmacy in Focus, Vol 37:01
What kind of “hazardous”

- NIOSH/OSHA standards are for exposure-a-health or physical chemical hazard
- Department of Transportation (DOT) hazardous material definitions are specific to transportation safety
- There are five federal statutory provisions that identify hazardous chemicals for things including worker-public exposure, community right-to-know reporting requirements and the Clean Air and Clean Water Act references
- RCRA is for Hazardous Waste
Hazardous Drugs

• National Institute for Occupational Safety & Health
  NIOSH 2004
  ◦ “Drugs are classified as hazardous drugs if studies in animals or humans indicate their potential to causing cancer, developmental or reproductive toxicity, or harm to organs”
  • Carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, structure and toxicity profile of new drugs that mimic existing drugs determined hazardous by the listed criteria
  ASHP 1990; OSHA 1995, 1999

• Appendix A of NIOSH Warning
  • 135 Chemicals (drugs) listed, updated in 2007
    • Antineoplastics; Immunosuppressive agents; Estrogens; Oxytocics; Contraceptives; 5-alpha reductase inhibitors; Androgens; Antivirals; Gonadotropins; Anti-infectives; Estrogen agonist-antagonists; Skin mitotic inhibitors; Cell stimulants and proliferants
  • All forms of drugs
Expanded Definition: NIOSH Hazardous Drug Alert

- Genotoxicity
- Carcinogenicity
- Teratogenicity/Development toxicity
- Reproductive Toxicity
- Organ toxicity at low dose
- Structure/toxicity profiles of new drugs mimic existing hazardous drugs
Sources of Contamination

- Contaminated vials: studies show drug may be on the outside of vials
- Contaminated packaging: studies show drug may be on the drug vial packaging
- Contaminated surfaces: studies show work surfaces are contaminated during routine compounding, administration and waste handling
- Poor technique in any handling may result in contamination of the air or work surfaces
**First American Urine Study, 2002**

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[technician (not in chemo area) urine levels of cyclophosphamide]

Am J Health-System Pharm. 2003; 60:2314-20
Slide courtesy of Larry Griffin, RPh
Summary Results of Human Contamination

![Graph showing CTX Urine Concentration over different times of day. The graph indicates a peak concentration at 12:30 PM, with lower concentrations at other times such as 6:50 AM, 7:45 AM, 12:10 PM, 3:55 PM, 6:40 PM, and 9:00 PM.]

Am J Health-System Pharm. 2003; 60:2314-20
Using PPE in Receiving & Transport

Double gloving is recommended for receiving, transport, stocking, ANY activity involving hazardous drugs.

Photo courtesy of Luci A. Power, MS Power Enterprises.
Storage: improve practice

- Storage of HD shall be separate
- Negative pressure area required
- Minimum of 12 ACPH

Per USP <797> 2008
Protection of Hazardous Drugs in Transit & Storage

- Labeling of cooler for refrigerated products
- Air pillows to protect product in transit
- High-walled shelf container

Photos courtesy of Robert DeChristoforo, MS Deputy Chief, Pharmacy Dept., NIH Clinical Center Pharmacy
Checked and Ready for Delivery

Photos courtesy of
Robert DeChristoforo, MS
Deputy Chief, Pharmacy Dept.,
NIH Clinical Center Pharmacy
Protection of Hazardous Drugs in Transit & Storage

Photos courtesy of Robert DeChristoforo, MS
Deputy Chief, Pharmacy Dept., NIH Clinical Center Pharmacy
Remember when…..
What NOT to do!
Horizontal laminar flow hoods offer no personnel protection
Personal Protective Equipment

- Gloves & gowns
- Eye & face protection
  - Face shield rather than safety glasses or goggles
- Respirator
  - Must be fit-tested
  - Trained based on OSHA Respirator Standard
  - Surgical masks DO NOT provide respiratory protection during a spill
- Shoe, hair coverings – sterile compounding
  - Shoe, hair covering should be removed with gloved hands

Photo courtesy of Luci A. Power, MS Senior Pharmacist, Manager, UCSF-IV Additive Service
Personnel Protective Equipment
Work Practices

What NOT to do today…..

