ONCOLOGY PRACTICE MANAGEMENT

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LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Evaluate oncology pharmacy services for compliance with established regulations, professional practice standards, and procedures for handling, administration, and disposal of hazardous drugs.
2. Select quality-improvement activities that enhance the safety and effectiveness of the medication-use process in oncology patient care.
3. Explain national accreditation and federal regulatory requirements for the care of cancer patients receiving chemotherapy or other hazardous drugs.
4. Explain medication reimbursement and patient assistance programs to optimize drug availability for oncology patients.
5. Evaluate policies and procedures related to conducting research involving investigational drugs, including drug management in patients with cancer.

CLINICAL PRACTICE AND REGULATORY STANDARDS

Question #1:

Which of the following is most correct about the standards set forth in USP<800>?

- **a. The term "must" indicates a requirement and "should" indicates a recommendation**
- **b. Only applies in hospital settings**
- **c. Outlines requirements for medical surveillance for health care workers handling hazardous drugs for the first time**
- **d. Recommendations mirror those in USP<797>**

A. **Annotated summary of Hazardous Drugs – Handling in Healthcare Settings USP Chapter <800>.[2] Compliance is required effective December 1, 2019.** Recommendations – "must" is used to denote a requirement; "should" indicates a generally acceptable recommendation

I.

B. Introduction and Scope:

1. Describes practice and quality standards for handling HDs, promoting patient safety, worker safety and environmental protection. Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and non-sterile hazardous products and preparations.

2. Applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs including pharmacies, hospitals, other healthcare institutions, patient treatment clinics, physicians' practice facilities, veterinary offices. Personnel impacted include but are NOT limited to pharmacists, pharmacy technicians, nurses, physicians, physician assistants, home healthcare workers, veterinarian, and veterinary technicians.

3. Occupational safety plan must include:

   a. A list of HDs

   b. Facility and engineering controls

   c. Competent personnel

   d. Safe work practices

   e. Proper use of appropriate PPE

   f. Policies for HD waste segregation and disposal

C. List of HDs

1. The National Institute for Occupational Safety (NIOSH) maintains a list of antineoplastic and other HDs used in healthcare. Facilities must maintain a list of HDs which are present and on-site, which must include any items on the current NIOSH list that the entity handles. This list must be reviewed at least every 12 months. Newly approved

agents or investigational drugs must be considered for addition to the list if potentially hazardous based on NIOSH criteria.

Answers to Question #1

Choice A is correct because the nomenclature consistently utilized by USP <800> for requirements is "must" and for recommendations is "should".

Choice B is incorrect because while USP<800> is enforceable in hospitals, it also enforceable in other non-hospital treatment settings such as physician-owned ambulatory infusion centers.

Choice C is incorrect because USP <800> outlines recommendations for surveillance for healthcare professionals handling hazardous drugs but the recommendations are not requirements.

Choice D is incorrect because the standards set forth in USP<800> have been removed from the updated USP<797> chapter.

Question #2:

Which of the following best summarizes the requirements for maintaining a hazardous drug list per USP<800>??

a. **The institution can opt out of maintaining a HD list if they have a low volume of chemotherapy patients**
b. **The institution is required to prepare a HD list and update it annually**
c. **The HD list must mirror the NIOSH list exactly**
d. **Investigational agents are exempt from the institutional HD list**

Comparison of 2014 2016 NIOSH and 1990 ASHP Definitions of Hazardous Drugs[1]

***Drugs are defined as hazardous if they meet one of the criteria in the table below.

NIOSH	ASHP
Carcinogenicity	Carcinogenicity in animal models, in the patient population, or both as reported by the International Agency for Research on Cancer.
Teratogenicity or other developmental toxicity*	Teratogenicity in animal studies or in treated patients.
Reproductive toxicity*	Fertility impairment in animal studies or in treated patients.
Organ toxicity at low doses*	Evidence of serious organ or other toxicity at low doses in animal models or treated patients.
Genotoxicity**	Genotoxicity (i.e., mutagenicity and clastogenicity in short-term test systems).
Structure and toxicity profile of new drugs that mimic existing drugs determined hazardous by the above criteria	

Containment Requirements

- Drugs on the NIOSH list that must follow the requirements in the chapter include:
  - Any HD API (active pharmaceutical ingredient)
  - Any antineoplastic requiring HD manipulation
- Drugs on the NIOSH list that do not have to follow all the containment requirements of this chapter if an assessment of risk is performed and implemented include:
  - Final dosage forms of compounded HD preparations and conventionally manufactured HD products, including antineoplastic dosage forms that do not require any further manipulation other than counting or repackaging (unless required by the manufacturer)
- For dosage forms of other HDs on the NIOSH list, the entity may perform an assessment of risk to determine alternative containment strategies and work practices.

2. Some dosage forms of HDs may not constitute a significant risk of direct occupational exposure (e.g., tablets or capsules – solid, intact medications that are administered to patients without modifying the formulation). However, dust from tablets and capsules may present a risk of exposure by skin contact and/or inhalation. If an assessment of risk is not performed, all HDs must be handled with all containment strategies defined in this chapter.
3. Assessment of risk for above intact dosage forms (must be reviewed annually):
   a. Type of HD (e.g., antineoplastic, non-antineoplastic, reproductive risk only)
   b. Dosage form
   c. Risk of exposure
   d. Packaging
   e. Manipulation

D. Types of Exposure

1. HD exposure routes: dermal and mucosal absorption, inhalation, injection, and ingestion (e.g., contaminated foodstuffs, spills, or mouth contact with contaminated hands). Containers of HDs have been shown to be contaminated upon receipt. Both clinical and nonclinical personnel at risk.

Examples of Potential Opportunities of Exposure Based on Activity

Activity	Potential Opportunity of Exposure
Receipt	Contacting HD residue present on drug containers, individual dosage units, outer containers, work surfaces, or floors
Dispensing	Counting or repackaging tablets and capsules
Compounding and other manipulations	Crushing or splitting tablets or opening capsules Pouring oral or topical liquids from one container to another Weighing or mixing components Constituting or reconstituting powdered or lyophilized HDs Withdrawing or diluting injectable HDs from parenteral containers Expelling air or HDs from syringes Contacting HD residue present on PPE or other garments Deactivating, decontaminating, cleaning, and disinfecting areas contaminated with or suspected to be contaminated with HDs Maintenance activities for potentially contaminated equipment and devices
Administration	Generating aerosols during administration of HDs by various routes (e.g., injection, irrigation, oral, inhalation, or topical application) Performing certain specialized procedures (e.g., intraoperative intraperitoneal injection or bladder instillation) Priming an IV administration set
Patient-care activities	Handling body fluids (e.g., urine, feces, sweat, or vomit) or body-fluid contaminated clothing, dressings, linens, and other materials
Spills	Spill generation, management, and disposal
Transport	Moving HDs within a healthcare setting
Waste	Collection and disposal of hazardous waste and trace contaminated waste

Answers to Question #2:

Choice B is correct because USP<800> specifies the requirement for creating an institutional HD list and ensuring that it is updated at least annually.

Choice A is incorrect because institutions are required to maintain a HD list regardless of their volume of chemotherapy dispensed.

Choice C is incorrect because institutions are provided flexibility to deviate from the NIOSH list of hazardous drugs based on their own internal risk assessment of individual drugs as potential HDs.

Choice D is incorrect because investigational agents should undergo a risk assessment to determine if they should be classified as an HD.

Question #3:

Which is the most appropriate setting for admixing HD compounded sterile products (CSPs)?

a. BSC (biologic safety cabinet) in a positive pressure room
b. BSC in a negative pressure room
c. LAFW (laminar air flow workbench) in a positive pressure room
d. LAFW in a negative pressure room

E. Responsibilities of Personnel Handling HDs

1. A responsible person who is qualified and trained must be designated for USP 800 compliance and ongoing monitoring.
2. All personnel who handle HDs are responsible for understanding risks associated with handling HDs and compliance with institutional standards for safety and compliance.

F. Facilities and Engineering Controls

1. Signage must be present for areas where HDs are handled, and access limited to authorized personnel. HD handling areas must not be proximal to breakrooms and refreshment areas for personnel, patients, or visitors.
2. Designated areas must be available for:
   a. Receipt, unpacking and storage of HDs
   b. Sterile and nonsterile HD compounding
3. Negative pressure engineering controls are required for compounding /manipulating areas for sterile and nonsterile HDs
4. Receipt: Unpacking must take place in an area that is neutral/normal or negative pressure relative to the surrounding areas and not in sterile areas.
5. Storage: HDs must be stored in a manner that prevents spillage or breakage if the container fails. No storage of HDs on the ~~floor..~~floor. HDs must be stored in an externally ventilated, negative pressure room with at least 12 air exchanges per hour (ACPH). Non-antineoplastic, reproductive risk only and final dosage forms of antineoplastic HDs may be stored with other inventory. Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH.
6. Containment:

- **A containment primary engineering control (C-PEC) is a ventilated device designed to minimize worker and environmental HD exposure when directly handling HDs. The containment secondary engineering control (C-SEC) is the room in which the C-PEC is placed. Supplemental engineering controls (e.g., CSTD) are adjunct controls to offer additional levels of protection.**
- **When compounding HD preparations in a C-PEC, a plastic-backed preparation mat should be placed on the work surface of the C-PEC. The mat should be changed immediately if a spill occurs and regularly during use and should be discarded at the end of the daily compounding activity.**
- **For entities that compound both nonsterile and sterile HDs, the respective C-PECs must be placed in separate rooms, unless ISO 7 classification for the room is maintained. If the C-PECs used for sterile and nonsterile compounding are placed in the same room, they must be kept 1 meter apart.**
- **Engineering control specifications for non-sterile and sterile compounding can be found in table below.**

Engineering Controls for Nonsterile HD Compounding

C-PEC	C-SEC Requirements
Externally vented (preferred) or redundant-HEPA filtered in series Examples: CVE (Containment Ventilated Enclosure, Class I or II BSC, CACI	Externally vented 12 ACPH Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas Surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets must be smooth, impervious, and non-shedding

Engineering Controls for Sterile HD Compounding

Configuration	C-PEC	C-SEC	Maximum BUD
ISO Class 7 buffer room with an ISO 7 anteroom	Externally vented Examples: Class II BSC or CACI	Externally vented 30 ACPH Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in <797>
Unclassified C-SCA (containment segregated compounding area)	Externally vented Examples: Class II BSC or CACI	Externally vented 12 ACPH Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in <797> for CSPs prepared in a segregated compounding area

Answers to Question #3:

Choice B is correct because USP<800> defines the requirement for HD CSPs to be prepared in a BSC externally vented in a negative pressure environment.

Choice A is incorrect because HD CSP must never be conducted in a positive pressure environment.

Choice C is incorrect because a LAFW is never appropriate for compounding HD CSPs nor is a positive pressure environment.

Choice D is incorrect because a LAFW is never appropriate for compounding HD CSPs.

7. Sink: A hand-washing sink must be placed in the anteroom at least 1 meter from the entrance to the HD buffer room to avoid contamination migration into the negative pressure HD buffer room.
8. Containment segregated compounding area (C-SCA): The C-PEC is placed in an unclassified C-SCA that has fixed walls, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas, and a minimum of 12 ACPH that is externally ventilated. A hand-washing sink must be placed at least 1 meter from the C-PEC.
9. Containment Supplemental Engineering Controls: Containment supplemental engineering controls, such as CSTDs, provide adjunct controls to offer an additional level of protection during compounding or administration.
    a. Until a published universal performance standard for evaluation of CSTD containment is available, users should carefully evaluate the performance claims associated with available CSTDs based on independent, peer-reviewed studies and demonstrated containment reduction.
    b. A CSTD **must** not be used as a substitute for a C-PEC when compounding. CSTDs **should** be used when compounding HDs when the dosage form allows. CSTDs **must** be used when administering antineoplastic HDs when the dosage form allows. CSTDs known to be physically or chemically incompatible with a specific HD must not be used for that HD.

G. Environmental Quality and Control

1. Environment wipe sampling for HD surface residue **should** be performed routinely (e.g., initially as a benchmark and at least every 6 months). Surface wipe sampling should include:
    a. Interior of the C-PEC and equipment contained in it
    b. Pass-through chambers
    c. Surfaces in staging or work areas near the C-PEC
    d. Areas adjacent to C-PECs (e.g., floors directly under C-PEC, staging, and dispensing area)
    e. Areas immediately outside the HD buffer room or the C-CSA
    f. Patient administration areas
2. There is currently no standard for acceptable limits for HD surface contamination. Common marker HDs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, fluorouracil, and platinum-containing drugs. An example of measurable contamination would be cyclophosphamide levels >1.00 ng/cm^2, which were shown in

some studies to result in uptake of the drug in exposed workers. Any measurable contamination must be contained. Repeat the wipe sampling to validate that mitigation steps have been effective.

Question #4:

According to USP<800>, which of the following is most correct regarding PPE requirements?

- **a. ~~Double gloving~~Double gloving is required only for compounding of HDs**
- **b. Laminate coated gowns are only required for administration of HDs**
- **c. Eye and face protection is required when working outside of a C-PEC or at eye level with HDs**
- **d. PPE that has not been subject of a spill event is not required to be disposed of as hazardous waste**

H. Personal Protective Equipment

1. Additional PPE may be required for treating a patient or cleaning a spill. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE use.
2. Gowns, head, hair, and shoe covers, and two pair of chemotherapy gloves are required for compounding sterile and nonsterile HDs. Two pairs of chemotherapy gloves are required when administering antineoplastic HDs. Gowns shown to resist permeability by HDs are required when administering injectable antineoplastic HDs. For all other activities, the entity's SOP must describe the appropriate PPE to be worn based on its occupational safety plan and assessment of risk (if used).
3. Appropriate PPE must be worn during all phases of handling HDs from receipt to administration. Deactivation, cleaning, disinfecting, spill control and waste disposal are included in the phases of handling for HDs.
4. Gloves: When chemotherapy gloves are required, they must meet American Society for Testing and Materials (ASTM) standard D6978 (or its successor). Chemotherapy gloves should be worn for handling all HDs including non-antineoplastics and for reproductive risk only HDs. Chemotherapy gloves must be powder-free and be inspected for physical defects before use. When used for sterile compounding, the **outer** chemotherapy gloves must be **sterile**. Chemotherapy gloves should be changed every 30 minutes unless otherwise recommended by the manufacturer's documentation and must be changed when torn, punctured, or contaminated. Hands must be washed with soap and water after removing gloves.
5. Gowns: When gowns are required, they must be disposable and shown to resist permeability by HDs. Disposable gowns made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials. Gowns must close in the back (i.e., no open front), be long sleeved, and have closed cuffs that are elastic or knit. Gowns must not have seams or closures that could allow HDs to pass through. Cloth laboratory coats, surgical scrubs, isolation gowns, clothing or other absorbent material are not appropriate outer wear when handling HDs because they permit the permeation of HDs and can hold spilled drugs against the skin. Washing of non-disposal clothing contaminated with HD residue should only be done according to facility policy as drug residue may be transferred to other clothing. Potentially contaminated clothing must not be taken home under any circumstances. Gowns must be changed per the manufacturer's information for permeation of the gown. If no permeation information is available for the gowns used, change them every 2 to 3 hours or immediately after a spill or splash. Gowns worn in HD handling areas must not be worn to other areas outside of the HD handling areas. Head, hair, shoe, and

sleeve covers: Head and hair covers (including beard and moustache, if applicable), shoe covers, and sleeve covers provide protection from contact with HD residue. When compounding HDs, a second pair of shoe covers must be donned before entering the C-SEC and doffed when exiting the C-SEC. Shoe covers worn in HD handling areas must not be worn to other areas. Disposable sleeve covers may be used to protect areas of the arm that may come in contact with HDs. Disposable sleeve covers made of polyethylene-coated polypropylene or other laminate materials offer optimal protection.

6. Eye and face protection: Appropriate eye and face protection must be worn when there is a risk for spills and splashes of HDs when working outside of a C-PEC (e.g., administration in the surgical suite, working at or above eye level, or cleaning a spill). A full-facepiece respirator provides eye and face protection. Face shields in combination with goggles provide a full range of protection against splashes to the face and eyes.
7. Respiratory protection: Personnel who are unpacking HDs that are not contained in plastic should wear an elastomeric half-mask with a multi-gas cartridge and P100-filter until assessment of the packaging integrity can be made to ensure no breakage or spillage occurred during transport. Surgical masks do not provide respiratory protection from drug exposure and must not be used when respiratory protection from HD exposure is required. A surgical N95 respirator provides the respiratory protection of an N95 respirator, and like a surgical mask provides a barrier to splashes, droplets, and sprays around the nose and mouth. For most activities requiring respiratory protection, a fit-tested NIOSH-certified N95 or more protective respirator is sufficient to protect against airborne particles. However, N95 respirators offer no protection against gases and vapors and little protection against direct liquid splashes (see the Centers for Disease Control and Prevention's (CDC's) Respirator Trusted-Source Information. An appropriate full-facepiece, chemical cartridge-type respirator or powered air-purifying respirator (PAPR) should be worn when there is a risk of respiratory exposure to HDs, including when:
    a. Attending to HD spills larger than what can be contained by a spill kit
    b. Deactivating, decontaminating, and cleaning underneath the work surface of a C-PEC
    c. There is known or suspected airborne exposure to powders or vapors
8. Disposal of Used Personal Protective Equipment: Consider all PPE worn when handling HDs to be contaminated with, at minimum, trace quantities of HDs. PPE must be placed in an appropriate waste container and further disposed of per local, state, and federal regulations. PPE worn during compounding should be disposed of in the proper waste container before leaving the C-SEC or contained in a sealable bag for discarding outside of the C-PEC. Chemotherapy gloves and sleeve covers (if used) worn during compounding must be carefully removed and discarded immediately into a waste container approved for trace contaminated waste inside the C-PEC or contained in a sealable bag for discarding outside the C-PEC.

