USP <800>: Challenges in the World of Oncology

Amy Billimoria, PharmD
Katie Plahn, CPhT, CSPT
University of Kentucky Markey Cancer Center

KENTUCKY HEMATOLOGY/ONCOLOGY
PHARMACY SYMPOSIUM 2020

Disclosures

- **Amy Billimoria: No relevant financial relationships to disclose**
- **Katie Plahn: No relevant financial relationships to disclose**

Learning Objectives

- Describe facility and engineering controls required to prepare sterile and non-sterile hazardous drugs
- Discuss the need for containment strategies in hazardous drug administration described in USP <800>
- Outline a plan for environmental surface sampling as described in USP <800>
- Identify a strategy to conduct medical surveillance for employees that handle hazardous drugs within your health system

Learning Objectives

- Identify strategies for deciding which drugs may need to undergo an Assessment of Risk
- Describe the different factors that must be considered at a minimum when assessing risk
- Discuss alternative containment strategies that may be used in handling hazardous drugs
- Define a process for documentation and review of assessments

Why do we need USP <800>?

- At the July 31, 2019 KY BOP meeting, the board voted to not adopt USP Chapter <800>
- Other entities such as pharmacy liability insurance providers, third-party payers, accreditation organizations, and other governmental agencies may require compliance
- Remember- USP 800 revolves around keeping the *healthcare worker* safe

What makes USP <800> so challenging to follow?

- Unlike Chapters <795> and <797> which focus primarily on compounding, <800> is wide, covering the entire enterprise or health system:
  - Receipt
  - Transport
  - Storage*
  - Compounding*
  - Administration*
  - Cleanup/Disposal

Storage requirements for HDs

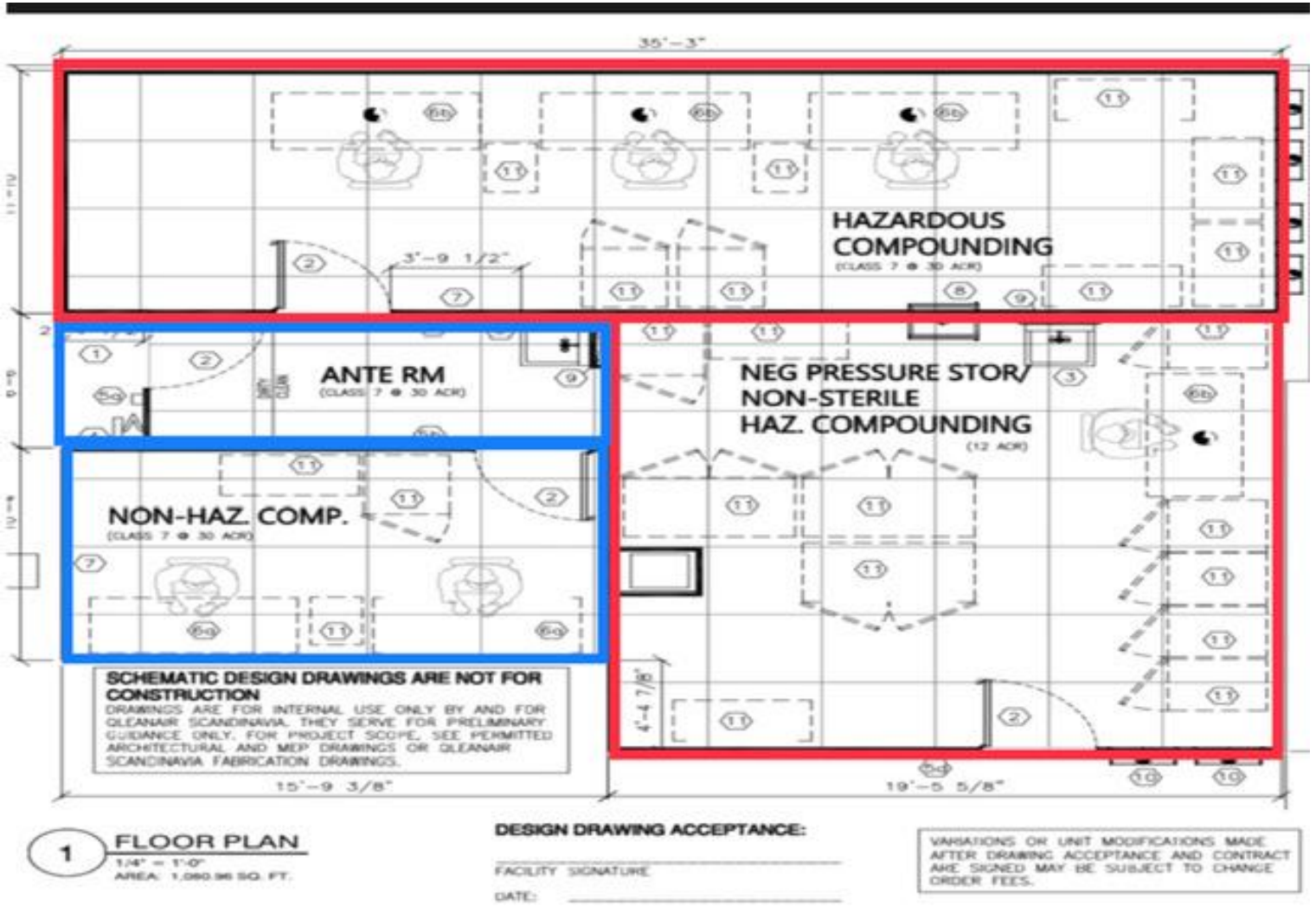
- Separate room with fixed wall separate from non-hazardous storage or non HD compounding
- External ventilation
- Negative pressure of 0.01 – 0.03 inches of water column
- At least 12 air changes per hour
- Remember, this includes your refrigerated HDs as well!
  - Consider solid state vs compressor based cooling
  - Compressors can generate and disperse particles
  - Condensation trays can promote mold and fungus growth