- Keep potentially contaminated PPE away from face, skin
- NEVER eat or drink in hazardous drug prep area
- Wear PPE properly

Photos courtesy of
Robert DeChristoforo, MS
Deputy Chief, Pharmacy Dept.,
NIH Clinical Center Pharmacy
Interface with USP 797 (2004)

- Protect patients from improperly compounded sterile products
- Initial version did not address airflow, air exchanges per hour, pressure gradients, containment procedures
- Positive-pressure isolators or Class II biological safety cabinets (BSCs) in positive-pressure environments inappropriate for hazardous drugs
Interface with USP 797 (2008)

- Protect patients from improperly compounded sterile products and protect personnel
- Specific environmental conditions designed to achieve containment
  - Negative-pressure ISO Class 7 buffer area
- Negative-pressure isolators or Class II biological safety cabinets (BSCs) in negative-pressure environments are required for hazardous drugs preparation
Ventilation

- Ventilated Cabinet: A type of ventilation or engineering control designed for the purposes of worker protection.
- Biological Safety Cabinet (BSC)
  - Class I BSC-orals
  - Class II BSC
  - Class III BSC
- Compounding Aseptic Isolator-NO
- Compounding Aseptic Containment Isolators (CACI)
Supplementary Controls
Recommendations

- Consider using CSTDs when transferring hazardous drugs from primary packaging to dosing equipment.
- Studies have shown a decrease in drug contaminants inside a Class II BSC when a closed system device was used.
  - Not eliminated 100%
  - Dirty vials
- NOT a substitute for ventilated cabinets; must be used within a ventilated cabinet
Work Practices: Disinfection vs Decontamination

- Wipe down hazardous drug vials before entry into BSC/CACI
- Spray or wipe BSC with 70% alcohol or other appropriate disinfectant
- Decontaminate work surface of BSC before and after compounding: high pH detergent, sodium hypochlorite solution, neutralizer, sterile IPA
- Alcohol does NOT deactivate hazardous drugs but may solubilize them and spread them around!
Hazardous Waste Primer

- Why you should care – evidence of endocrine disruption, fetal programming, other concerns
- Public opinion, legislative activity, regulatory activity
- What you need to know
  - OSHA hazardous drug vs EPA hazardous waste
  - Definitions of hazardous waste
Hazardous Drugs vs. Hazardous Waste
Where OSHA & EPA Meet

**OSHA HAZARDOUS DRUGS**
- Genotoxicity
- Teratogenicity
- Reproductive toxicity
- Carcinogenicity
- Organ toxicity at low doses

Examples:
- Chemotherapy agents
- Endocrine disruptors

**EPA TOXIC HAZARDOUS DRUG EXAMPLES**
- Arsenic trioxide
- Cyclophosphamide
- Mitomycin
- Melphalan

**EPA IGNITABLE HAZARDOUS DRUG EXAMPLES**
- Paclitaxel
- Valrubicin
- Etoposide

**EPA HAZARDOUS WASTE**
P&U Listed Examples:
- Epinephrine
- Warfarin
- Nicotine

Characteristic Examples:
- Formulations containing greater than or equal to 24% alcohol
- Formulations containing heavy metals
- Strong acids & bases
Immediate Compliance Risk

- Resource Conservation and Recovery Act (RCRA) enforcement increasing (EPA and state)
- Regulates the definition and management of solid and hazardous waste in the US
- Approximately 5% of drugs on the market become hazardous waste
- Compliant management includes a rigorous segregation, transport, treatment and reporting system
- Corporate fines can be levied up to $37,500/violation/day/location
Potential Liability for Rx Hazardous Waste Management
NY Fines Send Shock Waves

• New York Office of Attorney General settles with 2 hospitals, 3 nursing homes for inappropriate disposal of drugs, including flushing and hazardous waste violations

• More inspections on the horizon

• Precedent-setting action draws national attention

Impact of RCRA Regulations on Hospitals

- Knowledge of RCRA regulations as they apply to drug waste is new
  - No training for pharmacists, nurses, doctors
  - Virtually no enforcement for first 30 years
- New initiatives at EPA Office of Solid Waste and Office of Water
- Hospitals beginning to characterize waste pharmaceuticals and segregate for disposal
- Creates new “identifiable” pharmaceutical waste streams
Which Discarded Drugs Become Hazardous Waste?

