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USP 800: What you need to know about how the new regulations for handling hazardous drugs (chemo and non-chemo) will impact your veterinary practice.

Carrie C. Phillips, MS, PharmD, Executive Officer, Vermont Board of Pharmacy

Joanna Schmit, DVM, MS, DACVIM-Oncology, Burlington and Emergency Veterinary Specialists

USP 800 1st released in 2014 to set standards to protect patients, health care works and the environment

- Based on NIOSH, ASHP, OSHA and ONS (Onco Nurse Society) to create best practices
- Historically there was an exception for low volume compounding
    - No longer allowed and veterinarians will be held to these standards
- Enforceable Dec 1st 2019
    - Enforcement through federal, state and local agencies such as FDA, OSHA, State Regulatory Agencies and State Pharmacy Boards.

<u>Hazardous Drugs</u>

Human Health Care

- Over 8 million health care workers are exposed to HDs annually
- Over 12 billion doses of HDs are handled by medical professionals annually

Veterinary Health Care

- In 2010, an estimated 500,000 veterinary workers were potentially exposed to HDs or waste.
- Includes: Veterinarians, technicians, kennel staff/cleaning/maintenance staff-many of REPRODUCTIVE age
- Willingness to pursue advanced care is increasing and so is the exposure to HDs.

- ***Greatest risk: Antineoplastics and reproductive health***
    - **Reproductive Health Risks Associated with Occupational Exposures to Antineoplastic Drugs in Health Care Settings: A Review of the Evidence Thomas H. Connor, PhD. J Occup Environ Med. September 2015.** ***Included meta-analysis***
    - Women
        - Window of risk -1 mo before conception through pregnancy

        - Continued risk to infant if breastfeeding through 6 mo. of age due to still developing biotransformation/elimination systems.
    - Men-primary and secondary hormonal changes
        - sperm is vulnerable to hazardous exposures up to 2 mo before conception
        - reproductive issue can be transferred from occupationally exposed workers to their partners.
- ***The data-oncology nurses and pharmacists***
    - *NOTE-Most studies prior to 2004/USP 797 recommendations*
    - *Findings are a result of improper PPE/containment devices*
- Congenital anomalies
    - Multiple studies show increased risk with repeated exposure (OR 1.64)
    - Oncology nurses reported more birth defects vs. control group
    - Cleft lip and cleft palate most frequent in 1 study
- Miscarriage/Stillbirth
    - Overall risk of 46% in exposed workers
    - ORs for miscarriage were >1 (significant) in multiple studies
    - Fertility and time to pregnancy
    - Exposure associated with an increased risk of subfertility
    - Three-fold risk of menstrual cycle irregularities from occupational exposure
- Examples of HDs in daily practice: Apomorphine, Azathioprine, Cyclosporine, DES, Methimazole, Mycophenylate, Phenoxybenzamine, Tacrolimus, Fluconazole, Misoprostol, Zonisamide.

- <u>"Handling"</u> includes
    - Receipt
    - Transport
    - Dispensing
    - Compounding (Nonsterile and sterile)
    - Mixing
    - Clean spills or handle waste
    - Manipulating
- <u>"Manipulation"</u> includes
    - Counting

- Placement into prescription bottles, unit-dose or unit-of-use packaging
- Splitting or cutting tablets
- Crushing tablets
- Opening capsules
- Preparing a suspension from tablets or capsule contents
- Drawing up doses

Does the USP 800 apply to non-compounding facilities?

- Short answer…. ***YES***
    - USP <800> intended to protect healthcare personnel from exposure to HD, therefore it applies to ALL personnel in ANY setting that HANDLE HD
        - Touching, inhaling, ingesting HD
- Pharmacies or veterinary hospitals, that do not perform compounding, ***handle*** HD anytime they receive an order, open a box, place containers on shelves, fill Rx's, unit dose
- Remember, anyone who cleans or removes waste from your pharmacy and anyone who delivers HD are potentially exposed to risk

A risk assessment may be all you need

- What is an "**assessment of risk**"? An entity's determination of alternative methods to prevent exposure to HD
- Must identify all HDs, all dosage forms, all manipulations of them that take place in your practice setting and create work practices and/or containment
    - Anti-neoplastics
    - Non-antineoplastic
- What is an "**assessment of risk**"? An entity's determination of alternative methods to prevent exposure to HD
- Must identify all HDs, all dosage forms, all manipulations of them that take place in your practice setting and create work practices and/or containment
    - Antineoplastics
    - Non-antineoplastic
    - HD with reproductive risk
- Assessment of risk must be completed, documented and reviewed annually.
- Where to start
    - Get the NIOSH list, print it for comparison to your practice setting's inventory
    - Match up any of your drugs AND dosage forms to those on the list according to the following HD categories

- Active pharmaceutical ingredient (API) of any type of HD
- Antineoplastics that only need counting and/or packaging
- Antineoplastics that need greater manipulation (split, crush, open capsules, pouring etc)
- Non-antineoplastics
- Reproductive HDs.