https://www.cleanroomtechnology.com/news/article_page/Solid-state_fridges_to_fast_track_USP_800_compliance/147765#:~:text=Unlike%20units%20with%20compressors%20that,This%20is%20a%20significant%20advantage.

The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs- Handled in Health Care Settings In: USP 42- NF 37

Facilities

- Many pharmacies are facing cleanroom renovations to make their spaces USP <800> and <797> compliant.
  - Hazardous compounding: -0.01 – 0.03”, ACPH 30
  - Negative Pressure Storage: -0.01 – 0.03”, ACPH 12
  - Ante Room: +0.02 – 0.05”, ACPH 30
  - Non Hazardous Compounding: +0.02 – 0.05”, ACPH 30
- Consider involving cleanroom consultants to help guide you through the details.



Primary Engineering Controls

- Think of PECs as the direct compounding area- most commonly referred to as the “hood”
- C is for “containment”
- C-PEC is used when speaking of hazardous environment, and means containment primary engineering control
- Types of C-PECS used for sterile hazardous compounding are different than those for non-hazardous- you cannot use a LAFW, as it does not provide protection for the product + Healthcare worker
- Types of C-PECS used for hazardous sterile compounding are:
  - Biological Safety Cabinets (BSCs)
  - Containment Aseptic Isolator (CACI)
- Both BSCs and CACIs must be externally vented for HD compounding

BSCs: A2s or B2s?

- A2:
  - exhaust 30% of air externally, 70% is recirculated HEPA filtered air
  - Studies have shown that for minute quantities of volatile chemicals, A2 cabinets are sufficient
  - Easier to maintain and integrate to the facility
  - Estimated energy usage is moderate and annual operating cost ~$70,000
- B2:
  - exhaust 100% of air externally
  - Best for volatile drugs
  - Difficult to integrate in older and more restrictive facilities
  - Estimated energy usage high, annual operating cost ~ $116,000

Image obtained with permission from the Baker Company
Critical Point LLC Pearls of Knowledge January 2020

CACI

- CACI – Compounding Aseptic Containment Isolators are most commonly used for low volume settings and in areas in which your room is a containment segregated compounding area (C-SCA)
- CACI must still be externally vented and placed in a negative pressure C-SEC to compound HDs
- Must provide ISO 5 or better air quality

Image obtained with permission from The Baker Company

The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs - Handled in Health Care Settings In: USP 42- NF 37

Secondary Engineering Controls

- Think of secondary engineering controls as the room in which your compounding is performed and the PEC is placed in
- There are two different types of SECs you can use for hazardous sterile compounding:
  - ISO 7 buffer room
  - C-SCA (Containment Segregated Compounding Area)

ISO 7 Buffer Room

- Must follow the requirements outlined in USP <797>
  - Negative pressure must be maintained between 0.01 – 0.03 inches of water column
  - Must have a minimum of 30 air changes per hour of HEPA filtered supply air
  - External ventilation
  - Must have an ante room in which the buffer room is entered that is *positive* pressure
    - Ante room must provide ISO 7 quality air as well for an HD buffer room

The U.S Pharmacopeial Convention (USP) (2019). Chapter <797> Pharmaceutical Compounding – Sterile Preparations In: USP 42 NF 37

The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs - Handled in Health Care Settings In: USP 42- NF 37

Containment Segregated Compounding Area

- Air in a SCA can be unclassified (no ISO requirement)
- Must be a closed room with hard walls
- Must have a minimum of 12 air changes per hour of HEPA filtered supply air
- External ventilation
- Does not require an anteroom
- Sink for hand washing must be placed at least 1 meter away from the C-PEC
- BUD given to the compounded preparations must not exceed what is outlined in USP <797> for a SCA – **12 hours**