- **P-listed chemicals** *(acutely hazardous)*
  - Sole active ingredient; unused; empty containers

- **U-listed chemicals** *(toxic)*
  - Sole active ingredient; unused

- **Characteristic of D-listed hazardous waste**
  - Ignitability
  - Toxicity
  - Corrosivity
  - Reactivity
Examples of P-Listed Pharmaceutical Waste

- **Arsenic trioxide** P012
- Epinephrine base* P042
- Nicotine P075
- **Nitroglycerin** (weak) P081
- Phentermine (CIV) P046
- Physostigmine P204
- Physostigmine Salicylate P188
- Warfarin >0.3% P001

*Salts excluded federally as of Oct. 15th, 2007; Many states have accepted this position.

** Excluded from the P list federally and in many states.

*Items in red are chemotherapy agents
Examples of U-listed Pharmaceutical Waste*

- Chloral Hydrate (CIV) U034
- *Chlorambucil* U035
- *Cyclophosphamide* U058
- *Daunomycin* U059
- *Diethylstilbestrol* U089
- *Melphalan* U150
- *Mitomycin C* U010
- *Streptozotocin* U206
- Lindane U129
- Saccharin U202
- Selenium Sulfide U205
- *Uracil Mustard* U237
- Warfarin<0.3% U248

*Items in red are chemotherapy agents.*
Examples of U-Listed Pharmaceuticals
Does the Waste exhibit a Hazardous Waste Characteristic?

- Protection of Environment is Title 40, Part 260-299
  - 40 CFR 261.20: A solid waste, not excluded from regulation §261.4(b), is a hazardous if it exhibits one of the following characteristics:
    - Ignitability
    - Corrosivity
    - Reactivity
    - Toxicity
Characteristic of Ignitability

- Aqueous Solution containing 24% alcohol or more by volume & flash point < 140°F
- Non-aqueous solutions with flash points < 140°F
- Oxidizers
- Flammable aerosols
- Hazardous Waste Number: D001
- Examples:
  - Rubbing Alcohol
  - Topical Preparations
  - Injections
Characteristic of Corrosivity

- An aqueous solution having a pH < or = 2 or > or = to 12.5
- Examples: Primarily compounding chemicals
  - Glacial Acetic Acid
  - Sodium Hydroxide
- Hazardous waste number: D002
Characteristic of Reactivity

- Meet eight separate criteria identifying certain explosive and water reactive wastes
- Nitroglycerin formulations may be considered excluded federally from the P081 listing as non-reactive as of August 14, 2001, unless they exhibit another characteristics, such as ignitability.
- Many states have adopted the federal exclusion for nitroglycerin.
- Hazardous Waste Number for reactives: D003
Characteristic of Toxicity

- 40 chemicals which must be below specific leaching concentrations
- Must pass the Toxicity Characteristic Leaching Procedure (TCLP)
- Must evaluate IVs, such as PN (parenteral nutrition)—may come out of regulation due to dilution
- Hazardous Waste Number for toxicity: D004-D043
# Examples of Toxicity Characteristic Pharmaceutical Waste

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<td>D101</td>
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<tr>
<td>D011</td>
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Definition of “Empty”

- **“P” List**
  Containers of “P” listed chemicals are considered hazardous waste, unless they have been rinsed three times and the rinsate discarded as hazardous waste.

- **“U” List and D codes**
  Containers of “U” listed chemicals or D codes are empty only when all contents removed that can be removed through normal means and no more than 3% by weight remains.

  Example: “Empty” Cytoxan vial would be “trace” chemotherapy.

- Residue of “P” or “U” listed drugs in a used syringe is exempted federally and should be discarded as biohazardous waste or trace chemo in most states.
Chemotherapy Agents: Many Are Not Regulated by RCRA

- About 100 chemotherapy agents not regulated by EPA
- Examples:
  - Alkylating agents: Cisplatin, Thiotepa
  - Antimetabolites: Fluorouracil, Methotrexate
  - Hormonal (antiandrogen): Lupron® (leuprolide)
  - Hormonal (antiestrogen): Tamoxifen
  - Mitotic Inhibitor: Taxol® (paclitaxol)
Three Types of Chemotherapy Waste

- **Trace Chemotherapy Waste (yellow)**
  - Medical waste hauler protocols for “Chemo Waste”
  - Empty vials, syringes, IV’s, gowns, gloves, ziplock bags
  - Treated as infectious medical waste through regulated medical waste incineration

- **“Bulk” Chemotherapy Waste (black)**
  - If not empty, should be placed into RCRA Hazardous Waste container