I. Hazard Communication Program
    1. SOP s for training regarding proper labeling, transport, storage, and disposal of the HDs and use of Safety Data Sheets (SDS).
    2. Hazard communication program:
        a. Written standards
        b. Containers of HDs must be labeled
        c. SDS for all HDs
        d. SDS are readily available
        e. Staff potentially exposed to HDs must receive training prior to handling them
        f. Written consent from personnel of reproductive capability to handle HDs

J. Personnel Training
    1. HDs used on site and associated risks
    2. SOP's related to handling of HDs
    3. PPE use
    4. Proper use of equipment and devices (e.g., C-PEC)
    5. SOP for HD exposure for staff members
    6. Spill management
    7. Management of hazardous waste

K. Receiving
    1. The entity must establish SOPs for receiving HDs. HDs should be received from the supplier impervious plastic to segregate them from other drugs and to allow for safety in the receiving and internal transfer process. HDs must be delivered to the HD storage area immediately after unpacking. PPE, including chemotherapy gloves, must be worn when unpacking HDs (see Personal Protective Equipment). A spill kit must be accessible in the receiving area.
    2. The entity must enforce policies that include a tiered approach, starting with visual examination of the shipping container for signs of damage or breakage (e.g., visible stains from leakage, sounds of broken glass). Table below summarizes the steps for receiving and handling of damaged shipping containers.

Summary of Requirements for Receiving and Handling Damaged HD Shipping Containers

If the shipping container appears damaged	Seal the container without opening and contact the supplier If the unopened package is to be returned to the supplier, enclose the package in an impervious container and label the outer container "Hazardous" If the supplier declines return, dispose of hazardous waste
If a damaged shipping container must be opened	Seal the container in plastic or an impervious container Transport it to a C-PEC and place on a plastic-backed preparation mat Open the package and remove undamaged items Wipe the outside of the undamaged items with a disposable wipe Enclose the damaged item(s) in an impervious container and label the outer container "Hazardous" If the supplier declines return, dispose of as hazardous waste Deactivate, decontaminate, and clean the C-PEC (See Deactivating, Decontaminating, Cleaning and Disinfecting below) and discard the mat and cleaning disposables as hazardous waste

3. Damaged packages or shipping cartons must be considered spills that must be reported to the designated person and managed according to the entity's SOP.

L. Beyond Use Dating, Labeling, Packaging, Transport and Disposal

1. The entity must establish SOPs for the labeling, packaging, transport, and disposal of HDs. The SOPs must address prevention of accidental exposures or spills, personnel training on response to exposures, and use of a spill kit.
2. Beyond Use Dating (more detailed discussion in the USP<797> section that follows): HD CSPs prepared in an ISO Class 7 buffer room with an ISO Class 7 anteroom may use the BUDs described in <797>, based on the categories of CSP, sterility testing, and storage temperature.
3. Labeling: HDs must always be clearly labeled during their transport.
4. Packaging: Personnel must select and use packaging containers and materials that will maintain physical integrity, stability, and sterility (if needed) of the HDs during transport.
5. Transport: HDs that need to be transported must be labeled, stored, and handled in accordance with applicable federal, state, and local regulations. HDs must be transported in containers that minimize the risk of breakage or leakage. Pneumatic tubes must not be used to transport any liquid HDs or any antineoplastic HDs because of the potential for breakage and contamination.

6. Disposal: Disposal of all HD waste, including, but not limited to, unused HDs and trace-contaminated PPE and other materials, must comply with all applicable federal, state, and local regulations.

M. Dispensing Final Dosage Forms
   1. HDs that do not require any further manipulation, other than counting or repackaging of the final dosage forms, may be prepared for dispensing without any further requirements for containment unless required by the manufacturer or if visual indicators of HD exposure hazards are present (e.g., HD dust or leakage).
   2. Counting or repackaging of HDs must be done carefully. Clean equipment should be dedicated for use with HDs and should be decontaminated after every use. Tablet and capsule forms of antineoplastic HDs must not be placed in automated counting or packaging machines, which subject them to stress and may create powdered contaminants.

N. Compounding
   1. Standards for USP<795> and <797> must be followed.
   2. When compounding in a C-PEC, a plastic-backed preparation mat should be placed on the work surface of the C-PEC.
   3. Change the mat with each spill and regularly during use, discard at the end of each day.
   4. Disposable or clean equipment for compounding (e.g., mortar, pestles, and spatulas) must be dedicated for use with HDs.
   5. Bulk containers of liquid and API HD must be handled carefully to avoid spills. APIs and powered HDs must be handled in a C-PEC to protect against occupational exposure, especially during particle generating activities (e.g., crushing tablets, opening capsules, or weighing powder).

O. Administering
   1. HDs must be administered safely using protective medical devices and techniques. Examples of protective medical devices include needleless and closed systems. Examples of protective techniques include spiking and priming of IV tubing with a non-HD solution in a C-PEC and crushing tablets in a plastic pouch.
   2. Appropriate PPE must be worn when administering HDs.
   3. CSTDs must be used for administration of antineoplastic HDs when the dosage form allows.
   4. Healthcare personnel should avoid manipulating HDs such as crushing tablets or opening tablets if possible.

Answers to Question #4:

Choice A is incorrect because USP<800> requires use of ~~double gloving~~double gloving for handling activities of HDs beyond compounding such as administration.

Choice B is incorrect because laminate gowns are required for activities beyond administration such as dispensing.

Choice C is correct because USP<800> requires eye and face protection only for specialized procedures that may induced splashing or risk of HDs infiltrating the eyes.

Choice D is incorrect because all PPE must be discarded as hazardous waste following HD handling activities.

P. Deactivating, Decontaminating, Cleaning and Disinfecting

1. All areas where HDs are handled and all reusable equipment and devices must be deactivated, decontaminated, and cleaned. Additionally, sterile compounding areas and devices must be subsequently disinfected.
2. The entity must establish written procedures for decontamination, deactivation, and cleaning, and for sterile compounding areas disinfection. Written procedures for cleaning must include procedures, agents used, dilutions (if used), frequency, and documentation requirements.
3. All personnel who perform deactivation, decontamination, cleaning, and disinfection activities in HD handling areas must be trained in appropriate procedures to protect themselves and the environment from contamination. All personnel performing these activities must wear appropriate PPE.
4. The deactivating, decontaminating, cleaning, and disinfecting agents selected must be appropriate for the type of HD contaminant(s), location, and surface materials. The products used must be compatible with the surface material.

Cleaning Steps:

Cleaning Step	Purpose	Example Agents
Deactivation	Render compound inert or inactive	As listed in the HD labeling or other agents which may incorporate Environmental Protection Agency (EPA)-registered oxidizers (e.g., peroxide formulations, sodium hypochlorite, etc.)
Decontamination	Remove HD residue	Materials that have been validated to be effective for HD decontamination, or through other materials proven to be effective through testing, which may include alcohol, water, peroxide, or sodium hypochlorite
Cleaning	Remove organic and inorganic material	Germicidal detergent
Disinfection	Destroy microorganisms	EPA-registered disinfectant and/or sterile alcohol as appropriate for use

5. Deactivation: Renders a compound inert or inactive. Residue from deactivation must be removed by decontaminating the surface. There is not one proven method for deactivating all compounds. The goal should be complete surface decontamination. Damage to surfaces is exhibited by corrosion to stainless steel surfaces caused by sodium hypochlorite if left untreated.
6. Decontamination: Occurs by inactivating, neutralizing, or physically removing HD residue from non-disposable surfaces and transferring it to absorbent, disposable materials (e.g., wipes, pads, or towels) appropriate to the area being cleaned. It is imperative to adhere to manufacturer's use instructions. The work surface of the C-PEC must be decontaminated between compounding of different HDs. The C-PEC must be decontaminated at least daily (when used), any time a spill occurs, before and after certification, any time voluntary interruption occurs, and if the ventilation tool is moved. C-PECs may have areas under the work tray where contamination can build up. These areas must be deactivated, decontaminated, and cleaned at least monthly to reduce the decontamination level in the C-PEC.
7. Cleaning: Cleaning agents used on compounding equipment should not introduce microbial contamination. No cleaning step may be performed when compounding activities are occurring.
8. Disinfection: Disinfection must be done for areas intended to be sterile, including the sterile compounding areas after adequate cleaning.

Q. Spill Control

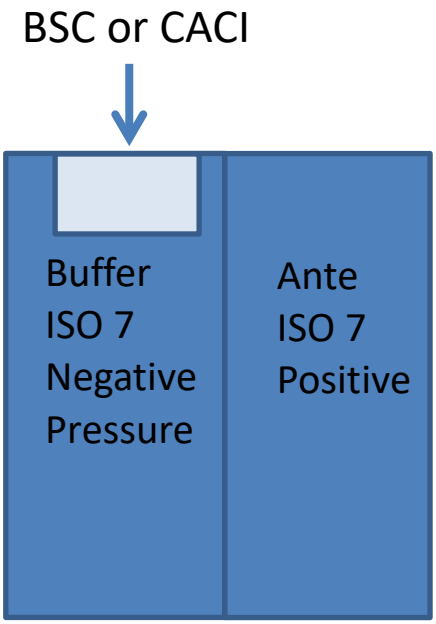
1. All personnel who may be required to clean up a spill of HDs must receive proper training in spill management and the use of PPE and NIOSH-certified respirators (see Personal Protective Equipment). Spills must be:
    a. Contained and cleaned immediately only by qualified personnel with appropriate PPE who are available at all times
    personnel
    b. Appropriate signage for restricting access to the spill area.
    c. Spill kits containing all the materials needed to clean HD spills must be readily available in all areas where HDs are routinely handled.

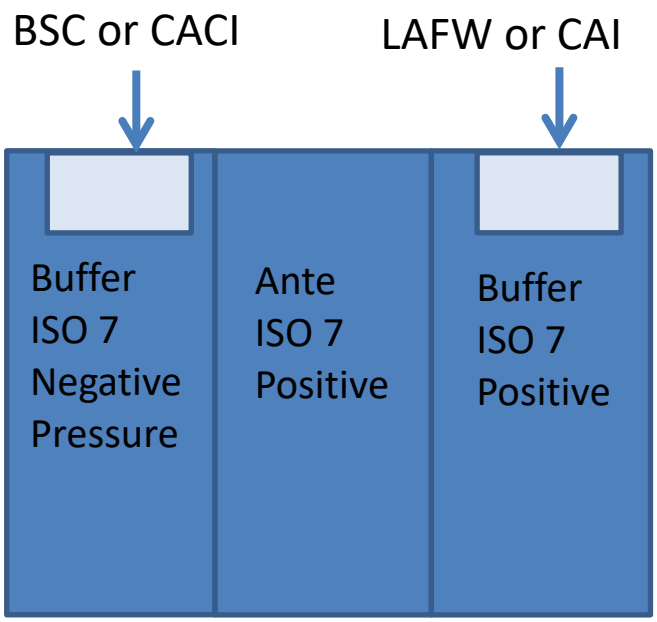
b. All spill materials must be disposed of as hazardous.
    a. The circumstances and management of spills must be documented. Develop SOPs for exposed staff members or patients/visitors for medical evaluation.
    b. SOPs must be developed to prevent spills and to direct the clean-up of HD spills.

R. Documentation and Standard Operating Procedures
1. The entity must maintain SOPs for the safe handling of HDs for all situations in which these HDs are used with review of these SOPs every 12 months.
2. The SOPs for handling of HDs should include:
    a. Hazard communication program
    b. Occupational safety program
    c. Receipt
    d. Storage
    e. Compounding
    f. Maintenance and use of proper engineering controls (e.g., C-PECs, C-SECs, and CSTDs)
    g. Hand hygiene and use of PPE based on activity (e.g., receipt, transport, compounding, administration, spill, and disposal)
    h. Deactivation, decontamination, cleaning, and disinfection
    i. Dispensing
    j. Transport
    k. Administration
    l. Environmental monitoring (e.g., wipe sampling)
    m. Disposal
    n. Spill control
    o. Medical surveillance
3. Document their training according to OSHA standards (see OSHA standard 1910.120 Hazardous Waste Operations and Emergency Response)

S. Medical Surveillance (Recommendations only)
1. Documentation of any exposure of potentially health-related changes due to HD exposure
2. Population health analysis of workers who handle HDs
3. Baseline evaluation of workers health and potential risk to health secondary to HD exposure
4. Plan for HD surveillance embedded in HR policies
5. Follow-up plan

T. Examples of Designs for Hazardous Drug Compounding Areas





II. ASHP Guidelines for Hazardous Drug Handling – updated in 2018

U. Purpose

1. Provide updates regarding new and continuing concerns for health care workers handling hazardous drugs (HDs)
2. Provide information on recommendations and requirements, including those regarding controls and equipment, for handling and compounding HDs.
3. Newer studies demonstrate that contamination is widespread in healthcare settings and that more workers than previously thought are exposed. These recommendations extend to any areas where HDs are received, stored, prepared, administered, or disposed.

V. Background

1. Routes of exposure:
   a. Entry of hazardous drugs through inhalation, accidental injection, ingestion of contaminated food or mouth contact with contaminated hands.
   b. Dermal contact with contaminated surfaces is the primary route of exposure to HDs
2. Hazard Assessment – two components:
   a. Identification – qualitative evaluation of the toxicity of a given drug
   b. Exposure assessment – the amount of worker contact with the drug
   c. NIOSH and USP<800> assessment of risk ~~are~~is supported by ASHP

W. HDs as Sterile Preparations

1. USP<797> outlines sterile product preparation guidelines

2. USP<800> describes containment strategies and engineering controls

X. Recommendations – “must” is used to denote a requirement; “should” indicates a generally acceptable recommendation

1. Safety Program (Specific details for USP<800> standards are outlined in the discussion section for USP<800>)

a. Comprehensive program for managing hazardous drugs must apply to all aspects of use throughout the facility and be a product of collaboration between pharmacy, nursing, medical staff, environmental services, transportation, facilities, employee health, risk management, clinical laboratories, and safety/security.

b. ASHP endorses facilities selecting a designated person to overseeing compliance with USP<800> standards

c. Ready access to Safety Data Sheets (SDS) (formerly Material Safety Data Sheets) for all staff is imperative. SDS sheets define appropriate handling precautions, necessary protective equipment, and spill management for individual drugs.

d. ASHP endorses maintenance of a list of all hazardous chemicals (drugs) in the workplace as part of the written hazard communication program per USP<800>

e. ASHP endorses annual training for employees handling HDs per USP<800> standards

f. Labels for HDs should clearly indicate that safe handling precautions are required during transport, storage, and use.

g. Outside of vials for HDs should be expected to be contaminated – this includes the package inserts and inside of the packing cartons. This impacts any staff member receiving shipping containers and repackaging drug product.

h. Manufacturer packing should be labeled with a distinctive identifier that notifies personnel receiving them to wear appropriate personal protective equipment (PPE) while handling. PPE provides workers protection to reduce exposure to HD aerosols and residues.

i. ASHP endorses the standard operating procedures (SOP) for handling and the return of damaged cartons or containers of HDs and policies and procedures for labeling, packaging, and transport of HDs per USP<800> standards.

2. Labeling, Packaging, Storing and Transport of HDs from Point of Receipt

a. ASHP endorses the USP<800> standards for drug packages, bins, shelves, and storage areas for HDs must bear distinctive labels for identifying special handling precautions.

b. ASHP endorses USP<800> procedures for unpacking HDs listed as antineoplastic HDs on the NIOSH HD list and all HD active pharmaceutical ingredients (APIs) and processing damaged shipping containers.

c. ASHP endorses USP<800> procedures for ensuring availability of spill kits and use of respirators when appropriate.

d. ASHP endorses USP<800> standards for segregation of HD stock from other drug inventory and overall drug storage recommendations. Consider "look-alike, sound-alike" drugs when organizing stock and label accordingly.

e. ASHP endorses uses of PPE as outlined in USP<800> and by NIOSH.

f. Carts and transport devices should be designed with guards to protect against falling and breakage of a HD package.

g. Individuals transporting HDs must have safety training that includes spill control and have spill kits readily available.

3. Environment

a. HDs should be compounded in a controlled area where access is limited to authorized personnel trained in handling requirements.

b. Sterile and non-sterile HDs must be compounded in environments that have a negative pressure relative to all adjacent areas. Nurses who administer HDs and care for patients receiving chemotherapy should meet the requirements of the Oncology Nursing Society (ONS) position statement on administration

c. During administration, access to the administration areas should be limited to patient receiving therapy and essential personnel. Eating, drinking, applying makeup and the presence of food should be avoided while HDs are being administered.

d. For inpatient units, administering HDs should be coordinated to avoid exposure of family members visiting a patient, and arrival of dietary trays.

e. For outpatient infusion clinics, care should be taken to minimize environmental contamination and maximize effectiveness of decontamination procedures.

f. Design of areas where HDs are administered must include surfaces that are readily cleaned and decontaminated – avoid carpeted and upholstered surfaces.

g. Administration of hazardous medications in unique treatment settings such as the operating rooms requires specialized procedures to prevent contamination and provide training to staff. Spill kits, containment bags, and hazardous drug disposal containers must be available in all areas where HDs are handled.

h. Techniques and ancillary devices which minimize the risk of open systems should be used when administering HDs through unusual routes or in nontraditional locations. All staff handling HDs should receive safety training that includes recognition of HDs and appropriate spill response.