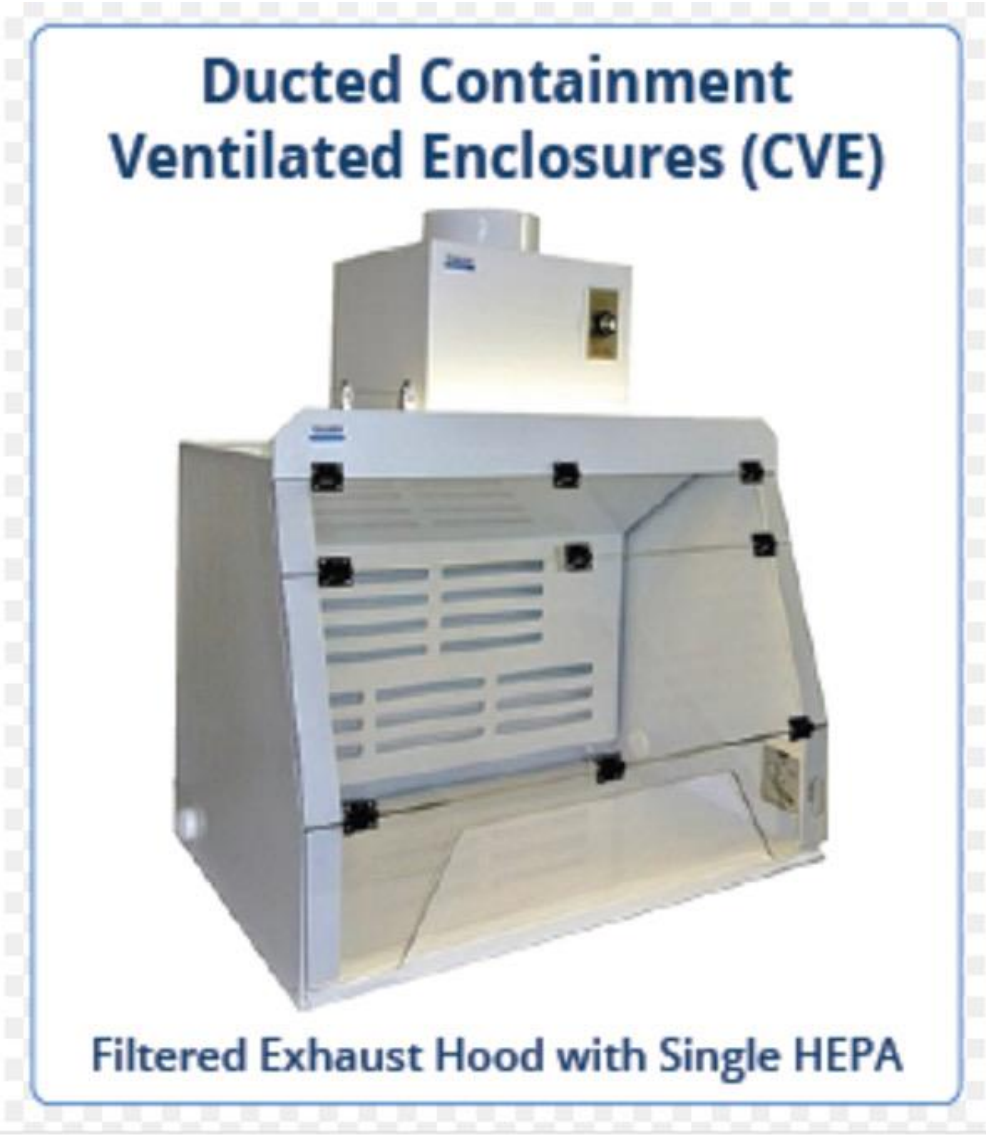
The U.S Pharmacopeial Convention (USP) (2019). Chapter <797> Pharmaceutical Compounding – Sterile Preparations In: USP 42 NF 37

The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs - Handled in Health Care Settings In: USP 42- NF 37

Negative Pressure

- Negative 0.01 - 0.03” is a tight range
- What happens when the room is too negative?
  - Difficulty with doors closing
  - Excess turbulence
  - Ceiling tiles can come loose
  - Draw in an excess of dirty air
- Involve your facilities department, certifier to help balance this air
- Consider involving clean room consultants

Non-Sterile Compounding



- Must follow the requirements outlined in USP <795>
- C-PEC must be externally vented OR have a redundant HEPA filtration series
- Must be performed in a C-SEC with negative pressure of 0.01 – 0.03
- CVE (Containment Ventilated Enclosure) = “powder hood” may be used. Or a Class I, II BSC or CACI
- USP <800> allows for *occasional* use of a BSC or CACI that is used for sterile compounding, but it must be thoroughly cleaned and disinfected prior to sterile compounding
- C-PEC not required if handling the final dosage form and no particle generation.