- Determine the risk of exposure during the continuum of manipulations necessary to get the HD to final dosage form.
- Use Table 5 in NIOSH list document to determine appropriate personal protective equipment and need for engineering controls.

<u>General principles</u>

- ALL the containment and work practices in USP <800> ***must*** be followed for
  - API of any HD
  - Antineoplastics that require manipulations beyond simply counting or packaging

<u>Examples of containment options</u>

- Purchase and dispense commercially unit-dosed HD
  - Ex-Atopica (cyclosporine)
- Wear chemo gloves when receiving, decontaminate outside of bottles, etc.
  - Cannot receive HD in positive pressure room
- Use dedicated equipment for HD that is decontaminated after use
  - Separate pill counter
- Store in clearly labeled, yellow, lidded containers with info regarding type of manipulations needed and required PPE
  - ***ONLY*** if HD is in ***final dosage form*** that needs ***only*** to be ***counted or packaged*** and ***do not produce powders or vapors***
  - Decontamination agents
    - EPA-approved oxidizing agent diluted per instructions
    - 2% bleach, neutralized by sodium thiosulfate

  <u>Containment strategies for non chemo drugs</u>
  - Use of closed system transfer device for injectable HDs that are not antineoplastics
    - Ex- injectable apomorphine
  - Use chemotherapy gloves for drugs that are not antineoplastics
    - Methimazole and misoprostol
  - Dedicated area in the practice
  - Dedicated equipment in this area

- Clear labeling of the work area/storage area for HDs and what personal protective equipment (PPE)is required. **Color code shelves or vial to draw visual attention**

Helpful resources

- http://www.ashpmedia.org/leader16/docs/handouts/511-L03%20(Breakout%20C)%20Slides.pdf
- https://www.pppmag.com/article/2012
- USP <800> http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare
- "The Chapter <800> Answer Book", Keinle, PC. © 2017, American Society of Health-System Pharmacists, Inc.

Definitions:

- Handling of HDs includes:
  - Receipt
  - Transport
  - Dispensing
  - Compounding*
  - Mixing
  - Manipulating dosage forms*
  - Administering
  - Handling of waste
  - Cleaning up spills
- Manipulation-includes but not limited to.
  - Counting, Placing in pill container, Splitting tablets, Opening capsules, Compounding sterile or non-sterile forms, drawing up a dose
- Compounding -DOES NOT include mixing, reconstituting and similar acts that are performed in accordance with the directions on the approved label.
  - **ANY deviation from the label is considered compounding by the FDA and USP**

NIOSH Definition of a HD

- Carcinogenic
- Genotoxic -Cellular damage-cytotoxicity and mitochondria damage
- Teratogenic- Disrupts fetal development
- Reproductive toxicity- Delayed time to conception/Spontaneous abortion
- Organ toxicity-low doses
  - Acute Effects-Skin rash, cough, dizziness, nasal sores

How exposure happens:

- Absorption-skin or MMs

- Aerosolization/inhalation
- Ingestion
- Needle sticks
- Exposure to bodily fluids-urine, feces and vomit.
- CLEAR, ODORLESS,PAINLESS =SILENT EXPOSURE

HD drug groups that affect Vet Med

- Group 1
    - Antineoplastics
    - Small molecule inhibitors
        - Palladia-blocks receptors responsible for new vessel growth
    - Megesterol
- Group 2
    - Apomorphine, azathioprine, chloramphenicol, cyclosporin, DES, lefunomide, methimazole, mycophenylate, phenoxybenzamine, progesterone, spironolactone, tacrolimus, darbepoetin
- Group 3-mostly a reproductive risk both men/women or women who are pregnant/breastfeeding
    - Fluconazole, misoprostol, oxytocin, pamidronate, valproic acid, zoledronic acid, zonisamide

Facilities

- Designated areas must be available for receipt, unpacking and storage of HDs
- HD handling areas must be clearly labelled, have restricted access and be located away from break room/refreshment areas
    - Think about HD workflow when creating these areas
- The designated room that houses the biological safety cabinet (hood) and in which HDs are prepared for administration needs to be separate from the room where the HD is administered
    - There are no engineering requirements for the room in which HDs are administered.