4. Ventilation Controls

a. ASHP endorses **ALL** the engineering/ventilation controls for compounding sterile and non-sterile HDs outlined in USP<800>

b. Class II BSCs have limitations wherein contamination with HDs has been shown in HD work areas and in urine of healthcare workers that handle HDs. Studies unequivocally show that HD contamination is present on the outside of vials from the manufacturers of HD drugs, work practices to maximize the effectiveness of the Class II BSC are not rigorously followed, and the potential vaporization of HD can all

place healthcare workers at risk. Class II BSCs do not eliminate contamination within the workspace of the BSC and effectiveness of the cabinet depends on the operator's use of proper technique and strict adherence to policies and procedures.

c. Class II BSC types A2, B1 or B2 are acceptable under USP <800> for compounding sterile HDs. Most Class II BSCs recirculate contaminated air within the cabinet through HEPA filters which may NOT trap all HDs. Specifics on the use of Class II BSCs are listed in Appendix B of the Guidelines.

d. Class III BSC is a totally enclosed, ventilated cabinet of leak-tight construction. The cabinet is maintained under negative pressure with the supply air drawn into the cabinet through HEPA filtration and exhaust air treated with double HEPA filtration. These cabinets are not exhausted through the general exhaust system. This equipment is typically reserved for highly infectious or toxic material and seldom used for extemporaneous compounding of sterile products because of the high cost.

e. CACI is a form of compounding isolator specifically designed for compounding pharmaceutical ingredients or preparations that provides worker protection from exposure to undesirable levels of airborne drug the compounding and material transfer processes and to provide an aseptic environment with unidirectional airflow for compounding sterile preparations. For compounding sterile preparations, the filtered air and airflow must achieve an ISO class 5 environment within the CACI. CACI must be continuously monitored for leaks in the gloves and in the fixed glove assembly. CACIs do not prevent the generation of contamination within the cabinet workspace and their effectiveness in containing contamination depends on proper technique.

f. The totally enclosed design of isolators may reduce the escape of contaminants during the compounding process and be less responsive to environmental drafts. However, isolators do not prevent generation of contamination within the cabinet workspace and there still exists the risk of drug contamination from the main cabinet to the pass-through.

g. Isolators that discharge air into the workroom, even though high-efficiency filters present exposure concerns like those of unvented Class II BSCs with vaporized HDs during compounding. USP<800> requires outside exhausting of CACIs.

5. Containment Supplemental Engineering Controls

a. Closed system drug-transfer device (CSTD) is a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system (NIOSH definition). NIOSH has NOT yet assigned a specific performance standard for CSTDs.

b. CSTDs are designated by the FDA as Class II medical devices, not requiring premarket approval. The FDA 510(k) process does not establish independent performance for devices submitted as "substantially equivalent" nor does it test or approve these devices. FDA created the product code (ONB) for closed antineoplastic and HD reconstitution and transfer system, although applications under this code are not independently tested by the FDA. Products that are

marketed as CSTDs but have not been cleared by FDA under the product code ONB should not be considered CSTDs.

c. Some CSTDs have been shown to limit the potential of generating aerosols and reduce HD contamination in the workplace, not all marketed CSTDs have been studied and no surrogate marker HD has been shown to be superior in measuring CSTD effectiveness.

d. NIOSH is attempting to develop protocols to test containment performance of both the physical and barrier type of CSTD and those designed to operate using air-cleaning technologies.

e. During administration of sterile HD product, no additional safeguards (e.g., ventilated engineering controls) exist for worker protection so USP<800> requires use of CSTDs for administration of HDs when the dosage forms allows whereas for compounding HDs the use of CSTDs is a recommendation.

6. Personnel Protective Equipment (PPE)

a. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE for use in the healthcare setting. USP<800> requires institutions to develop their own SOPs for use of PPE when handling HDs. ASHP endorses USP<800> and NIOSH standards for PPE.

7. Work Practices

a. Compounding Sterile HDs

i. Work practices differ from Class II and III BSCs and isolators

ii. All activities not requiring a critical environment (e.g., checking labels, dose calculations) should be done outside the BSC/isolator.

iii. Two pair of ASTM D6978 gloves must be worn to gather HDs and supplies.

iv. Fresh ASTM D6878 gloves should be donned and appropriately sanitized before aseptic manipulation. The outer pair of gloves must be sterile for sterile HD compounding.

v. Only supplies and drugs essential to compounding the dose or batch should be placed in the work area of the BSC or main chamber of the isolator.

vi. Spiking an IV set containing HDs or priming an IV set with HDs in an uncontrolled environment must be avoided. Priming the IV set with the diluent prior to adding the HD inside the C-PEC is an acceptable practice.

vii. CSTDs should be used if the dosage form allows when compounding sterile HDs. CSTD should achieve a dry connection between the administration set and the HD's final container. This connection allows for the container to be spiked with a secondary IV set and the set to be primed with backflow from a primary non-hazardous solution. This may be done outside of a BSC or isolator to reduce the potential for surface contamination. A new IV set must be used with each dose of HD.

viii. Avoid placing the IV set on the surface of the C-PEC during compounding to reduce the transfer of HD residue to the surface of the IV set.

ix. Transport bags must never be placed in the BSC or isolator work chamber to avoid inadvertent contamination on the outer surface of the bag.

x. Final preparations must be surface decontaminated after compounding is complete.

xi. In either a BSC or isolator, clean inner gloves must be worn when labeling and placing the final preparation into the transport bag.

xii. Handling final preparations with contaminated gloves transfers contamination to other workers or potentially patients. Don fresh gloves whenever there is doubt as to the cleanliness of the inner or outer gloves.

8. Working in any C-PEC

a. None of the ventilated engineering controls can provide 100% protection for the worker. The effectiveness of C-PECs in containing HD contamination depends on worker technique.

b. HD residue may be introduced into the workroom area via pass-throughs and airlocks.

c. Surface decontamination of the preparation before removal from the main chamber of an isolator is recommended with isopropyl alcohol, sterile water, peroxide, or sodium hypochlorite solutions provided that the packaging is not permeable to the solution and the labels remain intact.

d. In depth recommendations for working in C-PECs are listed in Appendix F of the original publication.

9. BSCs

a. Before working in the BSC, wash hands and don PPE per USP<797> recommendations

b. Non-sterile D6978 gloves are appropriate for cleaning activities

c. BSCs use vertical flow, HEPA-filtered air (ISO class 5) as their controlled aseptic environment.

d. The front shield of the cabinet should be lowered to the proper level to protect the face and eyes.

e. All drugs and supplies should be sanitized with 70% sterile alcohol.

f. All items should be placed away from the front of the unfiltered air at the front of the cabinet and perform manipulations at least 6 inches away from the sidewalls of the cabinet.

g. Do not obstruct airflow through the front and back grilles of the BSC.

h. A small waste-sharps container may be placed along the sidewall towards the back of the BSC.

i. A plastic-backed absorbent preparation pad should be placed on the work surface of the BSC. Avoid larger pads that could obstruct airflow from the front and back grilles of the BSC. Change the mat after any spills.

j. Equipment for HD compounding must be dedicated.

10. Class III BSCs and CACIs

    a. ASTM D6978 gloves should be worn to prepare for working in a Class III BSC or CACI. For sterile compounding, the gloves closest to the sterile preparation must be sterile.

    b. All drugs and supplies should be sanitized with 70% sterile alcohol.

    c. An enclosed tray with drug and supplies may be introduced into the main chamber for compounding use.

    d. Contaminated materials are removed using the closed trash system of the unit.

    e. A second sealable bag should be used for transport of the compounded product.

    f. Additional work practices for cleaning off the gloves or gauntlets and final preparation are recommended.

11. Aseptic Technique

    a. When reconstituting HDs in vials, it is critical to avoid pressurizing contents of the vial which increases risk of drug aerosolization. Too much negative pressure can cause leakage from the needle when it is withdrawn from the vial.

    b. Safe handling of HD solutions and vials or ampules requires the use of a syringe that is no more than 3/4 full when filled with the solution, to minimize the risk of plunger separating from the syringe barrel.

    c. HDs removed from an ampule should use an appropriate filter needle or filter straw attached to a syringe large enough that it will not be more than 3/4 full.

    d. Small volumes of diluent should be transferred slowly into the HD vial as equal volumes of air are removed.

    e. The final preparation should be labeled, including an auxiliary warning and the injection port covered with a protective shield.

    f. The final container should be placed, using clean gloves, into a sealable bag to contain any leakage.

12. Training and demonstration of competence

    a. OSHA and USP<800> require that all staff that will handle HDs require training.

    b. Compounding personnel of reproductive capability must confirm in writing that they understand the risks of handling HDs.

    c. Personnel must be trained PRIOR to handling HDs as part of their job responsibilities.

    d. Competency must be demonstrated by an objective method and assessed every 12 months.

13. Preparation and handling of non-sterile HD dosage forms

    a. Non-sterile compounding of HD dosage forms must adhere to USP<795> and <800>

b. USP<800> requires that compounding of non-sterile HDs take place in a C-PEC. A Class I BSC, CVE, Class II BSC or CACI may be used for this task. For occasional compounding of non-sterile ~~HDs~~HDs, a C-PEC used for sterile compounding can be utilized but must be decontaminated, cleaned and disinfected before resuming sterile compounding. A plastic-backed preparation mat should be placed on the work surface of the C-PEC. or CVE is acceptable for that task

c. A C-PEC is not required if manipulations are limited to handling of final dosage forms. (~~counting~~Counting or repackaging of tablets or capsules).

d. Dedicated clean ~~equipment should~~equipment should be used for compounding non-sterile HDs.

e. Manual counting of solid medications may be problematic if, for example, repeated handling of a large container of tablets has created a loose powder or residue of tablet dust. Exposure to the dust or residue may present a risk of powder inhalation or skin contact. USP <800> notes that an assessment of risk should be conducted to determine the appropriate containment strategies for the HD tasks required of the worker.

f. Procedures for the preparation and use of equipment (e.g., BSCs, bench-top hoods with HEPA filters) must be developed to avoid release of aerosolized powder or liquid into the environment during manipulation of hazardous drugs. Recommendations for preparation and handling of non-sterile HD dosage forms are listed in Appendix G of the document.

14. Decontamination, deactivation, and cleaning

a. ASHP endorses the USP<800> standards for decontamination, deactivation, cleaning, and disinfection. Decontamination occurs by inactivating, neutralizing, or physically removing HD residue from non-disposable surfaces (e.g., stainless steel C-PECs) and transferring it to absorbent, disposable materials (e.g., wipes, pads, towels) appropriate to the area being cleaned. The decontaminating, deactivating, cleaning, and disinfecting agents selected must be appropriate for the type of HD contaminant(s), location, and surfaces to be cleaned. Consult manufacturer or supplier information for compatibility with cleaning agents used. Agents used for decontamination, deactivation, and cleaning should be applied using wipes wetted with appropriate solution and not delivered as a spray to avoid aerosolizing and/or spreading HD residue.

b. The area under the work tray of the BSC should be cleaned at least monthly to reduce contamination levels.

c. The selection and use of disinfectants in healthcare facilities is guided by several properties, such as microbicidal activity, inactivation by organic matter, residue, and shelf life.

15. Administration of HDs

a. Contamination of infusion areas where HDs are administered document significant surface contamination with HDs.

b. Extensive guidelines for HD administration have been published by OSHA and the Oncology Nursing Society (ONS).

16. Spill management

a. ASHP endorses the USP<800> standards for spill management.

17. Worker contamination

a. Procedures must be in place to address worker contamination, and protocols for medical attention must be developed before the occurrence of any such incident. OSHA requires suitable facilities for quick drenching or flushing of the eyes and body where workers may be exposed to injurious corrosive materials.

b. Isotonic eyewash supplies and soap ~~should must~~must be readily available in areas where HDs are handled.

d. Workers who have skin or eye contamination with HDs require immediate medical attention. Covered below in section on disposing of HD waste/RCRA standards

18. Medical Screening and Surveillance; Alternative Duty

a. Medical screening and surveillance should be part of the comprehensive safety program for controlling workplace exposure to HDs, which must include engineering controls, training, work practices, and PPE.

b. Because reproductive risks have been associated with exposure to HDs, alternative duty (work assignments that do not involve handling HDs) should be offered to individuals who are pregnant, breast-feeding, or attempting to conceive or father a child.

c. Medical surveillance involves the collection and interpretation of data for the purpose of detecting changes in the health status of working populations. Medical surveillance programs involve assessment and documentation of symptom complaints, physical findings, and laboratory values (such as a blood count) to determine whether there is a deviation from the expected norms.

19. Robotics

a. There are currently several robots and automated devices that are marketed for sterile HDs and manufacturers should provide evidence-based data to support the use of any of these devices in compounding sterile HD doses to provide patient safety and worker safety. There may also be legal requirements when using these devices in a pharmacy licensed through a state board of pharmacy, and these devices must also meet provisions of USP Chapter 797 when used for sterile compounding.

b. Limited studies have been published examining the ability for robotics to reduce HD surface contamination during sterile compounding or to impact the safety of healthcare workers interacting with the robot during HD compounding.

20. Environmental Sampling for HDs

a. Surface wipe sampling should be done routinely, first to determine a benchmark of contamination and then at least every 6 months to monitor the effectiveness of safe handling programs. As no acceptable levels of HD surface contamination have been determined by any regulatory agency, surface wipe sampling should

determine an operational baseline of at least several marker HDs from which a facility action level may be determined.

b. Surface wipe sampling provides a way to determine the efficacy of HD handling equipment, ancillary devices, work practices, cleaning methods, and disposal, and is currently the method of choice to determine surface contamination of the workplace with these drugs.

c. No regulations or standards exist for allowable or acceptable HD surface concentrations in healthcare settings and many questions remain about the potential health risks associated with exposure to existing levels of environmental surface contamination. However, prudent practice dictates that levels of HD surface contamination should be reduced to as low as reasonably achievable.

III. USP<797> Revised Chapter published on November 1, 2022.[3]

A. Scope: Minimum standards for preparing compounded sterile products (CSPs) for humans and animals. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging or otherwise altering a drug or bulk drug substance to create a sterile medication. Requirements in the chapter aim to minimize harm/death from microbial contamination (non-sterility), excessive bacterial endotoxins, variability from the intended strength of correct ingredients, physical and chemical incompatibilities, chemical and physical contaminants and/or use of ingredients of inappropriate quality. Aseptic technique must be used when preparing CSPs and procedures must be in place to minimize contact with nonsterile surfaces, minimize introduction of particulate matter or biologic fluids and/or mix-ups with other products or CSPs.

B. Updated Beyond Using Dating Criteria:

Risk Category	Revised USP<797> Criteria for Beyond Use Dating (BUD)
Category 1	≤12 hours at room temperature ≤24 hours refrigerated
Category 2	Aseptically processed, no sterility testing, only sterile starting components: • 4 days at room temperature • 10 days refrigerated • 45 days in the freezer Aseptically processed, no sterility testing, one or more nonsterile starting components: • 1 day at room temperature • 4 days refrigerated • 45 days in the freezer Aseptically processed, passed sterility testing: • 30 days at room temperature • 45 days refrigerated

	• 60 days in the freezer Terminally sterilized, no sterility testing: • 14 days at room temperature • 28 days refrigerated • 45 days in the freezer Terminally sterilized, passed sterility testing • 45 days at room temperature • 60 days refrigerated • 90 days in the freezer
Category 3	Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs: • 60 days at room temperature • 90 days refrigerated • 120 days in the freezer Terminally sterilized, passed sterility tested, and passing all applicable tests for Category 3 CSPs: • 90 days at room temperature • 120 days refrigerated • 180 days in the freezer

Question #5:

The ASCO standards for safe handling of hazardous drugs call for more research to inform a recommended practice standard in which of the following areas?

a. The need for negative pressure rooms when compounding hazardous drugs

b. Use of ~~double gloving~~double gloving with outer sterile gloves when compounding sterile hazardous drug products

c. Generation of an institutional hazardous drug list

d. Use of closed-system transfer devices

IV. Safe Handling of Hazardous Drugs: ASCO standards[6] - Goal was to determine was constituted best evidence for safe handling of hazardous drugs and extensive review of the literature was conducted yielding five standards

- Standard #1: Endorsement of existing standards – endorsement of existing standards for safe handling of hazardous drugs issued by OSHA, UPS<800>, NIOSH 2004 Alert and ONS
- Standard #2: Medical Surveillance – workplace occupational health programs should include policies and procedures demonstrated to effectively monitor HD contamination in the health care setting and to monitor individuals who have been involved in an acute exposure (e.g., spill).

The role of routine monitoring programs for surveillance including medical screening, laboratory screening or other biologic monitoring is unclear.

- There are currently no data from well-designed programs to inform whether screening and monitoring within medical surveillance programs increases or decreases benefits or harms related to health outcomes for workers who handle HDs. In addition, there is a lack of valid tests or techniques for detecting early signs of disease, no established levels of exposure that have been linked to adverse health effects, and other limitations that are outlined in the main text of this document.
- As an alternative to routine ongoing medical surveillance programs, this ASCO standard endorses larger-scale data collection in the context of a registry of health care workers. This standard also endorses the collection of data to test research hypotheses, provided that the necessary sample size to detect significant differences can reasonably be achieved, that peer-reviewed publication plans are determined a priori, and that approval has been given by a research ethics board. Gathering data with the purpose of examining it periodically for a small alteration is not recommended.
- Workers should be encouraged to report occupational health issues to employee health services at the time that they are experienced.
- The Expert Panel will continue to monitor the literature for robust studies of the link between biologic markers and health outcomes and for studies that assess the outcomes of medical screening and biologic monitoring programs that may already be in place within specific institutions.