- **Spill Clean-up (black)**
  - Manage as RCRA Hazardous Waste
Gap Analysis-Risk Assessment

- Analyze Inventory
  - Database analysis
- Audit areas where pharmaceutical waste is generated
  - Receiving and Stocking
  - Pharmacy compounding areas
    - Sterile and non-sterile compounding
  - Nursing units
  - OR/ED/Radiology
  - Anywhere “classified” drugs are being administered and disposed
Percentage of RCRA & PharmE Haz®

PharmE® Inventory Analysis
Average for 149 Facilities

- Non Hazardous, 2,030, 86%
- PharmE Hazardous, 235, 10%
- Fed Haz, 88, 4%

Legend:
- Fed Haz
- PharmE Hazardous
- Non Hazardous
Pharmaceutical Waste Streams and Their Eventual Disposal

Compatible Hazardous Waste*  Aerosols  Trace Chemo (Sharps)  Trace Chemo (Soft)  Non-Hazardous Drugs  Red Sharps  Municipal Solid Waste  Sewer System

• Empty vials and ampules
• Empty syringes and needles
• Empty IVs
• Gowns
• Gloves
• Goggles
• Tubing
• Wipes
• Packaging

Federally Permitted Hazardous Waste Incinerator  Medical Waste Incinerator  Municipal Incinerator Permitted for Special Waste (inc. drugs)  Autoclave/Microwave (no drugs)

Ash  Ash  Ash  Shredded (Most states)

Lined Hazardous Waste Landfill  Lined Non-Hazardous Waste Landfill

POTW

* Dual waste for sharps
How Should RCRA Hazardous Waste Be Disposed?

- Either contract with a hazardous waste broker or develop internal expertise for:
  - Waste profiling
  - Manifest preparation
  - Land ban preparation

- Contract with a federally permitted RCRA hazardous waste incineration facility (TSDF: Treatment, Storage & Disposal Facility)
How Should Non-hazardous Drugs be Handled, Stored and Disposed?

- BMPs strongly discourage sewering and landfilling of non-hazardous drugs
- Organization can minimize risks by adopting BMPs
- Possible exception: controlled substances due to difficulty in rendering non-recoverable under Drug Enforcement Administration (DEA) regulations
- Consider segregating into white container with blue top
- Label “Incinerate Only”
- Dispose at a regulated medical waste incinerator or municipal incinerator that is permitted to accept non-hazardous pharmaceutical waste
EPA May Regulate Pharms in Drinking Water

- 104 chemicals being considered for possible regulation under the Safe Drinking Water Act
- Pharmaceuticals considered for the first time
- Several estrogens included:
  - estradiol, estrone, ethinyl estradiol, mestranol
- Also erythromycin (antibiotic) & nitroglycerin (cardiac)
- Collection and evaluation will take years (2013) but could result in drinking water standards for drugs
- [http://www.pharmecology.com/pedd/jsp/static/a6_news_alert.jsp](http://www.pharmecology.com/pedd/jsp/static/a6_news_alert.jsp)
“EPA estimates that it has gathered sufficient data from its site visits and outreach to **begin the development of best practices for unused pharmaceutical management at health care facilities.** During the next year EPA will continue to work with a variety of stakeholders in the development of these best practices and the means for their dissemination and adoption. EPA expects to have a draft of the development of these best practices for the final 2010 Plan.”

EPA Region 1, Janet Bowen, Hospital Email, Sept. 3, 2009
Summary

- Know what your state rules and regulations are re: pharmaceutical waste
- Analyze inventory and identify “classified” drugs
- Identify where “classified” drugs are stored, handled, prepared and disposed.
- Audit current disposal practices
- Identify gaps
- Educate and train staff
- Implement compliant disposal practices
- Audit for compliance
Resources

- NIOSH Hazardous Drug Alert

- ASHP Guidance on Handling Hazardous Drugs

- OSHA Technical Manual

- Healthcare Education Resource Center (HERC)
  - Blueprint on Pharmaceutical Waste Management (Revised)

- WMHS PharmEcology Services
  - www.pharmecology.com
  - FAQs, state and federal waste regulations, subscription search engine
  - PharmE™ Waste Wizard identifies RCRA hazardous waste plus NIOSH hazardous drugs, among additional criteria
Questions

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