Facilities: C-PEC " Chemo Hood"

- Containment primary engineering control (C-PEC)
    - Ventilated device to minimize environmental and worker exposure when directly handling HDs
    - Recommended to be certified every 6 months
        - If contaminated must be decontaminated/source addressed
    - Not needed if handling final dosage that do not produce particles, aerosols or gases
        - Oral chemotherapies-CCNU, Cyclophosphamide, Melphalan
    - At BEVS-Class II BSC Type A2, Appropriate for sterile compounding
        - Adjunct controls for additional levels of protection
            - Closed transfer devices: Equashield or Phaseal

Containment secondary engineering control (C-SEC) " Hood Room"

- The room where the "hood" is placed
    - With or without an ante-room
    - If without an ante-room will affect some drug storage limitations
- Must be externally vented
- Must have 12 air exchanges per hour
- Negative pressure of the room tightly controlled
    - 0.01-0.03" of water column

- Fixed walls
- All surfaces must be impervious, free from cracks/crevices, non-shedding and cleanable

Drug storage requirements

- HDs that CAN be stored with other non-HD inventory
    - Non-antineoplastic HDs
    - Reproductive risk only drugs
- HDs that MUST be stored separated from other non-HD inventory
    - Anti-neoplastic drug or HDs API requiring manipulation other than counting
    - Store in negative pressure room with at least 12 ACPH
    - Refrigerated antineoplastic drugs-store in DEDICATED HD refrigerator.

PPE

- Gloves-MUST meet ASTM standard D6978
    - Double gloving required for administration except administration of intact capsule/tablet.
    - Sterile gloves if compounding.
- Gowns- Less standardized. Can use ASTM standard F739.
    - Do not use surgery or isolation gowns
    - Must be disposable, lint free and resist permeation by HDs.
    - CANNOT be reused.
- Face Shield/Eye protection
    - Required when there is risk of spill-ex intracavitary chemo
    - NOT required when working in a hood that has a sash in the proper position
    - If eye protection is needed, a face shield is not sufficient
- Mask- N95
    - Required when known or suspected airborne exposure to particles or vapors
        - Working outside of a C-PEC
        - Cleaning in the hood
        - Cleaning up a spill
        - **Strongly recommended-too late once the spill happens.
- Booties-required for entering the hood room to draw up antineoplastics
    - Normal type for surgery or Iso-no special requirements
    - 2 pairs if in sterile compounding room

Closed System Transport Device-CSTD

- Mechanically prohibits transfer of environmental contaminants into the system and HD vapors out of system.
- Leakproof/ Very easy to use
- Complies with the strictest aseptic technique requirements and guidelines set forth by NIOSH and OSHA.
- Has two chambers, the proximal liquid chamber, and the distal air chamber that is located at the end of the piston.
- Maintains constant pressure equalization inside the vial and prevents the escape of vapors.
- **REQUIRED FOR ADMINISTRATION OF ANTI-NEOPLASTICS WHEN THE DOSAGE FORM ALLOWS FOR IT.**

Receiving HDs when delivered

- Must be from supplier in impervious plastic to segregate from other drugs
- Must be delivered to the HD storage area immediately when unpacking
- A spill kit must be available
- Required PPE includes gloves +/- respiratory protection
- SOP required for receiving and handling of damaged shipping containers
- Trace chemo documented to be on boxes and outer packaging

Transport, disposal and spill clean up

- HD's must be labeled, handled and transported in containers that limit breaking or leakage
- Disposal of all contaminated materials must comply with applicable regulations
- ALL staff (even custodial staff) must be trained in how to handle HDs.
- SOPs must be developed to prevent spills and direct the cleanup of spills.
    - Spill kits must be readily available.

Hazard Communication Program

- Develop policies and procedures to ensure worker safety during HD handling
- All containers of HDs must be labelled, tagged or marked
- Safety data sheets must be available for all HDs
- Personnel must be provided information and training before initial assignment.
- All personnel must be trained appropriately to handle, clean up and decontaminate a spill and wear appropriate PPE
- Personnel of reproductive capability must confirm in writing that they understand the risks

How to be compliant in practice

- Use drug already in CSTD (UVM)
- Use required PPE-for handling, transport and administration
- Have appropriate YELLOW biohazard bin/service
- Have chemotherapy spill kit
- Have appropriate "chemo admin room"-minimal traffic, away from break room and other patients

Additional resources

- Sept 2020 - NIOSH will have a training pro-type for the handling of HDs specifically for veterinarians
- https://javma/NIOSH.vet
- The AVMA is putting together resources for USP 800-stay tuned
- https://www.cdc.gov/niosh/docs/2016-161