- Standard #3: CSTD – to inform a standard on this topic, a standardized testing protocol is needed for CSTDs. In addition, there is a need for a process to identify and certify effective CSTDs.
    - Within a recent systematic review, the quality of the published literature on CSTDs was rated as low quality and at high risk of bias using the GRADE methodology. After implementation of CSTDs, some studies have noted a decrease in the percentage of surface sampling wipes that have detectable levels of antineoplastic drugs and/or a decrease in the percentage of workers who have detectable levels of antineoplastic drugs in their urine. There are no short- or long-term data to inform whether specific CSTDs have an impact on health outcomes.
    - NIOSH recommends using CSTDs when transferring HDs from primary packaging to infusion bags, bottles, or pumps. USP <800> requires use of CSTDs for nursing administration of hazardous drugs and recommends use for sterile product compounding of hazardous drugs.
    - Currently, there is no standardized testing protocol to assess the performance of available CSTDs. NIOSH is in the process of developing an independent vapor containment performance protocol for CSTDs in healthcare settings. These ASCO standards will be revised to incorporate the NIOSH CSTD testing protocol when it becomes available.
    - ASCO encourages NIOSH to develop a certification process so that practices can identify effective CSTDs.

- Standard #4: External ventilation of C-SECs and C-SCAs may be viewed as suite of protective measures that are designed to reduce the likelihood of exposure. Institutions should assess current engineering controls and may choose to incorporate external ventilation where it has not already been implemented
    - Although there is no long-term clinical evidence to inform a standard, engineering controls such as barriers, enclosures, negative pressure, contaminant capture, and elimination (e.g., use of external venting) are protective measures that may be used to potentially reduce health care workers' risk of exposure to HDs. None of these controls are expected to eliminate the risk of exposure to workers as standalone measures.
    - External ventilation of C-SECs or C-SCAs is required by USP 800.
    - Preparing HDs off site and consolidating preparation activities in an externally ventilated location are alternative options that may be considered where external ventilation is not possible within existing facilities because of structural or other constraints.
    - More research is needed on the optimal environment for workers who handle HDs.
- Standard #5: Alternative duty: The health care setting has a policy that identifies potential alternative work options, where possible, for workers who are actively trying to conceive, are pregnant, or are breastfeeding. Health care workers are given information at the time of hire regarding the capacity of the organization to reassign to alternative duty. Reviewing the options for alternative work, where available, should be the shared responsibility of the employee and employer.

V. Joint Position Statement from the ONS and the Hematology/Oncology Pharmacy Association (HOPA) Ensuring Healthcare Worker Safety When Handling Hazardous Drugs[7]

- Settings in which HDs are present will establish evidence-based policies and procedures for safe handling that comply with regulatory requirements and standards.
- Settings in which HDs are present will ensure that PPE indicated for handling HDs is available to all staff to minimize exposure.
- Settings in which antineoplastic HDs are prepared and administered will provide and maintain primary engineering controls, such as biologic safety cabinets and compounding aseptic containment isolators, in conjunction with secondary engineering controls, such as buffer rooms or segregated compounding areas, consistent with USP chapters.
- Settings in which antineoplastic HDs are administered will ensure the use of supplemental engineering controls at the point of compounding and administration when the dosage form allows
- Settings in which HDs are present will provide education and training specific to each staff member whose work puts them at risk for exposure to HDs. Education, training, and competency evaluation will include the risks of exposure, including the reproductive and developmental effects, the recommended precautions for specific handling activities, safe handling of contaminated patient excreta, proper disposal of contaminated waste, and how to handle acute exposure.
- Settings in which HDs are present will protect the rights of staff who are trying to conceive, who are pregnant, or who are breast feeding to engage in alternative duty that does not require HD handling.
- Settings in which HDs are present will ensure that patients who receive these drugs and their caregivers receive education about safe handling to minimize unintended exposure in both the institutional and home setting.
- Settings in which HDs are present will ensure that HD waste is disposed of according to regulatory guidelines and in a manner that protects staff and the environment.
- Settings in which HDs are present should engage in medical surveillance of staff.
- Settings in which HDs are present should conduct surface wipe testing as a measure of exposure control to aid in the continuous process improvement for handling HDs.
- Our professional societies support and encourage continued research and the generation of new knowledge about the risks of HD exposure and the efficacy of risk-reduction strategies.
- Our professional societies will continue to explore evidence-based strategies for mitigation of risk associated with handling HDs and share recommendations with our respective members.
- Our professional societies support and encourage compliance with all NIOSH recommendations, USP compounding standards, and regulatory requirements.
- Our professional societies support and encourage advocacy efforts to make recommendations and standards into enforceable laws that best protect staff and the environment.

Comparison of the Major Safe Handling Statements

Parameter	USP<800>	ASHP	ASCO	HOPA/ONS
Definition of HD	√	√		
HD List Generation	√	√		
Chain of Custody for HDs	√	√		√
Exposure Risks for HDs	√	√		
Staff Responsibilities for Handling HDs	√	√		√
Engineering Controls	√	√	+/-	
PPE	√	√		
Training for Staff	√	√		√
Compounding	√	√		√
Administration	√	√		√
CSTDs	√	√	+/-	√
Wipe Studies	√	√		√
Cleaning Procedures	√	√		
Spills	√	√		
Documentation Procedures	√	√		√
Medical Surveillance	√	√	+/-	
Pharmacy Work Practices		√		√
Pregnant/Attempting to Conceive Staff			+/-	√
Future Research			√	√
Codify Existing Regulations into Law				

Answers to Question #5:

Choice D is correct because ASCO states in the guidelines that a certified standard is needed to gauge the effectiveness of the commercially available CSTDs.

Choice A is incorrect because negative pressurization is required by USP<800> and ASCO states that in their guidelines that unless otherwise stated that they endorse the USP<800> standards.

Choice B is incorrect because double-gloving when handling HDs is required by USP<800> and ASCO states that in their guidelines that unless otherwise stated that they endorse the USP<800> standards.

Choice C is incorrect because creation of an institutional HDs list is required by USP<800> and ASCO states that in their guidelines that unless otherwise stated that they endorse the USP<800> standards.

Question #6:

Which of the following FDA-approved agents can now be discarded as non-hazardous waste because of the Hazardous Waste Pharmaceuticals amendment to RCRA?

a. Warfarin

b. Cyclophosphamide

c. Nicotine patches

d. Melphalan

VI. Hazardous Waste

A. Hazardous Waste Containment and Disposal[3,4]

1. Resource Conservation and Recovery Act (1976):

a. EPA had established guidance for management of hazardous waste (HW) under the Resource Conservation and Recovery Act (RCRA). However, until 2019 there were no regulations under RCRA Subtitle C regulations that govern HW from hospitals, pharmacies, reverse distributors, and other healthcare-related facilities.

b. A new proposal which creates Subpart P under 40 CFR part 266 will provide tailored, sector-specific regulatory framework for managing HW – these new regulations will replace the current regulations in RCRA Subtitle C which were not drafted specifically with managing HDs generated at healthcare facilities. Health care facilities are left to interpret compliance standards that were written for other industries that generate HW. The "generator" requirements in Subtitle C for transporting, storing, treating, and disposing of HW are typically what health care facilities adhere to. RCRA divides HW into three categories – Small Quantity Generators (SQG), Large Quantity Generators (LQG), and Conditionally Exempt Small Quantity Generators (CESQGs) depending on the total amount of monthly HW production.

RCRA Definitions:

Characteristic Waste: Waste that is **ignitable, corrosive, reactive, or toxic**. Some pharmaceuticals are prepared in alcohol bases which may result in their classification as hazardous.

LQG: Facilities that generate 1,000 kg or more of HW or more than 1 kg of acute HW (e.g., P-listed waste), or more than 100 kg of any residue or contaminated soil, waste or other debris resulting from the clean-up of a spill, into or on any land or water of any acute HW.

SQG: Facilities that generate more than 100 kg but less than 1000 kg of HW.

CESQG Facilities that generate less than or equal to 100 kg of HW and less than or equal to 1 kg of acutely HW (i.e., P-listed) and less than or equal to 100 kg of any residue or contaminated soil, waste or other debris resulting from the clean-up of a spill, into or on any land or water of any acute HW.

P-listed waste: Commercial chemical products that are categorized as acutely hazardous under RCRA. One of the primary criteria for including a drug on the P-list as acutely hazardous is an oral lethal dose of 50 mg/kg (LD50) or less. LD50 is the amount of a material, given all at once which causes the death of 50% of a group of test animals.

U-listed waste: Agents are listed primarily for their toxicity. Similar to P-listed waste, when a drug waste containing one of these chemicals is discarded, it must be managed as HW if two conditions are satisfied:

1. The discarded drug waste contains a sole active ingredient that appears on the U list.
2. It has not been used for its intended purpose.

As with P-listed waste, there is no concentration limit or dilution exclusion for U-listed waste.

Empty Containers of U-Listed Wastes: Considered "RCRA empty" if:

1. All the contents have been removed that can be removed using normal means, such as drawing liquid out with a syringe
2. No more than 3% by weight remains

*If both criteria are not met, the container must be managed as HW. Any residues removed from the empty container must be managed as HW

General Categories of Hazardous Waste:

Examples of P-listed Waste	Examples of U-listed Waste
Arsenic trioxide	Azaserine
Epinephrine	Chloral Hydrate
Nicotine	Chlorambucil
Nitroglycerin	Chloroform
Phentermine	Cyclophosphamide
Physostigmine salicylate	Daunomycin
Physostigmine	Dichlorodifluoromethane
Warfarin (greater than 0.3%)	Diethylstilbestrol
	Formaldehyde
	Hexachlorophene
	Lindane
	Melphalan
	Mercury
	Mitomycin C
	Paraldehyde
	Phenacetin
	Phenol
	Reserpine
	Resorcinol
	Selenium sulfide
	Streptozocin
	Trichloromonofluoromethane
	Uracil mustard
	Warfarin (≤0.3%)

c. Trace-contaminated HD waste may include “RCRA-empty” containers, needles, syringes, trace-contaminated gowns, gloves, pads and empty IV sets which may be incinerated at regulated medical waste incinerator.

2. Bulk HW

a. Differentiates containers that held either (1) RCRA-listed or characteristic HW or (2) any HDs that are not RCRA empty or any materials from HD spill cleanups.

b. These wastes should be managed as hazardous.

3. HDs not listed as HW

a. RCRA regulations have not kept up with drug development and consequently there are over 100 HDs that are not listed as HW.

b. Regulations may vary by state – for example, Minnesota listed hormonal agents as HW.

4. HW and mixed infectious-hazardous waste

a. Most HW vendors cannot manage regulated medical waste or infectious waste; therefore, they cannot accept used needles or other items contaminated with blood. Hazardous waste must not be combined with needles or blood. For example, yellow bucket (trace chemo), red bucket (Blood), and black bucket (HD waste >3%)

b. Properly labeled, leak proof, and spill-proof containers of non-reactive plastic are required for areas where HW is generated.

c. HDs may be in thick, sealable, plastic bags before being placed in approved satellite accumulation containers.

d. Waste contaminated with blood or other body fluids should not be mixed with HW.

e. Transport of HW containers from satellite accumulation to storage sites must be done by individuals who have completed OSHA mandated HW awareness training.

f. More information on hazardous waste disposal may be found at www.hercenter.org

B. **Amendment to RCRA**: Hazardous Waste Pharmaceuticals and Amendment to Nicotine Listing (P075) Final Rule – April 2019 – published in Federal Register February 22, 2019

1. Goals:
   a. Creates regulation to better fit healthcare sector for management of HW
   b. Eliminate intentional sewering of HW pharmaceuticals
   c. Provide regulatory clarity and national consistency on how RCRA applies to reverse distribution and reverse logistics
   d. Reevaluate whether nicotine replacement therapies should be regulated as acute HW
2. Nicotine replacement therapies that are FDA-approved for over-the-counter use will no longer be included in the P075 listing for HDs

a. Nicotine patches, gums, and lozenges can be discarded as non-HW
b. Nicotine continues to be listed as acute HW – this includes e-liquids in e-cigarettes/cartridges, prescription nicotine, nicotine in pesticides, nicotine used in research facilities

3. Reverse logistics/distribution – logistics centers that evaluate unsold retail items including nonprescription pharmaceuticals, analyze secondary markets and assess the suitability of the unsold retail items for reuse in those secondary markets
   a. Final rule reaffirms EPA's long-standing policy that **nonprescription** pharmaceuticals (e.g., OTCs) that are sent through reverse logistics are not wastes at the healthcare or retail facility if they have a reasonable expectation of being lawfully reused for their intended purpose.

Reverse distribution for prescription pharmaceuticals moving through reverse distributors are considered wastes at the healthcare facility

Reverse Distribution	Reverse Logistics
Rx Pharmaceuticals	Non-Rx pharmaceuticals • E.g., OTCs, dietary supplements All other unsold retail items
No redistribution occurs	Redistribution sometimes occurs via: • Donation • Liquidation (secondary market)
Rx pharmaceuticals sent to reverse distributors are solid wastes at the healthcare facility	Non-Rx pharmaceuticals and other unsold retail items sent to reverse logistics <u>are not solid wastes</u> IF there is a reasonable expectation of legitimate use/reuse or reclamation
In Part 266 Subpart P, which is • Effective in non-authorized states August 21, 2019 • Effective in authorized states when states adopt Subpart P	Newly codified in Part 266 Subpart P. Affirms existing policy • Effective immediately federally • Check with your state

4. Revised definitions:

s – Includes, but not limited to:

- Dietary supplements
- Prescription drugs
- OTC drugs
- Homeopathic drugs
- Compounded drugs
- Investigational new drugs
- Pharmaceuticals remaining in non-empty containers
- PPE contaminated with pharmaceuticals
- Electronic nicotine delivery systems (e.g., e-cigarettes, vaping pens)
- Does NOT include dental amalgam, sharps, medical waste

Types of Hazardous Waste Pharmaceuticals

- Non-creditable HW pharmaceutical – broken, leaking, repackaged, dispensed, expired (>1 year), investigational new drug, contaminated PPE, floor sweepings, clean-up material
- Potentially creditable HW pharmaceutical – original manufacturer packaging (except recalls), undispensed, unexpired or less than 1-year past expiration

- Evaluated HW pharmaceutical – no further evaluation or verification of manufacturer credit is necessary

Healthcare facility

- Wholesale distributors
- Third-party logistics providers
- Military medical logistics facilities
- Hospitals/psychiatric hospitals
- Ambulatory surgical centers, health clinics, physician offices
- Optical and dental providers
- Chiropractors
- Long-term care facilities
- Ambulance services
- Pharmacies, long-term care pharmacies, mail-order pharmacies, retailers of pharmaceuticals (includes vape shops), veterinary clinics and hospitals

5. Scope/Application
    a. No generator categories under Part 266 Subpart P
    b. All healthcare facilities are regulated the same for their HW pharmaceuticals
    c. All reverse distributors are regulated the same for their HW pharmaceuticals
    d. Healthcare facilities and reverse distributors do not have to keep track of how much HW pharmaceuticals they generate per month or segregate the acute and non-acute HW pharmaceuticals
6. Not subject to RCRA regulation:
    a. Pharmaceuticals that are not solid wastes because they are legitimately reused or reclaimed
    b. OTC pharmaceuticals, dietary supplements or homeopathic drugs that are not solid waste because they have a reasonable expectation of being legitimately used/reused or reclaimed
    c. Recalled pharmaceuticals
    d. Pharmaceuticals under preservation order, or during an investigation or judicial proceeding
    e. Investigational new drugs
    f. Household waste pharmaceuticals
7. Healthcare facility management standards
    a. Accumulation containers must be labeled with the words “Hazardous Waste Pharmaceutical”
    b. No HW codes or other labeling requirements
    c. Containers must be structurally sound, nor react with contents and remain closed and secured in a manner that prevents unauthorized access to contents – accumulation time limit – 1 year
    d. No labeling, container standards or accumulation time for potentially creditable HW pharmaceuticals
8. Sewer prohibition
    - HW pharmaceuticals may not be sewered (e.g., no disposal down the drain and no flushing)
    - Sewer prohibition applies to:

- All healthcare facilities, including VSQG
- All reverse distributors
- Hazardous wastes that are DEA controlled substances are also subject to the sewer prohibition
- EPA discourages sewering of ANY pharmaceuticals by any entity

9. Take back of controlled substances
    a. Applies to RCRA hazardous wastes that are also DEA controlled substances
    b. Retail pharmacies and hospitals can amend DEA registration to become "collectors" of household pharmaceuticals – kiosks for collection may be installed at the facilities
    c. Pharmaceuticals must be destroyed after being collected
    d. Agents include chloral hydrate, fentanyl sublingual spray, phenobarbital, testosterone, diazepam

Answers to Question #6:

Choice C is correct because the Hazardous Waste Pharmaceutical amendment to RCRA allows for FDA-approved nicotine replacement therapies such as patches and gum to be discarded as non-hazardous waste.

Choice A is incorrect because warfarin is still listed as a U-listed hazardous waste drug per RCRA.