Picture displayed with permission from Cleatech LLC

The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs - Handled in Health Care Settings In: USP 42- NF 37

Administration

- There are not many engineering controls surrounding the administration of HDs
- IV tubing must be attached to HD when dispensed from pharmacy so that there is not risk to nursing when spiking the IV bag
- Supplemental engineering controls = closed system transfer devices = CSTDs
- USP <800> specifies that CSTDs are required when administering HDs (for compounding it is not required but recommended)
- Think of areas in which doses are dispensed outside of the typical IV infusion environment
  - Urology bladder irrigations
  - OR (Intraperitoneal or irrigation)

Occupational Safety and Health Administration (OSHA). Controlling Occupational Exposure to Hazardous Drugs.https://www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html. Accessed August 2020

The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs- Handled in Health Care Settings In: USP 42- NF 37

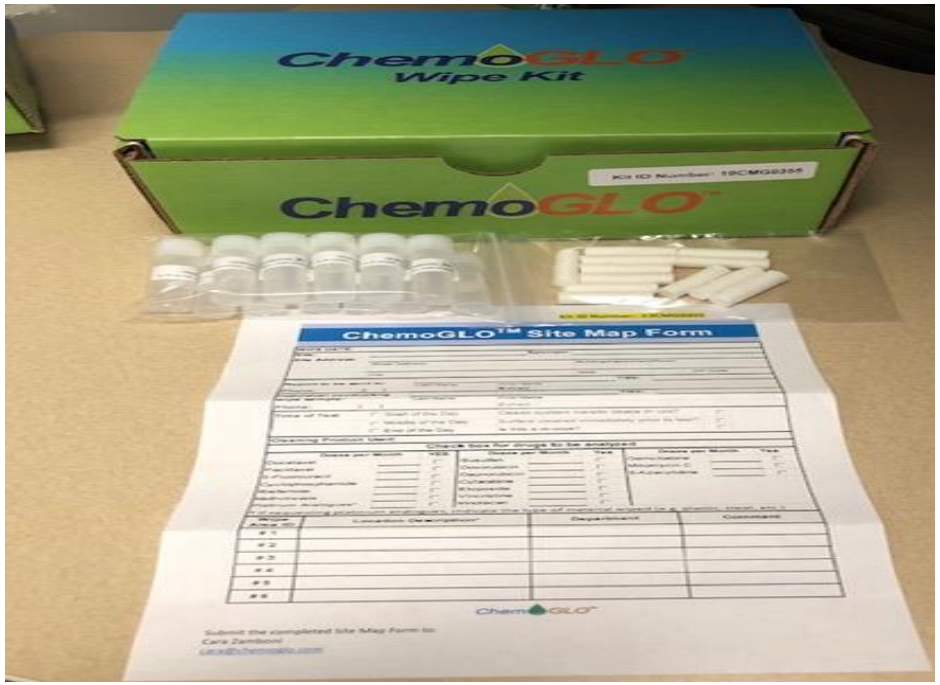
HD environmental sampling

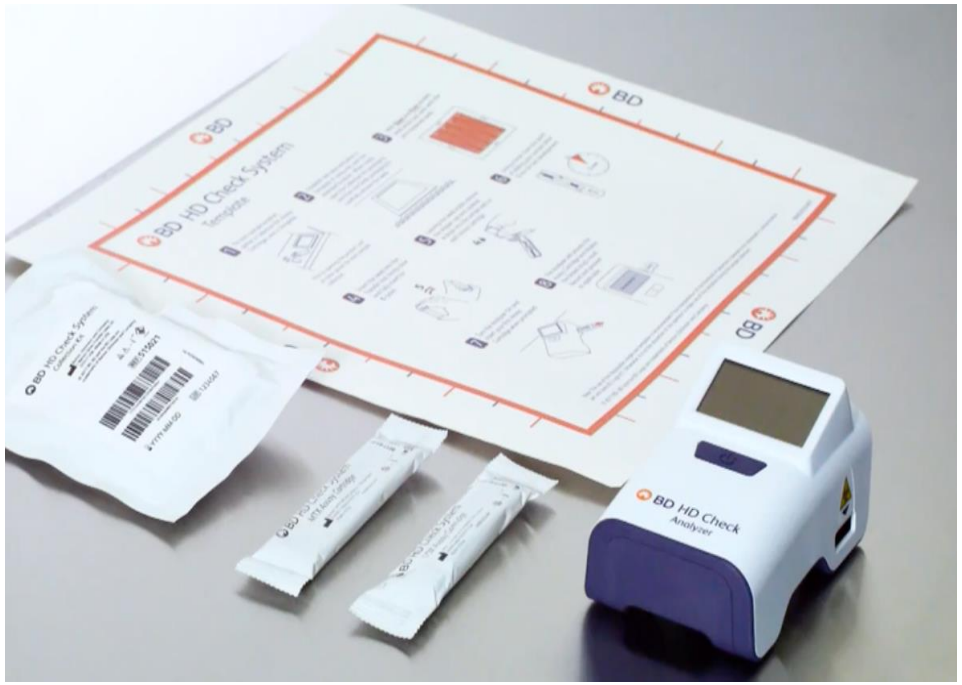
- USP <800> recommends routine wipe sampling for HD surface residue (“should” not “must”)
- Consider at least every 6 months
- Sample areas not just in the pharmacy, but administration as well.
- There is not a kit that will test for any and all existing HDs
- Common marker HDs are cyclophosphamide, ifosfamide, methotrexate, fluorouracil and platinum agents.
- Measurable contamination should be documented and action may include re-training personnel, better deactivation, decontamination and cleaning process, improving engineering controls.