Choice B is incorrect because cyclophosphamide is still listed as a U-listed hazardous waste drug per RCRA.

Choice D is incorrect because melphalan is still listed as a U-listed hazardous waste drug per RCRA.

VII. NIOSH: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in the Health Care Settings[8]

A. NIOSH Warning: Working with or near HDs in health care settings may cause skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancers.
B. Adherence to guidelines for handling HDs is sporadic and measurable concentrations of some HDs have been found in the urine of health care workers.
C. Potential for Worker Exposure
    1. Exposure may occur from manufacture to transport/distribution to use in health care
    2. The number of workers exposed to HDs in the US is approximately 5.5 million. These include shipping and receiving personnel, pharmacists, pharmacy technicians, nursing personnel, physicians, operating room personnel, environmental services personnel, and workers in veterinary practices.
D. Conditions for Exposure – recommendations have been incorporated into USP<800>
E. Exposure Routes
    1. Exposure to HDs may occur through inhalation, skin contact, skin absorption, ingestion, or injection.
    2. Detectable concentrations of HDs have been found on BSCs, floors, counter tops, storage areas, tables and chairs in patient treatment areas, and locations adjacent to drug-handling areas.
F. Evidence for Worker Exposure
    1. Evidence indicates that workers are being exposed to HDs and are experiencing serious health consequences despite current work practice guidelines.
    2. Factors that affect worker exposure include:
        - Drug handling circumstances (preparation, administration, or disposal)
        - Amount of drug prepared

- Frequency and duration of drug handling
- Potential for absorption
- Use of ventilated cabinets
- PPE
- Work practices

3. CSTD usage for 6 months reduced both the concentration of cyclophosphamide and ifosfamide in the urine of exposed health care workers and the percentage of samples containing these drugs.

G. Evidence for Health Effects in Workers

1. Mutagenicity - Multiple ~~studies document~~studies documents that antineoplastic drugs may cause increased genotoxic effects in pharmacists and nurses exposed in the workplace.
2. Developmental and Reproductive Effects - Antineoplastic drugs have reproductive effects such as increased fetal loss, congenital malformations, low birth weight, congenital abnormalities, and infertility.
3. Cancers - An increased risk of leukemia has been reported in oncology nurses from a Danish cancer registry from 1943-87.

VIII. NIOSH List of Antineoplastic and Other HDs in Healthcare Settings, 2016[9]

G. History – First NIOSH Alert (Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings) originally published in September 2004 (http://cdc.gov/niosh/docs/2004-165/). Appendix A listed a sample list of major HDs, which was updated in 2010, 2012, 2014 and ~~2016..~~2016. See below regarding the proposed updated from NIOSH in 2020, which has not yet been finalized.

H. Current Format for Listing of HDs per NIOSH as of 2016.

1. Group 1: Antineoplastic drugs (AHFS classification 10:00) – Many of these drugs pose a reproductive risk for susceptible populations.
2. Group 2: Non-antineoplastic drugs that meet one or more of the NIOSH criteria for a HD. Some of these drugs may pose reproductive risks for susceptible populations.
3. Group 3: Drugs that primarily pose a reproductive risk to men and women who are actively trying to conceive and women who are pregnant or breast feeding, because some of the drugs may be present in breast milk.

I. Listing of the individual drugs is found within the publication with Tables for Groups 1, 2, and 3 noted above

J. NIOSH has published a **draft** of the NIOSH List of Hazardous Drugs in Healthcare Settings, 2020. (https://www.cdc.gov/niosh/topics/hazdrug/default.html) – Comments were accepted through June 30, 2020. The finalized document will be published on the NIOSH website.

Drugs in the proposed/revised Table 1 meet the following classification criteria:

- **Drugs which contain manufacturer special handling information (MSHI), and/or**
- **Drugs which meet NIOSH definition of a hazardous drug and are classified by National Toxicology Program (NTP) as "known to be human carcinogen" and/or/ classified by International Agency for Research in Cancer (IARC) as "carcinogenic" or "probably carcinogenic"**
- **Many of these drugs are cytotoxic and the majority are hazardous to males or females who are actively trying to conceive, women who are pregnant or may become pregnant and women who are breast feeding because the drugs are excreted in breast milk.**
- **Not all drugs in Table 1 are antineoplastic**
- **Drugs reviewed for this update were new drug approvals or received safety related new warnings from FDA in the period between Jan 2014 and Dec 2015.**
- **New drugs were added in 2020 were specified in red in the table published on the NIOSH website**

• **This table provides information for each drug on AHFS classification, whether MSHI guidance is available and supplemental information specific to each drug**
<u>Drugs in the proposed/revised Table 2 meet the following classification criteria</u>: • **The drugs in Table 2 meet the NIOSH definition of a hazardous drug but are not drugs which have MSHI and are not classified by the NTP as "known to be a human carcinogen" and/or classified by the IARC as "carcinogenic" or "probably carcinogenic"** • **These drugs exhibit one or more of the types of toxicity described in the NIOSH definition of a hazardous drug** • **Some of these drugs may present an occupational hazard to males or females who are actively trying to conceive, women who are pregnant or may become pregnant and women who are breast feeding because they may present in breast milk** • **Drugs reviewed for this update were new drug approvals or received safety related new warnings from FDA in the period between Jan 2014 and Dec 2015.** • **New drugs were added in 2020 were specified in red in the table published on the NIOSH website** • **This table provides information for each drug on AHFS classification and supplemental information specific to each drug generally focusing on what specific NIOSH criteria was used to classify the agent as hazardous**

***Changes from the 2016 list are annotated in a third table**

Other Regulatory Agencies of Interest to Oncology Practitioners
Regulatory Agencies:

Agency	Role
Food and Drug Administration (FDA)[10]	• The FDA is an agency within the U.S. Department of Health and Human Services. It consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations. • Website houses information on drug approvals links to product labeling, deliberations of advisory committee meetings, and drug shortages. • Drug Quality and Security Act of 2013 expands FDA's authority to regulate compounding such that a compounding outsourcing facility must comply with current good manufacturing practices, be subject to inspection by the FDA, and report information about compounded products including adverse events.[12] • Other regulated items include medical devices, radiation-emitting products, vaccines, veterinary medications, cosmetics, and tobacco products.
State Boards of Pharmacy	• Oversee licensure for individual states for pharmacists and pharmacy technicians • Set regulations for controlled substance prescribing within a state • Outline standards for physical pharmacy space – retail and institutional
Drug Enforcement Agency (DEA)[11]	• Section of the United States Department of Justice • Enforcement agency for controlled substance act • Provides registration for providers to prescribe, procure and dispense controlled substances
Joint Commission[12]	• Mission is to improve health care for the public by evaluating health care organizations and inspiring them to excel in providing safe and effective care of highest quality and value • Accredits and certifies more than 20,000 health care organizations and programs in the US. • Establishes standards for hospitals and other health care organizations to adhere to for regulatory compliance • Publishes annual report on Quality and Safety • Sets National Patient Safety Goals

2022 Joint Commission Hospital National Patient Safety Goals[12]

NPSG.01.01: Identify patients correctly: Two patient identifiers (name and date of birth) when providing care, treatment, and services

NPSG.02.03.01: Improve effectiveness of communication among caregivers: Report critical test results and diagnostic procedures on a timely basis.

NPSG.03.04.01: Improve the safety of using medications: Label all medications, medication containers and other solutions on and off the sterile field in perioperative and other procedural settings. Note – medication containers include syringes, medicine cups and basins. Medications or other solutions in unlabeled containers are unidentifiable. This unsafe practice neglects basic principles of safe medication management.

NPSG.03.05.01: Reduce the likelihood of harm associated with the use of anticoagulant therapy – this does NOT apply to routine situations in which short-term prophylaxis anticoagulation is used for preventing venous thromboembolism (for example, related to procedures or hospitalization)

NPSG.03.06.01: Maintain and communicate accurate patient medication information.

NPSG.06.01.01: Improve the safety of clinical alarm systems.

NPSG. 07.01.01: Reduce the risk of health care-associated infections. Comply with either the current Center for Disease Control and Prevention (CDC) hand hygiene guidelines or the current World Health Organization (WHO) hand hygiene guidelines.

NPSG.15.01.01: The hospital identifies safety risks inherent in its patient population. Identify patients at risk for suicide. This requirement applies only to psychiatric hospitals and patients being treated for emotional or behavioral disorders in general hospitals.

UP.01.01: Conduct a pre-procedure verification process

UP.01.01.01: Mark the procedure site.

UP.01.03.01: A time-out performed before the procedure.

Question #7:

Which of the following is not addressed in the ASCO/ONS safety standards with relevance to oncology pharmacy practice?

a. **Guidelines for preparation and handling of hazardous drugs**
b. **Adjudication of verbal orders for chemotherapy regimens**
c. **Policy requirements for preparation of intrathecal chemotherapy**
d. **Tracking of cumulative doses of chemotherapy drugs with significant end-organ toxicity**

QUALITY

I. Quality Oncology Practice Initiative (QOPI)

A. QOPI® is a quality measurement tool developed by the ASCO to benchmark oncology outpatient practices against accepted standards of practice. Certified practices are evaluated against a comprehensive set of quality measures and standards.

B. For details on the requirements to achieve QOPI Certification please review the materials below. QOPI Certification Program measures performance thresholds and site standards against publicly available standards. Standards and measures are continually re-assessed to maintain certification.

C. **ASCO/ONS Chemotherapy Administration Safety Standards[13]**

1. American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) initiated a collaborative project in 2008 (most recently updated in 2016) to develop standards for safe chemotherapy administration to adult cancer patients in the outpatient setting. The most recent update includes standards for pediatric oncology.

2. The scope of the project was limited to patient safety and included both parenteral and oral chemotherapy regimens. Summary of the standards are listed in the table below i

QOPI Safety Standards are based on the ASCO/ONS Chemotherapy Safety Standards[13]

Domain 1: **Creating a safe environment – Staffing and general policy**
• Detailed institutional policy for health care providers that order, prepare, and administer chemotherapy • Baseline training and ongoing educational requirements for all staff • At least one clinical staff member is BLS certified during chemotherapy administration • Before administration of a new chemotherapy regimen, the following is documented in the medical record: Pathologic confirmation of diagnosis; staging; medical history/physical exam/pregnancy status; allergy history; patient/caregiver comprehension of diagnosis and treatment; psychosocial assessment; chemotherapy treatment plan; patient follow-up schedule, and monitoring plan • For each clinical encounter or day of treatment, the following patient assessments are documented: Functional/performance status; vital signs; weight; height; age; allergies and/or previous treatment toxicities; new treatment toxicities; pain assessment • Staff assesses and documents psychosocial concerns with each treatment cycle • Referrals for financial, psychosocial, or other cancer support services • Medication lists are updated when a change occurs • 24/7 triage and access to an oncology savvy provider for treatment-related toxicities and emergencies • Standard documentation and communication for toxicities, modifications in dose/schedule of treatment or discontinuation of treatment • Policy for safe handoff between treatment settings • Policy for reporting adverse events and near misses with a formal process for collecting and reviewing such data
Domain 2: **Treatment Planning, Patient Consent and Education**
• Policy that documents a standardized process for obtaining and documenting chemotherapy consent or assent which is obtained prior to starting treatment

- Patients are providing verbal and written or electronic information as part of a formal education program, the content of which is documented
- Education will include: diagnosis; goals of treatment (e.g. cure vs. palliation); planned duration of treatment; treatment schedule; drug names including supportive medications; information on drug-drug and/or drug-food interactions; plan for missed doses; long-term and short-term toxicities; symptoms/adverse events that require the patient to contact the health care setting or seek immediate attention; symptoms/events that require immediate discontinuation of oral or self-administered medications; procedures for handling medications at home – including storage, safe-handling; and management of unused medications; procedures for handling body secretions and waste in the home; follow-up plans – e.g. labs, provider visits; contact information for providers including after hours; follow-up for missed appointments; education of family/caregivers for the patient

Domain 3: **Ordering, Preparing, Dispensing and Administering Chemotherapy**

- Institution defines standard treatment regimens – including references
- Institution verifies IRB review of research protocols
- Chemotherapy orders are signed manually or by electronic signature code by licensed independent practitioners who are determined to be qualified by the institution
- Policy exists to handle chemotherapy regimens that vary from standard practice – supporting reference or authorization from a second license independent practitioner are required
- Rationale for exception orders as above are documented in the medical record
- No verbal orders for chemotherapy are allowed except to hold or stop chemotherapy; new orders and/or change orders are documented in the medical record
- Institution uses standardized, regimen-level, pre-printed or electronic forms for IV chemotherapy regimens
- **Chemotherapy orders** include the following elements: Patient name; second patient identifier; date; regimen/protocol name; cycle number and day; use of generic drug names; drug dose is written following standards for abbreviations, trailing and leading zeros; dose calculation and methodology for the dose calculation; variables used to calculate the dose including frequency by which they are re-calculated; date of administration; route of administration; allergies; supportive care including premedications, hydration, growth factors and hypersensitivity medications; parameters for holding a dose of a particular medication; sequence of drug administration when applicable; rate of drug administration; number of cycles for which the order is valid
- **Prescriptions for oral chemotherapy** include the following elements: patient name with a second identifier; full generic drug name; date; calculation methodology; drug dose including standards for abbreviations and preceding/trailing zeros; route of administration including special instructions; drug quantity to be dispensed; schedule of administration; duration of therapy; number of refills
- Chemotherapy is prepared by a licensed pharmacist, pharmacy technician, physician or registered nurse with documented chemotherapy preparation training and annual competence validation
- Licensed pharmacist verifies all orders before administration or dispensing of chemotherapy in health care settings that treat pediatric patients under age 18
- A second person – a practitioner or other personnel approved by the health care setting to prepare or administer chemotherapy- performs **three independent verifications**: two patient identifiers; drug name and dose; route and rate of administration; calculations for dosing including variable utilized; treatment cycle and day of cycle
- Upon **preparation** – a second person approved by the health care setting to prepare parenteral chemotherapy verifies – the drug vials; concentration; diluent type and volume; administration fluid type and tubing

- Prior to each chemotherapy **administration**, at least two practitioners approved by the health care setting to administer or prepare chemotherapy verify and document the accuracy of the following elements: drug name and dose; infusion volume or drug volume in a syringe; rate and route of administration; expiration dates and times; appearance and physical integrity of the drugs; rate set on IV infusion pump
- Elements required on **chemotherapy labels**: patient name; second patient identifier; full generic name; drug dose; drug administration route; total volume required to administer the drug; date of administration; expiration dates/times; sequencing of drug administration and total number of products to be given when medication is provided in divided doses; warning or precautionary sticker for storage or handling.
- **Labels** for medications dispensed by the health care setting to be **taken at home** include: patient name; second patient identifier; full generic name; drug dosage form and strength; quantity dispensed; within each container; number of pills per dose when the container holds more than one dose; administration schedule for number of doses per day, food ingestion and other medications; warning or precaution statement with respect to handling/storage; warning or precautionary sticker; storage conditions; prescriber name. Medication label requirements must also meet state board of pharmacy regulations.
- **Intrathecal chemotherapy**: policy outlining preparation guidelines; storage in an isolated container or location following preparation; labeled with uniquely identifiable intrathecal administration medication label; delivered to patient only with other medication intended for CNS administration; administered immediately following a time out, double-check procedure that involves two licensed practitioners
- **Health care settings that administer intrathecal chemotherapy have a policy that specifies that intravenous vinca alkaloids are only to be administered by infusion** – e.g., minibags.
- Chemotherapy mixed off-site: the health care setting maintains a policy that accounts for quality control of that chemotherapy including that the off-site pharmacy complies with applicable regulations
- Health care setting that maintains its own pharmacy – policy regarding the safe storage of chemotherapy including the separation of look-alike, sound-alike products and investigational drugs
- Chemotherapy is administered by a qualified physician, physician assistant, registered nurse, or advanced practice nurse
- Before initiation of each chemotherapy administration cycle, the practitioner who is administering the chemotherapy confirms the treatment with the patient, including at a minimum name of drug, route of administration, any infusion-related symptoms to report
- Two individuals in the presence of the patient confirm that patient's identity using two patient identifiers; when treatment is in the home setting a single practitioner may use another identifier such as a driver's license
- Documentation of chemotherapy administration confirms the verification of the eight elements of chemotherapy administration identified previously
- Extravasation management procedures are defined and align with current literature and guidelines; antidote order sets and antidote medications are available within an appropriate timeframe

Domain 4: **Monitoring after chemotherapy is administered, including adherence, toxicity, and complications**
• Health care setting uses standard, disease-specific processes, to monitor treatment response and has a policy that determines the appropriate time interval for regimen-specific laboratory and organ-function tests that are based on evidence and national guidelines when available

- Health care setting has a policy for emergent treatment of patients that aligns with current literature guidelines and addresses: availability of appropriate treatment agents; procedures to follow and to plan for escalation of care when required for life-threatening emergencies
- Availability of appropriate treatment agents
- Procedures to monitor an initial assessment of adherence to chemotherapy that is administered outside the health care setting
- Policy that requires ongoing assessment of each patient's chemotherapy adherence and toxicity at each clinical encounter to address any issues identified
- Cumulative doses of chemotherapy are tracked for agents associated with cumulative toxicity

Answers to Question #7:

Choice A is correct because the 2016 update of the ASCO/ONS safety standards does not address safe handling of hazardous drugs or engineering controls required to compound cytotoxic agents safely.

Choice B is incorrect because Domain 3 states that no verbal orders for chemotherapy should be accepted except to hold or discontinue the orders.

Choice C is incorrect because Domain 3 speaks to the requirement for a policy for preparation of intrathecal chemotherapy and assurance that vinca alkaloids will be prepared in an IV piggyback to avoid inadvertent intrathecal instillation.

Choice D is incorrect because Domain 4 requires that cumulative dose of chemotherapy be tracked such that agents such as anthracyclines can be monitored for the risk of cardiac toxicity.

Question #8:

Which of the following is most correct regarding core measures assessed by QOPI?

a. On-site reviewers from ASCO will abstract chart data for compliance
b. Reported core measures are the sole criteria for QOPI certification
c. Core measures are required for each malignancy that has treatment guidelines written by National Comprehensive Cancer Network (NCCN)
d. Institutions are required to self-report compliance with core measures to ASCO ahead of an on-site visit

QOPI Core Certification Measures (2022):[14]

Core Measures
1. Pathology report confirming malignancy
2. Staging documented within one month of first office visit
3 - 6. Pain addressed appropriately and intensity documented (by at least second office visit)
9. Documented plan for chemotherapy, including doses, route, and time intervals
10. Chemotherapy intent (curative vs. palliative) documented
11. Chemotherapy intent discussion with patient documented
13. Chemotherapy planning completed appropriately (document performance status, plan for oral chemotherapy monitoring)
14-16. Signed consent for chemotherapy with documentation in the clinician note
21-23. Smoking status/tobacco use documented in past year/Cessation efforts
24. Patient emotional well-being assessed by second office visit
25. Action taken to address emotional well-being by second office visit
25b. Height, weight and BSA documented prior to chemotherapy
Symptom/Toxicity Management Module measures
30. Appropriate antiemetic therapy with moderate/high emetic risk chemotherapy
31. Antiemetic therapy for low/minimal emetic risk chemotherapy - avoidance of overuse
33. Infertility risks discussed prior to chemotherapy with patients of reproductive age
Breast Cancer Module measures
52. Combination chemotherapy **recommended** within 4 months of diagnosis by women under 70 with AJCC stage I (T1c) to III ER/PR negative breast cancer*
52a. Complete staging for women with invasive breast cancer including HER-2, and ER/PR status
53. Combination chemotherapy **received** within 4 months of diagnosis by women under 70 with AJCC stage I (T1c) to III ER/PR negative breast cancer
54. Test for Her-2/neu gene overexpression
55 Trastuzumab prescribed for Her-2/neu positive disease in Stage I – III patients
57a. Appropriate treatment for patients with stage I (T1c) – III HER-2 (+) breast cancer
58-59. Tamoxifen or AI received within 1 year of diagnosis by patients with AJCC stage I (T1c) to III ER or PR positive breast cancer*
61. Bone modifying agents (IV bisphosphonate or denosumab) administered for breast cancer bone metastasis; renal function assessed for bisphosphonate use
62. PET, CT or radionuclide bone scan ordered by practice with 60 days after diagnosis to Stage I, IIA or IIB breast cancer or between day 61 and 365 for those treated with curative intent
62c. Serum tumor marker ordered by practice within 30 and 365 days after diagnosis of breast cancer with curative intent treatment
62d. GCSF administered to patients who received chemotherapy for metastatic breast cancer **(lower is better)**
Colorectal Cancer Module measures
68. Adjuvant chemotherapy received within 4 months of diagnosis by patients with AJCC stage III colon cancer*
74. KRAS/NRAS testing for patients with metastatic colorectal cancer who receive MoAb therapy.
Non-Small Cell Lung Cancer Module measures
81. Adjuvant cisplatin-based chemotherapy received within 60 days after curative resection – stage II or IIIA NSCLC.
82. Adjuvant cisplatin-based chemotherapy received within 60 days after curative resection – stage IA NSCLC. **(Lower is better)**

83. Adjuvant radiation therapy recommended for patients with AJCC stage IB or II NSCLC. **(Lower is better)**
84. Performance status documented for patients with initial stage IV or distant metastatic NSCLC.
88. Patients with Stage IV NSCLC with adenocarcinoma histology with an activating EGFR mutation or ALK gene rearrangement who received first-line EGFR tyrosine kinase inhibitor or other targeted therapy
89. Patients with Stage IV NSCLC with adenocarcinoma histology with unknown EGFR mutation or ALK gene rearrangement who received first-line EGFR tyrosine kinase inhibitor or other targeted therapy **(lower is better)**
89a. GCSF administered to patients who received chemotherapy for metastatic NSCLC **(lower is better)**
90. PET or PET-CT ordered by the practice between 0 and 12 months after treatment with curative intent for patients with Stage I or II NSCLC **(lower is better)**
91-92. Molecular testing/turnaround time for patients with Stage IV NSCLC with adenocarcinoma histology
93. Concurrent chemoradiation for patients with a diagnosis of Stage IIIB NSCLC
Small Cell Lung Cancer Module measures
118. Prophylactic Cranial Irradiation for Patients with Limited Stage (LS) Small Cell Lung Cancer (SCLC)
119. Overtreatment of SCLC Patients with Platinum-Based Chemotherapy **(lower is better)**
120. Early Thoracic Radiotherapy (TRT) for Patients with a Diagnosis of Limited Stage SCLC

Answers to Question #8:

Choice D is correct because institutions are required to collate data from select patient chart on compliance with QOPI core measures and submit to ASCO for review prior to an on-site certification visit.

Choice A is incorrect because institutional staff are required to do the data abstraction for core measures from patient charts, not ASCO staff.

Choice B is incorrect because performance with core measures is only part of the criteria for QOPI certification. An on-site visit by an ASCO surveyor assessing practice compliance with ASCO/ONS safety standards also is an important determinant of certification.

Choice C is incorrect because the number of diseases represented in the core measure reporting is limited to lung, prostate, breast, colon, and gynecologic oncology.

Question #9:

Which of the following are quality metrics that oncology practices, participating in the Center for Medicare and Medicaid Services (CMS) Oncology Care Model, are required to submit to CMS?

a. **Appropriateness of prescribing erythroid colony stimulating factors**
b. **Percentage of patients that utilize the emergency room during cancer treatment**
c. **Number of patients that a practice enrolls in NCI-sponsored phase III clinical trials**
d. **Patient compliance with oral oncolytic therapy**

II. CMS Oncology Care Model (OCM)[15]

A. The innovation Center at CMS published the first major payment modification for oncology services in February 2015. The OCM focuses on an episode of cancer care, specifically a chemotherapy episode of care.

B. The goals of OCM are to utilize appropriate aligned financial incentives to improve:

1. Care Coordination
2. Appropriateness of care
3. Access for Medicare beneficiaries undergoing chemotherapy

C. Financial incentives encourage participating oncology practices to work collaboratively to comprehensively address the complex care needs of beneficiaries receiving chemotherapy treatment and encourage the use of services that improve health outcomes.

D. How does OCM work?

1. Episode based: Payment model targets chemotherapy and related care during a 6-month period following the initiation of chemotherapy treatment.
2. Emphasizes practice transformation: Physician practices are required to engage in practice transformation to improve the quality of care they deliver.
3. Multi-payer model: Includes Medicare fee-for-service (FFS) and other payers working in tandem to leverage the opportunity to transform care for oncology patients across the population.

E. Physician practices that are Medicare providers and furnish chemotherapy may apply to participate in OCM – there are six requirements for participation:

1. Provide 24/7 patient access to an appropriate clinician who has real-time access to the patient's medical records.
2. Use an ~~oncology-certified~~oncology certified EMR and attest to Stage 2 of meaningful use (MU) by the end of the third model performance year and MU Stage 1 by the end of the first model performance year.
3. Utilize data for continuous quality improvement – The CMS Innovation Center will provide participating practices with rapid cycle data feedback reports to aid in quality improvement. Practices are expected to use this data to continuously improve OCM patient care management.
4. Provide core functions of patient navigation: Practices are required to provide patient navigation to all OCM patients. The National Cancer Institute provides a sample list of patient navigation activities.
5. Document a care plan for every OCM patient that contains the 13 components in the Institute of Medicine's Care Management Plan. Plan components include treatment goals, care team, psychosocial support and estimated out-of-pocket costs.
6. Treat patient with therapies consistent with nationally recognized clinical guidelines. Practices must report which clinical guidelines (NCCN® or ASCO) they follow for OCM patients or provide a rationale for not following the clinical guidelines.

F. Payers

1. OCM covers Medicare fee-for service (OCM-FFS) and other payers (OCM-OP). Other payers may include commercial payers, state Medicaid agencies, or other governmental payers (including Tricare, FEHBP and state employee health plans).

2. Payer participation will drive the geographic scope of the model. The CMS Innovation Center will publish lists of payers and practices who submit letters of intent to participate in OCM and expects other payers to plan for OCM participation with their associated practices.

G. Operations of OCM:

1. Commit to participation in OCM for its 5-year duration and begin performance period within 90 days.
2. Sign a memorandum of understanding with the Innovation Center.
3. Enter into agreements with OCM practices that include requirements to provide high quality care.
4. Share model methodologies with the Innovation Center.
5. Provide payments to practices for enhanced services and performance as described in the RFA (request for applications).

H. Quality Improvement Measures – Align practice quality and performance measures with OCM.

I. Data Sharing – Provide participating practices with aggregate and patient-level data about payment and utilization for their patients receiving care in OCM, at regular intervals.

J. Medicare beneficiaries who meet each of the following criteria will be included in OCM-FFS:

1. Eligible for Medicare Part A and enrolled in Medicare Part B.
2. Have Medicare FFS as their primary payer.
3. Do not have end-stage renal disease.
4. Are not covered by United Mine Workers.
5. Receiving treatment with chemotherapy for cancer under management of an OCM participating practice.

K. Episode Definition:

1. OCM-FFS includes nearly all types of cancer.
2. Episodes initiate when a beneficiary starts chemotherapy
3. The Innovation Center has devised a list of chemotherapy drugs that trigger OCM-FFS episodes, including endocrine therapies but excluding topical formulations of drugs.
4. All Medicare A and B services that Medicare FFS beneficiaries receive during episodes will be considered included services. Certain Part D expenditures will also be included.
5. OCM-FFS episodes extend 6 months after a beneficiary's chemotherapy initiation.
6. Beneficiaries may initiate multiple episodes during the 5-year model performance period.

L. Payment

1. Per-beneficiary-per-month (PBPM) payment – Monthly Enhanced Oncology Service (MEOS)

a. $160 payment is given to the practice each month for enhanced services required by OCM that is paid during the chemotherapy for 6 month “episodes” – while the patient is receiving active treatment for cancer

b. If the beneficiary enters hospice, the payments cease.

2. Performance-based payment

a. Incentive to lower the total cost of care and improve quality of care for beneficiaries over the 6-month episode period.

b. Retrospective payment that is calculated based on the practice’s historical Medicare expenditures and achievement on selected quality measures.

c. CMS will calculate benchmark episode expenditures participating practices based on historical data, geographical variation and trended to applicable performance period.

d. A discount will be applied to the benchmark to determine a target price for OCM-FFS episodes. (e.g., Benchmark = $100 with 4% Discount = Target Price of $96.

e. If actual OCM-FFS episode Medicare expenditures are below target price, the practice could receive a performance-based payment. (e.g., Actual cost = $90 from example (d) above the performance-based payout could be up to $6.)

f. The amount of the performance-based payment may be reduced based on the participant’s achievement and improvement on a range of quality measures.

g. Risk Arrangement for Shared Savings may be one-sided or two-sided:

i. One-sided: participants are NOT responsible for Medicare expenditures that exceed target price; Medicare discount 4%; must qualify for performance-based payment by the end of year 3.

ii. Two-sided: participants are responsible for Medicare expenditures that exceed target price; option to take downside risk beginning in year 3; Medicare discount 2.75%; must qualify for performance-based payment by end of year 3.

iii. Clinical trial participants are included.

h. Risk adjustments will be made for episodic expenditures including beneficiary expenditures, episode characteristics, disease characteristics and type of service furnished.

M. Quality Measures:

1. Clinical quality of care

2. Communication and care coordination

3. Person and caregiver centered experience and outcomes

4. Population health

5. Efficiency and cost reduction

6. Patient safety

7. Quality measures are culled from data sources such as practice-reported data, Medicare claims and patient surveys

OCM Quality Indicators:

Quality Domain	Recommended Practice Requirement or Quality Measurement	NQF #	Source
Communication and Care Coordination	# of ED visits per OCM-FFS beneficiary per episode		Claims data
Communication and Care Coordination	# of hospital admissions per OCM-FFS beneficiary per episode		Claims data
Communication and Care Coordination	% of all Medicare FFS beneficiaries managed by the practice admitted to hospice for < 3 days	#0216	Claims data
Communication and Care Coordination	% of all Medicare FFS beneficiaries managed by the practice who experience ≥ 1 ED visit in the last 30 days of life	#0211	Claims data
Person- and Caregiver-Centered Experience and Outcome	% of OCM-FFS beneficiaries face-to-face encounters with the participating practice in which there is a documented plan of care for pain and pain intensity is quantified	#2100	Reported by practice
Person- and Caregiver-Centered Experience and Outcome	Score on patient experience survey (modified CAHPS)		Administered by CMS contractor
Person- and Caregiver-Centered Experience and Outcome	% of OCM-FFS beneficiary face-to-face encounters in which the patient is assessed by an approved patient-reported outcomes tool and that receive psychosocial screening/intervention at least once per episode		Reported by practice

N. Monitoring and Evaluation

1. Tracking of claims data
2. Patient surveys
3. Site visits
4. Analysis of quality measurement data
5. Time and motion studies
6. Medical record audits, tracking of patient complaints and appeals
7. OCM will use match-comparison groups to detect changes in utilization, costs and quality that can be attributed to the model
8. The OCM performance period ended on June 30, 2022. The program will be replaced by the Enhancing Oncology Model (EOM) in July 2023.

O. Milestones[16]

Number of Participants	126 practices across the US 5 commercial payers – Aetna, Blue Cross/Blue Shield of South Carolina, Cigna, Priority Health, University of Arizona Health Plan
Impact on Total Episode Payments for Medicare	All episode payments increased (most likely due to increasing drug costs) but the OCM episodes were $297 less than non-OCM episodes; the impact was exclusively in Part A and B payments, not Part D
Gross savings to Medicare vs. Provider payments for MEOS/PBP	Over 4 performance periods the net loss to Medicare was $315,665,814
Impact of OCM on Cancer Treatment Patterns	Chemotherapy drugs used to treat common cancers were similar in the OCM and non-OCM practices and evolved similarly over time; no savings was realized by Medicare Episode payments in the OCM practices increased less for non-chemotherapy drugs (e.g., supportive care) compared to non-OCM practices
Patient Experience	Cancer patients rated their care very highly regardless of OCM participation
ED Visits/Hospitalizations/Chemotherapy-Related Toxicity	Despite efforts to identify and monitor high-risk patients there was no impact on the rates of ED visits, hospitalization, or chemotherapy-related hospitalization
End-of-Life Hospitalization	Hospitalization in the last month of life declined slightly for OCM practices
Hospice Utilization/Timing	Despite utilization of palliative care specialists and efforts for documenting patient EOL wishes there was no observable impact on hospice use, duration, or timing

Answers to Question #9:

Choice B is correct because the OCM has set the number of visits to the emergency room during a specific treatment episode and the usage of the emergency department during the last 30 days of life as reportable quality metrics.

Choice A is incorrect because the OCM is not focused on reviewing drug prescribed within a certain class of medications.

Choice C is incorrect because OCM is focused more so on continuity of care issues and not whether patients are participating in a clinical trial.

Choice D is incorrect because OCM is not focusing on specifics of drug therapy such as adherence.

III. Other general quality improvement tools used in oncology pharmacy:

A. Root Cause Analysis (RCA) – structured, step-by-step techniques for problem solving. The goal is to determine and correct the ultimate cause(s) of a problem, not just the visible symptoms, to ensure that it does not occur again.[17]

1. RCA consists of determining what happened, why it happened and what can be done to prevent it from happening again
2. The Joint Commission requires all accredited organizations to conduct an RCA of any sentinel event (an unexpected occurrence involving death or serious physical or psychological injury, or risk thereof).
3. The five whys technique – consists of asking why an event occurred repeatedly until the root issue is uncovered.
4. Cause and effect diagram – can use a "fishbone" diagram where the head of the fish is the problem and branches are considered different categories of causes.

B. Failure Mode Effects Analysis (FMEA) – originally developed by the US military in the 1940's to assess equipment failure. It has since been adopted in many industries to evaluate service failure. Joint Commission requires use of FMEA or a similar tool to reduce the potential for failure of a process. FMEA classically involves the following steps:[18]

1. Identification of the process to be evaluated.
2. Team training: use of FMEA in health care will typically involve personnel from multiple department – e.g., pharmacy, nursing, environmental services, laboratory, etc.
3. Develop a detailed process flowchart, including all steps in the process.
4. Identify each step in the process
5. Identify potential failures (e.g., failure modes) at each step in the process
6. Determine the worst possible outcome of each failure mode.
7. Identify the contributory factors for each potential failure.
8. Identify any failure "controls" that are currently present. A control reduces the likelihood of a failure event or reduces the severity of the consequences of a failure.
9. Rate the severity of each failure (typically a 1 to 10 scale).
10. Rate the likelihood that each failure cause will occur (typically a 1 to 10 scale).
11. Rate the effectiveness of each control (again, a 1 to 10 scale).
12. Multiple the three above ratings by each other to obtain the risk priority number (RPN) for each cause or contributory factor.
13. Use the RPNs to prioritize problems for corrective actions.
14. Develop an improvement plan to address the targeted causes.