The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs - Handled in Health Care Settings In: USP 42- NF 37

HD environmental sampling

- Different types of HD sampling kits exist. Chemo Glo is an example of a kit that can test for up to 17 different HDs. Samples must be mailed off for analysis and can take approximately 30 days to result.
- BD HD Check is a system that can be used more independently. Results are as fast as 10 minutes, but only currently able to detect 3 HDs.





HD environmental sampling

Table 1: Results from the August 23, 2019 Wipe Study in ng/ft^2 and ng/cm^2

Wipe	Location	Department	Cyclophosphamide Concentration ng/ft^2 (ng/cm^2)	Ifosfamide Concentration ng/ft^2 (ng/cm^2)	Cytarabine Concentration ng/ft^2 (ng/cm^2)	Vincristine Concentration ng/ft^2 (ng/cm^2)	Platinum Analogues Concentration ng/ft^2 (ng/cm^2)
1	Room ~~A11.222~~ Patient Commode	Nursing Administration	ND	ND	ND	ND	ND
2	Room [redacted] Computer Keyboard	Nursing Administration	ND	ND	ND	ND	ND
3	[redacted] Pharmacy Floor	Pharmacy	ND	ND	ND	ND	ND
4	[redacted] Pharmacy Refrigerator Bin	Pharmacy	304.40 (0.33)	ND	ND	ND	ND
5	[redacted] Pharmacy Keyboard	Pharmacy	ND	ND	ND	ND	ND
6	~~EQMC~~ Black Bucket Lid	Environmental Mgmt.	ND	ND	ND	ND	53.60 (0.06)

[1] Data tables are color coded according to risk levels as follows: Green – Non-Detectable; Blue – Low Risk (10–99.99 ng/ft^2); Yellow – Medium Risk (100-999.99 ng/ft^2); Orange – High Risk (1000-1999.99 ng/ft^2); Red – Severe Risk (≥2000 ng/ft^2)

Medical Surveillance

- Employees that handle HDs face risk and it may not be immediately evident
- Employees should be monitored over time to find trends from possible exposure to HDs
- To design and implement a surveillance program, a team approach is needed:
  - pharmacy
  - oncology nursing
  - quality and safety
  - occupational or employee health
- Select your participants
  - Initially you may need to start only with those working in the oncology department
- Program should include the following:
  - Questionnaire
  - Blood sample
  - Urine sample
  - Results should be reviewed with the employee

Reeves J. Creating an Employee Medical Surveillance Program. Pharmacy Purchasing and Products. 2012; 9(7):14

Medical Surveillance

- Regular interval for surveillance should be identified (e.g. annually)
- Sample questions for employees to fill out may include:
  - Reproductive history- any problems conceiving a child?
  - Exposure history- frequency of HD handling, most commonly handled HDs, PPE used
  - Family history
  - Past medical history
  - Review of systems

Reeves J. Creating an Employee Medical Surveillance Program . Pharmacy Purchasing and Products. 2012; 9(7):14

Assessments of Risk for Hazardous Drugs

Background Information

- USP <800> along with the 2016 NIOSH list give recommendations for the PPE and engineering controls that should be used when handling hazardous drugs (as identified by the NIOSH list)
- USP <800> allows for certain drugs and dosages forms to considered exempt from its guidelines if alternative containment strategies are identified, documented and observed in work practices
- When taken together this identification, planning, execution and documentation of practices other than those outlined in either document constitutes an “Assessment of Risk”

- NIOSH [2016]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings.
- USP general chapter <800> Hazardous drugs—handling in healthcare settings.

Determining Drugs to Assess

- When reviewing your facility's HD list, make a separate list of HDs that may be able to be contained using alternative strategies.
- This may include:
  - HDs that only require counting or packaging (bulk tablets, oral liquids)
  - HDs that come in unit dose or unit-of-use packaging (UD tablets/capsules, patches)
  - Commercially available, ready-to-use oral liquids, topical products
  - Table 2 or 3 non-antineoplastics
  - Table 3 reproductive risk only
- This may NOT include:
  - Active pharmaceutical ingredient of any HD on any table of the list
  - Any Table 1 antineoplastic HD that is manipulated beyond counting or packaging

- Critical Point Pear of Knowledge. "Performing a Risk Assessment." May 2020

Minimum Considerations

- Drug - which NIOSH Table, classification (antineoplastic, non-antineoplastic or reproductive risk only)
- Dosage Form – Final dosage forms such as UD tablets may require less complex strategies than forms that require significant manipulation, such as powders
- Risk of Exposure – What risks are posed by each drug in each formulation and how severe are those risks? (Example: low risk of dermal absorption during packaging of a tablet vs higher risk of mucosal/ dermal absorption or ingestion during crushing or cutting of the same tablet)

- USP Education. *General Chapter <800> Handling Hazardous Drugs in Healthcare Settings*. June 13, 2019.