C. ASHP outlines MUE objectives, methodology, and pharmacists' role in MUEs in their published guidelines for MUE.[19]

D. Institute for Safe Medication Practices (ISMP)- only non-profit organization devoted entirely to medication error prevention and safe medication use.[20] Certified as a Patient Safety Organization by the US Agency for Healthcare Quality and Research.

1. Established targeted medication safety best practices for hospital for 2022-23.

    a. Best practice #1 – Dispense vincristine (and other vinca alkaloids) in a mini bag of a compatible solution and not in a syringe.

    b. Best practice #2 – Use a weekly dosage regimen default for oral methotrexate in electronic systems when medication orders are entered. Require a hard stop verification of an appropriate oncologic indication for all daily oral methotrexate orders. Provide specific patient/family education for all oral methotrexate discharge orders.

    c. Best practice #3 – Weigh each patient as soon as possible on admission and during each appropriate outpatient or emergency department encounter. Avoid the use of a stated, estimated, or historical weight. Measure and document patient weights in metric units only.

    d. Best practice #4 – Ensure that all oral liquids that are not commercially available as unit dose products are dispensed by pharmacy in an oral or ENFit syringe that meets the International Organization for Standardization (ISO) 80369 standard. (ARCHIVED)

    e. Best practice #5 – Purchase oral liquid dosing devices (oral syringes / cups / droppers) that only display the metric scale. (ARCHIVED)

    f. Best practice #6 - Eliminate glacial acetic acid from all areas of the hospital. (ARCHIVED)

    g. Best practice #7 – Segregate, sequester, and differentiate all neuromuscular blocking agents (NMBs) from other medications, wherever they are stored in the organization.

    h. Best practice #8 – Administer medication infusions via a programmable infusion pump utilizing dose error-reduction software.

        a. Maintain a 95% or greater compliance rate for the use of dose-error reduction systems.

        b. Monitor compliance with the use of smart pumps monthly.

        c. If administering a bolus dose (or loading dose) from a continuous infusion, use a smart pump that allows for programming of the bolus and separate limits for both the bolus and continuous IV infusion.

    i. Best practice #9 – Ensure all appropriate antidotes, reversal agents, and rescue agents are readily available. Have standardized protocols and/or coupled order sets in place that permit the emergency administration of all appropriate antidotes, reversal agents and rescue agents used in the facility. Have directions for use/administration readily available in all clinical areas where the antidotes, reversal agents and rescue agents are used.

    j. Best practice #10 – Eliminate all 1,000 mL bags of sterile water (labeled for “injection”, “irrigation”, or “inhalation”) from all areas outside the pharmacy. (ARCHIVED)

k. **Best Practice #11 – When compounding sterile preparations; perform an independent verification to ensure that the proper ingredients (medications and diluents) are added, including confirmation of the proper amount (volume) of each ingredient prior to its addition to the final container.**

l. **Best Practice #12 – Eliminate the prescribing of fentanyl patches for opioid-naïve patients and/or patients with acute pain.**

m. **Best Practice #13 – Eliminate injectable promethazine from the formulary.**

n. Best Practice #14 – Seek out and use information about medication safety risks and errors that have occurred in other organizations outside of your facility and take action to prevent similar errors.

o. **Best Practice #15 – Verify and document a patient's opioid status (naïve versus tolerant) and type of pain (chronic vs. acute) before prescribing and dispensing extended-release or long-acting opioids.**

p. Best Practice #16 - Limit the variety of medications that can be removed from an automated dispensing cabinet (ADC) using the override function. Required a medication order prior to removing any medication from an ADC, including those removed during an override function. Monitor ADC overrides to verify appropriateness, transcription of orders and documentation of administration. Periodically review for appropriateness the list of medications available using the override function.

q. Best Practice #17 – Safeguard against error with oxytocin use**.**

r. **Best Practice #18 - Maximize the use of barcode verification prior to medication and vaccine administration by expanding use beyond inpatient care areas.**

- **a. Target clinical areas with a short/limited patient stay (~~e.g.~~e.g., ED, perioperative areas)**
- **b. Regularly review compliance and other metric data to assess utilization and effectiveness of this safety technology.**

s. **Best Practice #19 – Layer numerous strategies throughout the medication-use process to improve safety with high-alert medications.**

- **a. Outline a robust set of processes for managing risk**
- **b. Address system vulnerabilities in each stage of the medication-use process and apply to prescribers, pharmacists, nurses and other practitioners involved in medication-use.**
- **c. Avoid reliance of low-leverage risk-reduction strategies (~~e.g.~~e.g., high-alert stickers on medication storage bins)**
- **d. Limit the use of independent double-checks to select high-alert medications with the greatest risk for error within the organization (~~e.g.~~e.g., chemotherapy, opioids, heparin)**

e. **Regularly assess for risk the in the systems and practices used to support the safe use of medications by using information from internal/external sources (~~e.g.~~e.g., Joint Commission, ISMP)**

f. **Establish outcome and process measures to modify safety and routinely collect data to determine the effectiveness of risk-reduction strategies.**

INFORMATICS

I. Electronic Medical Record (EMRs) – oncology EMRs lagged behind other computerized physician order entry applications[21,22]

A. Clinical components of an EMR: Results reporting information system (RRIS), computerized physician order entry (CPOE), clinical decision support system (CDSS)

B. Baseline elements in oncology-specific EMR: Tumor staging; multidisciplinary and data-intensive workflow; chemotherapy dosing and administration; toxicity assessment and management; clinical trial and protocol management; drug inventory management; survivorship care.

C. Oncology specific EMR functionalities identified by ASCO: Chemotherapy/drug management; oncology-specific billing; calendar/scheduler; clinical trials and research; compliance safeguards.

D. Error rates with oncology EMRs are significant in oncology patients given the complexity of treatment regimens – 7% in outpatient adults and 18% in pediatrics[23]

E. Chemotherapy order set development and maintenance[24]

1. Interdisciplinary team identifies clinically relevant chemotherapy treatment plans to create pre-printed orders based on a paper process
2. Orders are transposed to a standard template build for an EMR
3. Build and validation steps are tracked to track barriers and outcomes
4. Newly created oncology regimen content is amenable to CPOE by credentialed physicians and barcode medication administration by nursing

F. Other relevant technology**:**

1. Software-based workflow management of IV compounding:
   a. Volumetric verification - utilizes digital photo and barcoding to verify step-by-step compounding of sterile IV products
   b. Volumetric and gravimetric - IV software system monitoring of pharmaceutical compounding that uses bar-code scanning and gravimetric analysis[25]
   c. Gravimetric vs. Robotic[26]

System and Variance Analysis	2016 Robot N=10,684	2016 Gravimetric N=183	2017 Robot N=13,623	2017 Gravimetric N=7,537	2018 Robot N=17,822	2018 Gravimetric N=10,416
Accuracy (%)	3%	8%	3%	2%	2%	1%
Preparations with 4 – 10% variance (%)	2%	5%	2%	1%	2%	<1%
Preparations >10% variance (%)	1%	3%	<1%	1%	<1%	<1%

Timing

	Time to Start Preparation (minutes)	Compounding Time (minutes)	Final Validation Time (minutes)
Gravimetric	10:23	2:39	4:50
Robot	13:27	6:07	4:43

Error Characterization

	Robot (N=42,129)	Gravimetric (N=18,136)
All Errors	3,677 (8.7%)	3,468 (19.1%)
Operator Error	409 (1%)	89 (0.5%)
Wrong diluent	580 (1.4%)	1,136 (6.3%)
Wrong drug	59 (1.4%)	937 (5.2%)
Preparation	2,629 (6.2%)	1,306 (7.2%)

Question #10:

Which of the following characteristics of clinical pathways is being advocated by national professional oncology societies?

a. Oncology pathways should include issues beyond drug treatment regimens such as survivorship and end-of-life care

b. Pathway compliance should approximate 100% with well-written pathways

c. Commercial entities such as drug wholesalers should not draft/support oncology clinical pathways

d. Diversity and variation in application of commercially pathways supports physician autonomy in therapeutic decision making

G. Oncology Clinical Pathways:[28, 29, 30]

1. Goal is to standardize practice for ordering chemotherapy regimens with use of evidenced-based clinical pathways based on disease and stage.
2. Compliance – goal for on-pathway rate approximates 70 to 80% considering patient-specific factors such as end-organ dysfunction, tumor genomics, patient performance status, and access to care.
3. Major commercial vendors: ClinPath (Via) Oncology; US Oncology – McKesson; Cardinal Health.
4. ASCO released a policy statement on clinical pathways

a. National approach is needed to remove the unsustainable administrative burden of multiple, unmanaged oncology pathways

b. Oncology pathways should be developed in a consistent and transparent process

c. Oncology pathways should reflect diagnostic, medical, surgical, and radiation treatments which encompass imaging, labs, survivorship, and end-of-life care

d. Oncology pathways should reflect best clinical evidence and be updated routinely

e. Oncology pathways should recognize physician autonomy, patient variability, and recognize that 100% concordance with pathways is impossible

f. Oncology pathways should be implemented in ways that promote administrative efficiencies for oncology providers and payers

g. Oncology pathways should promote education, research, and access to clinical trials

h. Robust criteria must be developed to support certification of oncology pathways programs

i. Pathway developers, users, and private and governmental funding agencies should support research to understand pathway impact on care and outcomes

5. Clinical data:[28]

a. Data from eight community practices for treatment of NSCLC patients

i. Drug costs: on-pathway - $18,042 vs. off-pathway $27,737; no difference in overall survival.

b. Utilization of clinical pathways among multiple private oncology physician practices demonstrated an 88% compliance rate with physicians and a decrease in regimen usage from 168 to 136

Answers to Question #10:

Choice A is correct because ASCO has advocated that clinical pathways provide guidance to medical oncologists beyond drug prescribing such as recommendations for end-of-life care, survivorship, surgical intervention and radiation therapy.

Choice B is incorrect because ASCO and pathway developers both acknowledge that compliance with clinical pathways reaching 70 to 80% is a best-case scenario given patient-specific factors such as end-organ function and performance status.

Choice C is incorrect because most of the commercially available pathways are written by corporate entities such as drug wholesalers (e.g., Cardinal, McKesson) and large publication houses (e.g., Elsevier).

Choice D is incorrect because ASCO is advocating for a more uniform approach to pathway development and application, not divergent.

FINANCE

I. Reimbursement for outpatient oncology drugs:[31, 32,33]

A. Reimbursement rates under Medicare for IV drugs provided by hospitals/office-based clinics in the outpatient setting —the average sale price (ASP) of the drug plus 6% per CMS guidelines.

B. The federal government budget sequester has reduced the payment from ASP plus 6% to ASP plus 4.3%. Payment limits are updated quarterly on the CMS website.

C. Medicare Part D for prescription drug coverage:

1. Offers beneficiaries the option of enrolling for prescription drug coverage administered by a private insurer starting in 2006.

2. Costs have been 40% lower than originally forecast by the Congressional Budget Office largely due to competition between plans, use of generic drugs and beneficiary choice of low-premium plans.

3. Most plans have a deductible with a co-insurance of 25%. Once a cumulative expense of approximately $3,000 is reached the patient is responsible for the full cost of the drugs until total expenditure reaches approximately $5,000. This is coverage gap has been termed the "doughnut hole". The Affordable Care Act will gradually phase out the doughnut hole.

4. Subsidies are available for economically disadvantaged patients.

5. Medication Therapy Management (MTM) being incorporated into multiple plans and disease states.

II. Diagnostic related group (DRG) payment (Medicare Part A benefit): CMS payment method for inpatient hospitalization. Chemotherapy drugs are not individually reimbursed as part of a hospitalization stay and therefore the cost would be deducted from a DRG payment to the hospital for a specific hospital admission.[33]

III. Drug purchasing

A. Heterogeneity in Drug Pricing:[34]

1. Average Wholesale Price (AWP) – "sticker price" – that does not directly correspond to any actual market transaction. It is not an average of prices charged by wholesalers to providers, but a price reported to publishing houses (e.g., Redbook). Medicare's use of AWP for payment on pharmaceuticals ended in January 2005.

2. Wholesale Acquisition Cost (WAC) – this "list" price from wholesalers may not accurately reflect what is being paid by providers due to discounts and price concessions offered by manufacturers. In general terms: AWP = 1.2 x WAC

3. Average Sales Price (ASP) – Replaced AWP as the basis for most drugs covered under Medicare's medical benefit (Part B) in January 2005. ASP is calculated by CMS based on market data for manufacturer selling price which includes rebates, volume discounts, etc. Many private payors have gravitated to ASP to base their reimbursement for oncology drugs.

4. 340B – federal program requiring manufacturers to provide significant discounts for outpatient drugs by eligible covered entities. These covered entities include public and not-for-profit hospitals, children's hospitals, critical access hospitals and federally qualified health centers and specialty clinics that serve a disproportionate percentage of low-income patients (approximately 12% or greater of payor mix). In 2010, the Accountable Care Act expanded the 340B eligibility to free standing cancer centers.[35]

    a. Physician office practices or inpatient settings are not eligible for 340B drug pricing

    b. Patients must receive services from providers at the covered entity to be eligible for 340B

    c. For cancer clinics to be eligible for the 340B program they must be listed on the Medicare cost report for the facility, the clinic must operate under the same license as the hospital, clinical and financial operations must be integrated between the clinic and hospital (including physician and administrative oversight), medical records must be integrated between the clinic and hospital, and the clinic must publicly declare its affiliation with the 340B hospital.

    d. An oncology clinic may retain eligibility for 340B even if the physicians are not employed by the hospital if the requirements listed in C above are met and the hospital retains ownership of the clinic and purchases the drugs.

    e. A non-340B hospital may form a contractual agreement with a 340B hospital for joint ownership or equity in a clinic that may be eligible for 340B.

    f. Typically, eligibility for a new clinic for 340B is determined the summer following the end of the year that the clinic was reported on the 340B hospital's Medicare cost report. The clinic is not eligible to purchase drugs at the 340B pricing until approved by Health Resources and Services Administration (HRSA) of the federal government, which administers the program.

    g. Medicaid patients are not eligible for 340B drug pricing since they already qualify for discounted drug pricing.

    h. CMS has issued a final rule for reimbursement for 340B purchased drugs effective January 1, 2018:[35]

        i. ASP +6% changes to ASP **minus 22.5%** for 340B purchased drugs
        ii. Rural sole community hospitals, PPS-exempt cancer hospitals, and children's hospital will be exempt from this policy in 2018
        iii. Expected savings is $1.6 billion

5. The Supreme Court ruled against CMS for the proposed reimbursement cuts going back to 2018 in the summer of 2022. CMS will reimburse hospitals participating in the 340B Drug Pricing Program at the default rate of 22.5%. Hospitals participating in the program will also receive the difference between the default rate and the old rate

(average sales price minus 22.5 percent) for claims paid after the court ruling. It is yet to be determined as to when and how CMS may reimburse hospitals for variance in reimbursement for 340B patients during that time frame Following the Supreme Court's ruling, HHS announced it would reimburse hospitals for administering 340B-covered drugs the same as non-340B drugs starting Jan. 1, ~~2023.~~.2023.
Average Manufacturer Price (AMP): created by OBRA 1990 for the purpose of calculating rebates paid by manufacturers to states for drugs dispensed to their Medicaid beneficiaries. AMP is defined as the price available to the retail class of trade and reflected any discounting or rebates to the purchasing entity. In 2005, the federal government mandated that AMP be used instead of AWP to calculate the Federal Upper Limit (FUL) for reimbursement to outpatient prescriptions for the facilities classified as retail class of trade (community pharmacies, mail order pharmacies, and physician offices.

6. Group Purchasing Organizations (GPO): Alliances of health care providers or pharmacies that form an alliance to increase negotiating leverage by increasing purchasing volume.

IV. **MACRA (Medicare Access and CHIP Reauthorization Act) – Replaced the SGR (Sustained Growth Rate which detailed physician payments from CMS)** [36]

A. MIPS (Merit-Based Incentive Payment System)
   1. Consolidates existing programs: Physician Quality Reporting System (PQRS), Value-based Payment Modifier, Electronic Health Record (HER) Incentive program and adds a fourth component: clinical practice improvement activities
   2. Eligible physicians may see +/-4% to payments in 2019 based on 2017 performance
   3. Domain weighting: quality activities (60%), clinical improvement activities (15%), advancing care informatics performance activity (25%), and cost/resource use (0%)
   4. Practices that accrue less than $30,000 in Medicare Part B allowed charges or see less than or equal to 100 Medicare patients are exempt from participation in MIPS. This represents 32% of Medicare clinicians by 5% of Medicare spending.