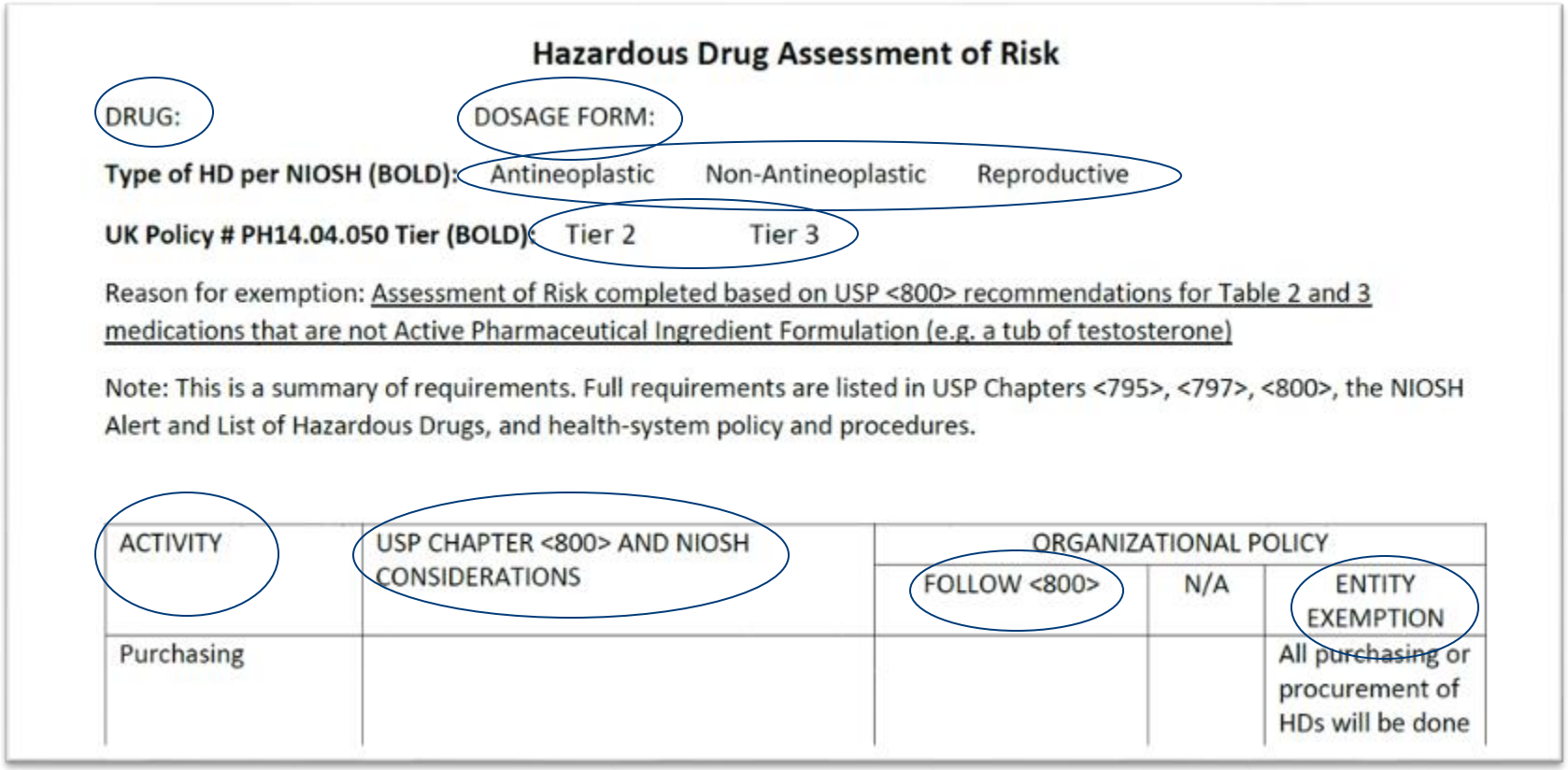
Minimum Considerations (continued)

- Packaging – Bulk tablets, capsules and oral liquids or multi-dose vials may require different or more complex strategies than unit dose or unit of use containers due to the need to repackage/prepare single doses.
- Manipulation – Consider all those who have a need to handle the drug throughout the facility. (Different risk for pharmacy technician preparing IV bag vs. nurse administering IV bag vs. environmental worker removing sealed waste containers)

Alternative Containment Strategies

- Should be specific to each drug ***and*** each dosage form.
  - One plan for Mycophenolate Mofetil capsules for oral administration and a separate plan for Mycophenolate Mofetil for IV administration
- Should address all aspects of handling each drug form as it moves through the facility.
  - Assessments should address receiving, storage, preparation/packaging, transport, administration and waste/disposal
- Should outline specific practices and workflows to mitigate the risk to personnel
  - Dexrazoxane (a Table 2 drug) IV formulation will be compounded in a CPEC, using CSTDs
  - Lenalidomide (a Table 2 drug) oral tablet formulation will be packaged manually using dedicated "HD" equipment, the equipment will be decontaminated after packaging and packager will wear gloves while handling drug and used equipment
  - Fluconazole (a Table 2 drug) oral liquid formulation syringes will be disposed of by nursing staff in a black, hazardous waste bin after administration and outside of waste bin will be decontaminated after sealing
  - Fluconazole (a Table 2 drug) oral tablet formulation empty packaging will be disposed of by nursing staff in a yellow, trace hazardous waste bin after administration and outside of waste bin will be decontaminated after sealing

Documentation & Review



Hazardous Drug Assessment of Risk

DRUG: DOSAGE FORM:

Type of HD per NIOSH (BOLD): Antineoplastic Non-Antineoplastic Reproductive

UK Policy # PH14.04.050 Tier (BOLD): Tier 2 Tier 3

Reason for exemption: Assessment of Risk completed based on USP <800> recommendations for Table 2 and 3 medications that are not Active Pharmaceutical Ingredient Formulation (e.g. a tub of testosterone)

Note: This is a summary of requirements. Full requirements are listed in USP Chapters <795>, <797>, <800>, the NIOSH Alert and List of Hazardous Drugs, and health-system policy and procedures.

ACTIVITY	USP CHAPTER <800> AND NIOSH CONSIDERATIONS	ORGANIZATIONAL POLICY		
		FOLLOW <800>	N/A	ENTITY EXEMPTION
Purchasing				All purchasing or procurement of HDs will be done

Elements of Assessment Form *(Example)*

- Drug name
- Dosage form
- Type of HD risk
- Facility Tier
- Type of handling activity
- USP <800>/ NIOSH considerations
- Columns to describe handling workflow
  - Follow USP <800>
  - Not applicable for drug/ dosage form
  - Entity exemption (alternative strategies)

- UK Healthcare Pharmacy Department. "Hazardous Drug Assessment of Risk." Accessed August 12, 2020

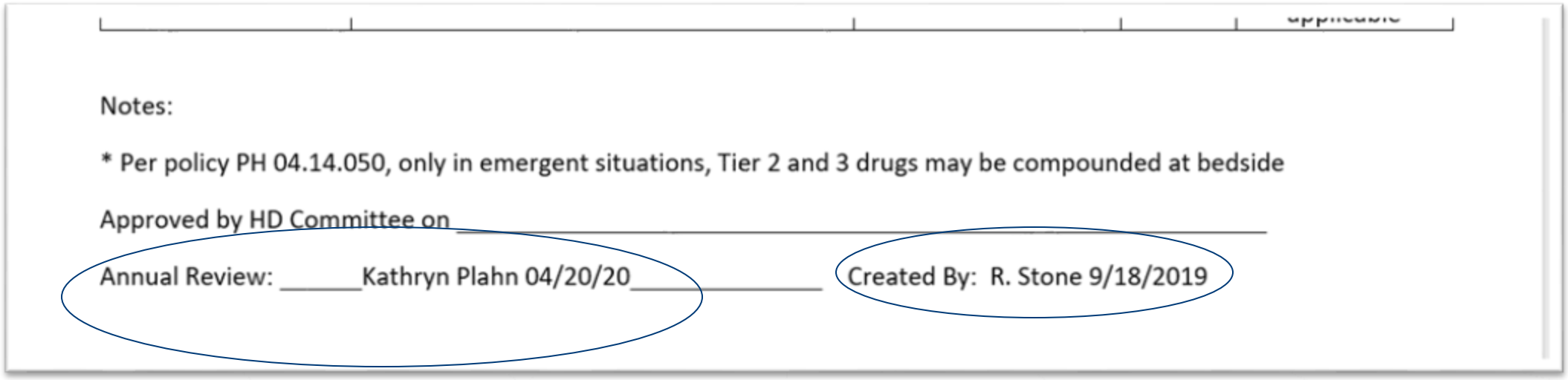
Documentation & Review (continued)

Transport from storage to dispensing area(s)	In container that minimizes risk of breakage or leakage	x		
Non-sterile compounding area(s)	Meets USP <795> and <800> requirements			Powder hood in non-certified air. See policy PH 04.014.050 And gNU-61
Sterile compounding area(s)	Meets USP <797> and <800> requirements			All CSPs should be compounded according to USP <797> standards*
Garbing				See policy PH 04.014.050 And gNU-61
Splitting or crushing	Meets USP <795> and <800> requirements and NIOSH HD list recommendations			Splitting or crushing Tier 2 and 3 drugs to be performed by pharmacy only. No bedside option.
Transport finished preparations to on-site or off-site	In container that minimizes risk of breakage or leakage			

Completing the Assessment

- If USP <800> guidelines will be followed, no alternative strategies are necessary
- Not every activity will apply to every drug, in every dosage form
- Containment strategies that differ from those in <800>/ NIOSH should be detailed and applicable policies should be referenced

Documentation & Review (continued)



Notes:

* Per policy PH 04.14.050, only in emergent situations, Tier 2 and 3 drugs may be compounded at bedside

Approved by HD Committee on _____

Annual Review: _____Kathryn Plahn 04/20/20_____ Created By: R. Stone 9/18/2019

Creation and Review

- Should be completed for eligible drugs upon approval for use in the facility, or determination of hazard level
- Should be reviewed annually following initial completion to check for:
    - Completeness – Have any handling activities been omitted or have new activities been undertaken?
    - Accuracy – Are all handling activities still performed at the facility, following the same processes?
    - Feasibility – Are the same resources and personnel available for utilization? (Example: If PPE or decontaminants are in short supply, strategies may change to facilitate conservation.)

Conclusions

- Primary and secondary engineering controls in conjunction with proper technique and protective garb will help keep compounding personnel safe
- Due to limited administration engineering controls, CSTDs must be used as well as limiting any manipulation of the HD by personnel administering the product
- Environmental sampling for HD detection can be costly, but is crucial to identify and improve areas in which contamination may exist
- Implementing a medical surveillance program for employees that handle HDs will require a collaborative effort from a multi-disciplinary team
- Assessments of Risk will identify alternative strategies for containment in all aspects of handling, and requires thorough review and documentation of a facility's HD list

Audience Response Question #1

- HD storage requires a room with at least ___ air changes per hour. While a C-SCA requires at least ___ air changes per hour for compounding, and a buffer room requires ___ air changes per hour for compounding.
  - A. 12, 30, 30
  - B. 12, 12, 30
  - C. 10, 12, 30
  - D. 30, 30, 30

Audience Response Question #2

- Which of the following is an accurate statement regarding environmental monitoring which detects HD contamination.

A. USP <800> requires that this must be performed every 6 months
B. Some detection devices/kits can produce results as fast as 10 minutes
C. Some detection kits may require samples to be sent off via mail and take as long as 30 days to result.
D. A and C
E. B and C

Audience Response Question #3

All of the following must be considered when completing an Assessment of Risk for a hazardous drug EXCEPT:

A. Packaging
B. Storage Conditions
C. Risk of Exposure
D. Manipulations

References

- The U.S. Pharmacopeial Convention (USP) (2019). Chapter 800 Hazardous Drugs- Handled in Health Care Settings In: USP 42- NF 37
- Cleanroom Technology. Solid State Fridges to Fast Track USP 800 Compliance. October 2018 https://www.cleanroomtechnology.com/news/article_page/Solid-state_fridges_to_fast_track_USP_800_compliance/147765#:~:text=Unlike%20units%20with%20compressors%20that,This%20is%20a%20significant%20advantage. Accessed August 2020
- Critical Point LLC Pearls of Knowledge: Biological Safety Cabinets (BSCs) for Sterile Hazardous Drug Compounding: Information To Consider Before Choosing an A2 versus B2. January 2020
- The U.S Pharmacopeial Convention (USP) (2019). Chapter <797> Pharmaceutical Compounding – Sterile Preparations In: USP 42 NF 37
- Occupational Safety and Health Administration (OSHA). Controlling Occupational Exposure to Hazardous Drugs. https://www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html. Accessed August 2020
- Reeves J. Creating an Employee Medical Surveillance Program. Pharmacy Purchasing and Products. 2012; 9(7):14

References

- NIOSH [2016]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication Number 2016-161 (Supersedes 2014-138)
- United States Pharmacopeia and National Formulary (USP 41-NF 36). Rockville, MD: United States Pharmacopeial Convention; 2016. https://online.uspnf.com/uspnf/document/GUID-AC788D41-90A2-4F36-A6E7-769954A9ED09_1_en-US. Accessed August 12, 2020.
- USP Education. *USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings.* June 13, 2019
- Critical Point Pearls of Knowledge. "Performing and Assessment of Risk." May 2020.
- Kienle, Patricia. Practical Strategies for Compliance with USP <800>: Performing an Assessment of Risk. Presented at: 21st Annual ASHP Conference for Leaders. October 2016.
- University of Kentucky Healthcare, Pharmacy Department. "Hazardous Drug Assessment of Risk." Accessed August 12, 2020.