B. APMs (Alternate Payment Models)
   1. Advanced APM – provider that must bear more than nominal risk under the reimbursement model – a potential downside of 8% of all Medicare reimbursements or 3% of the expected expenditures for which the provider is responsible for in the APM
   2. CMS is exploring options for which clinical track may participate in APMs

C. QPP (Quality Payment Program)
   1. Goal is to reward delivery of high-quality patient care through MIPS and Advanced APMs

D. PTAC (Physician-Focused Payment Model Technical Advisory Committee

E. PFPM (Physician-Focused Payment Models)

F. Strategic Objectives:
   1. To improve beneficiary outcomes and engage patients through patient centered Advanced APMs and MIPS policies
   2. To enhance clinician experience through flexible and transparent program design and interactions with easy-to-use program tools
   3. To increase the availability and adoption of robust APMs
   4. To promote program understanding and maximize participation through customized communication, education, outreach, and support that meet the needs of the diversity of physician practices and patients, especially the unique needs of small practices

5. To improve data and information sharing to provide accurate, timely and actionable feedback to clinicians and other stakeholders
6. To ensure operational excellence in program implementation and ongoing development

Question #11:
Which of the following is most correct regarding the difference between the FDA approval process for generic drugs and biosimilars?
a. The biosimilar pathway involves drugs with a wide range of molecular weights
b. The endpoint for approval for generic drugs and biosimilars is +/-20% bioavailability
c. Biosimilars are generated in the lab from reproducible steps of chemical synthesis
d. Biosimilars must demonstrate similar safety, purity, and potency

V. **Biosimilars**[38,39]

A. Definition – A biotechnologic product comparable to an already approved biotechnological product in terms of quality, safety, and efficacy. The FDA requires that biosimilar drug is highly similar to existing reference product (innovator/originator molecule) notwithstanding minor differences in clinically inactive components and that there are **no clinically meaningful differences** between the biosimilar product and the reference product in terms of **safety, purity, and potency**.

B. Timeline:

Year and Legislation	Impact
1902 – Biologics Control Act	Mandated licensure of manufacturers of "viruses, serums, toxins, and analogous products"
1906 – Pure Food and Drug Act	Instituted rules about labeling of drugs that included mandated disclosures about addictive substances" Required evaluation of drug safety to be submitted to FDA
1938 – Food, Drug and Cosmetic Act	Placed biologics under the purview of Public Health Service
1944 – Public Health Service Act	Mandated assessment of drug efficacy
1967 – Kefauver-Harris amendments	Biologics oversight transferred to FDA
1972 1984 – Hatch-Waxman Act	Created an abbreviated application for versions of approved drugs (generic drugs) and created the 505(b)(2) pathway which allow for similar but not bioequivalent drugs to be tested

1988 – Creation of CBER and CDER	Post-approval oversight for biologics – Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER)
2009 – Biologics Price and Competition and Innovation Act	Passed as part of the Patient Protection and Affordable Care Act in 2010 created an abbreviated application pathway for biosimilars that was modeled after that for drug in the Hatch Waxman Act

C. Drugs that could be considered for biosimilar product development in oncology[40]

Drug Class	Example
Cytokines/glycoproteins	Granulocyte (and macrophage) colony stimulating factors Interferons/interleukins Epoetin/darbepoetin
Monoclonal antibodies (with and with drug conjugates)	Rituximab Trastuzumab Bevacizumab
Enzymes	Asparaginase Glucarpidase

D. Differences in Biosimilar and Generic Drugs

Property	Biosimilar	Generic Drugs
Molecular composition	High molecular weight, complex biologic agent	Small molecular weight, reproducible structure
Comparison with reference drug	Same amino acid sequence May have different posttranslational modifications, protein folding, excipients	Identical active ingredient Same bioequivalence, purity
Manufacturing	Uses living cellular systems Unique cell lines and production steps	Chemically synthesized Stepwise process of identified chemical reactions
FDA approval process	Biosimilar biologics license application Demonstrates similar safety, purity, potency, and efficacy	Demonstrates bioequivalence

E. Posttranslational modifications (PTMs)

1. Natural consequences of the use of eukaryotic cellular systems in their production. This is observed in both reference (innovator) and biosimilar products. Examples:
    a. Glycosylation – may impact Fc binding
    b. Deamidation/oxidation – may cause proteins to aggregate, degrade or denature that may influence the incidence of drug toxicity

F. Requirements of the Biologics Price Competition and Innovation Act

1. Created a new process:
    a. Allows the FDA to approve a biologic product based on less than a full complement of preclinical and clinical data if the sponsor could provide analytic studies showing the product was highly similar to an approved biologic product
2. Required animal studies data demonstrating:
    a. "Safety, purity, and potency" and clinical studies for use in which the reference product was originally approved
3. Two specific types of biosimilar specified under the Acct

a. Standard biosimilar product with “no clinically meaningful differences” in safety, purity and potency compared to the approved biologic
b. An interchangeable product – a biosimilar that can be expected to produce the same clinical result as the approved biologic in any given patient. The FDA would determine the level of testing required to meet these standards

4. Naming convention:
    a. FDA adds a random, lower-case four-letter suffix to the generic name of the biologic for each biosimilar product.
    b. The goal is to optimize pharmacovigilance efforts and to provide consistency in referencing a manufacturer’s specific biosimilar product.
5. Monoclonal Antibody properties evaluated for biosimilars

Quality Attributes	Variable	Relationship with Pharmacokinetics
Physicochemical Properties	Isoelectric Point Metabolic oxidation of CH2 domains High-mannose glycan	Cellular uptake FcRn binding Mannose receptor binding
Biological Properties	Soluble antigen binding Cell-surface antigen binding FcRn binding* FcγR binding	Disposition as an immune complex Disposition via cellular uptake Recycling Disposition via intracellular uptake or phagocytosis

*FcRn binding – leads to recycling of monoclonal antibodies

** FcγR binding contributes to apoptosis and/or antibody mediated cytotoxicity

G. **ASCO Policy Statement**[41]

Clinical trials to demonstrate sufficiently similar safety, efficacy, and immunogenicity in biosimilars would be necessary in most, if not all, cases.

While FDA should be given substantial discretion in forging the regulatory pathway for approval of individual classes of biosimilars products, transparency in the process is essential so that clinicians and the public can be satisfied that the process contains adequate safeguards. Notice-and-comment procedures would be appropriate in fashioning the contours of the biosimilars pathway on a class-specific basis. Guidance documents—either on a class-specific basis or in some cases on a product-specific basis—should be published to ensure consistency of standards and predictability of regulatory action.

In any instance in which FDA decides that clinical trials are not necessary for follow-on products, the agency should publicly disclose that decision and provide a detailed rationale.

No system should be adopted that would limit physician choice among" biosimilar" products or require substitution of products that have been designated "interchangeable". In every instance, the physician should decide which among similar products should be prescribed.

Biosimilar products should be subject to initial review and oversight post-approval by the Office to which the original innovator product is assigned, rather than a separate "generics" office.

Every biosimilar product should be subject to meaningful post-marketing safety surveillance.

Interchangeability should be determined only through clinical trials adequate to support substitution of the biosimilar product for the innovator product without sacrificing safety or efficacy.

Non-patent data exclusivity should be adequate to ensure continued innovation both in new products and in new indications for existing products. Additional years of exclusivity should be provided as an incentive to development of new indications.

Legislators should extend "pediatric exclusivity" incentives to biologics in a manner consistent with those for drug products to enhance incentives for research in specific pediatric indications.

Congress should ensure that FDA is provided adequate resources to meet the new demands of assessing bioequivalence in the number of biosimilar products that will be presented to the agency once standards are in place.

H. **FDA Guidance**[42]

Scientific Consideration in Demonstrating Biosimilarity to a Reference Product: Guidance to Industry. Final Guidance April 28, 2015.

Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. Final Guidance. April 28, 2015.

Answers to Question #11:

Choice D is correct because the FDA definition of a biosimilar states that a biosimilar product must show no difference in terms of safety, purity, and potency to the reference product.

Choice A is incorrect because biosimilars are biologically based complex molecules that have a high molecular weight.

Choice B is incorrect because the +/- 20% bioavailability only applies to generic drugs – biosimilars have additional pre-clinical and clinical data requirements to demonstrate being “highly similar”.

Choice C is incorrect because biosimilars are generated from cell lines not from chemical synthesis in the lab.

VI. **Investigational Drug Services**

A. ASHP Guidelines on Clinical Drug Research[43]

Health-System Organization and Oversight

Health-system reviews and approves a protocol in the context of federal, state, and local laws. Determine appropriateness of investigational new drug (IND) application for drugs not commercially available and approved drugs for unlabeled uses.

Mechanism for review and approval for financial aspects of drug research including contractual agreements.

All clinical research is reviewed by an IRB per federal regulations. Appropriate pharmacists are members of the IRB and are consulted by the committee whenever drug studies are reviewed.

Investigational drugs are used only under the supervision of the principal investigator or sub investigators – such as pharmacists.

The principal investigator or designee is responsible for obtaining informed consent from each subject eligible for participation in a clinical trial.

The principal investigator is responsible for the proper maintenance of case report forms.

Medication-use system requirements:

- Drugs are properly packaged
- Drugs are properly labeled
- Adequate supply of study drug stock
- SOP for breaking the study drug blind when clinically warranted
- Appropriate information is provided to professional staff called on to dispense or administer investigational drugs
- Proper storage for investigational drugs
- Only authorized providers may prescribe investigational drugs
- Records are maintained for investigational drug receipt, dispensing and return to sponsor for 15 years after study closure
- Suitable arrangements are made for transfer of drug to another facility
- Platform for disseminating pharmacy records for investigational drugs to clinical investigators

ASHP-recommended Pharmaceutical Services:

Copy of IRB-approved research protocol and investigator drug brochure is maintained (including all amendments)

Pharmacy should prepare an investigational drug data sheet

When practical, investigational drugs should be stored in a pharmacy

Pharmacy shall maintain a perpetual inventory record for investigational drugs stored in the pharmacy. These records are subject to audit by the sponsor, the sponsor's representatives, or FDA.

Investigational drug services will be integrated into the medication-use system for the institution; however, labels will indicate "investigational drug". Verification that informed consent has been obtained is required.

Patient education and monitoring for investigational drugs should be explicitly spelled out.

When the study concludes, all unused investigational drug should be returned to the sponsor per their instruction.

Annual descriptive summary of investigational drug services including number of studies, list of all investigational drugs and financial records should be included.

Drug costs and other clinical care expense with drug studies should be properly allocated and reimbursed.

Investigational drugs should be stored in appropriate environmental control in a limited-access area separate from routine drug stocks and shall be inventoried on a routine basis.

Develop an SOP for handling investigational drugs provided by an investigator at a nonaffiliated practice setting.

Pharmacists must maintain the integrity of drug studies by managing access to treatment-assignment records in blinded studies.

When necessary, IDS pharmacists can delegate dispensing authority to other pharmacists within the health-system with appropriate control to maintain continuity of quality dispensing services.

Pharmacists' role for promoting adherence in investigational drug studies should be outlined.

B. ASHP Guidelines for the management of investigation drug products[44]
   1. Clinical research pharmacy models
      a. Size, scope, and staffing will depend on volume and complexity of research conducted at the institution
      b. Funding model to sustain services is required – can include direct cost recovery from the sponsor, indirect funding (e.g., overhead costs), foundation underwriting of the research, and/or the institution absorbing the costs

2. Facilities, security, and limited access
    a. Investigational study drug should be stored in a secure site as specified by the sponsor and in accordance with all applicable regulatory requirements per GCP
    b. Each institution must evaluate its ability to provide secure storage with limited access to investigational drug products
3. Temperature control and monitoring
    a. Sponsor communicates appropriate storage temperature, storage conditions (e.g., protect from light), and storage times for PI and/or clinical research pharmacies
    b. Standards from USP for controlled temperature storage should be followed by clinical research pharmacy and pharmaceutical manufacturers
    c. Allowable out-of-range temperatures and maximum allowable deviation time should be communicated from sponsor prior to opening the trial
    d. Study drug that does not meet criteria for storage as outlined by the sponsor should be quarantined and sponsor notified
    e. Study drug sensitive to humidity may require monitoring as such which would be the responsibility of the clinical research pharmacy
    f. All locations storing investigational drug (e.g., refrigerators, freezers, ambient room) require temperature monitoring with the temperature monitoring system calibrated to meet standards of National Institute of Standards and Technology
    g. Daily record of maximum and minimum temperatures must be maintained
    h. Equipment used to store investigational drug must be supported by a back-up power system
4. Site qualification
    a. Conducted by sponsor – policies and procedures should be made available to sponsor for study drug storage/dispensing procedures
    b. Sponsor written reports for site qualification should be shared with clinical research pharmacy
5. Clinical research pharmacy staff responsibilities
    a. Pre-IRB feasibility assessment for any dispensing/handling, study drug management issues
    b. Pharmacists should review protocol, investigator drug brochure, pharmacy manual
6. Pharmacist listing on Statement of Investigator
    a. Listing on Form FDA 1572 depends on the contribution of the pharmacist to the study – e.g., if the pharmacist will make a significant and direct contribution to the data or is involved in the treatment/evaluation of patients then the pharmacist should be listed. Dispensing responsibilities do not constitute criteria for listing on FDA 1572
    b. Pharmacist should be listed in the investigator study records as an individual to whom specific responsibilities have been delegated (e.g., dispensing)
7. Delegation of authority to technicians and pharmacy support staff
    a. Pharmacy technicians may be delegated tasks under institutional policy that do not require a pharmacist license
    b. Clinical research pharmacist is tasked with ensuring compliance for technician work tasks with applicable laws and regulations

8. Clinical research pharmacy staff training
    a. Pharmacy-specific training from the sponsor should take place to discuss dispensing logistics
    b. Clinical research pharmacy should provide sponsor standard operation procedures for temperature logs, drug destruction, etc. for review
    c. Pharmacy responsibilities are documented on the Delegation of Authority form signed by both the PI and pharmacist
    d. All dispensing staff should receive appropriate training for GCP and study-specific procedures
    e. Provide pharmacist CV to sponsor if they are listed on the Form FDA 1571 (Investigational New Drug Application) or Form FDA 1572 (Statement of Investigator)
9. Clinical research pharmacy study setup
    a. Creation of dispensing guidelines, model physician orders, and a template drug label are required
    b. Initiation of drug study file
    c. Any repackaging of study drug should include the statement: “Caution: New Drug – Limited by Federal (or United States) law to investigational use.”
10. Considerations for blinded studies
    a. Dispensing guidelines must be designed to maintain the blind to all appropriate personnel
    b. Minimize communication between blinded and unblinded staff
    c. Active and placebo drug products must be identical in appearance, labeling, preparation time, expiration date/time, and supplies used
    d. Unblinding process that allows treatment assignment to be determined
11. Barcoding of investigation drug products
    a. Lack of a standard system with investigational drugs
12. Investigational drug product accountability and documentation
    a. Records must identify the investigator to whom study drug is being shipped and date, quantity, and batch of such shipment
    b. Expiration date may not be provided but can be requested from sponsor
    c. Routine inventory count should be conducted
    d. Transfer of stock must be tracked
13. Investigational drug product receipt
    a. Ensure proper labeling
    b. Immediate packaging container must include: “Caution: New Drug – Limited by Federal (or United States) law to investigational use.”
    c. Maintain and process packing slip and verify against received stock
    d. Verify shipment temperature records
14. Investigational drug product dose preparation and dispensing
    a. Develop study- and site-specific dispensing guidelines
    b. Partial or empty non-hazardous vials of study drug may be stored in a designated, limited-access site
    c. Partial or empty hazardous study drug should be destroyed per institutional policies
15. Remote site or clinic dispensing
    a. Clinical research pharmacy should assess for best dispensing option

b. Physician-dispensing may be required
c. Clinical research pharmacy should perform audits of remote site

16. Investigational drug products returned from participants
    a. PI or clinical research pharmacy (per delegation from PI) may document study drug returns
    b. Hazardous drug returns should not be stored on-site – they should be destroyed per institutional standards
17. Investigational drug product final disposition
    a. Destruction on-site or returns to sponsor must be documented
    b. Hazardous drug destruction must follow all applicable regulations
    c. Controlled substances must follow DEA regulations for shipping if sent back to the study sponsor
18. Clinical research study file
    a. Create to include all necessary documentation associated with each study
    b. Retain throughout the conduct of the study and must be available for review
    c. Both sponsor-provided files (e.g., Investigator Drug Brochure) and site-prepared documents (e.g., any IRB-related communications) must be included
19. Monitoring visits or audits of the clinical research pharmacy
    a. Clinical research associate (monitor) will review records and verify accuracy of source documentation
    b. Accommodation must be made for monitor visits for blinded studies
    c. Monitor should verify drug accountability, storage conditions and drug returns
20. Monitoring visit logs
    a. Document monitoring visits and reason for visit
    b. Document any outstanding requests from the monitor
21. Study close and archiving of clinical research pharmacy study files
    a. Retain all records for 2 years following market approval or after investigation is discontinued if the drug is not approved
    b. Collaborate with PI to determine who will retain pharmacy-related records
22. Clinical research pharmacists as IRB members
    a. Any potential conflicts of interest should be disclosed
    b. Standard procurement and dispensing activities should not represent a conflict of interest for a study

C. HOPA Investigational Drug Service (IDS) Best Practice Standards[45]

Purpose

Discuss regulatory and guiding principles for medication use in human subject research

Delineate the role of pharmacy department and staff in clinical research

Outline best practices for investigational drug services for pharmacists

Establish uniform IDS practices

IDS Responsibilities

Inventory control of investigational drugs
- Study initiation
- Investigational drug acquisition
- Accountability
- Study closeout

Storage and handling of investigational drugs
- Safe handling
- Temperature monitoring

Preparation and dispensing of investigational drugs
- Labeling, blinding, protocol compliance

Disposal, destruction or return of investigational drugs

Investigational drug management
- Transferring investigational drugs between protocols
- Using patient's own investigational drugs
- Using an investigational medication from another institution

Investigational medication shortages

Inventory Maintenance

Drug accountability forms should include:
- Investigator name
- Investigator site
- Dispensing location
- Protocol number
- Full protocol title
- Medication name, strength, formulation
- Transaction types (e.g., medication receipt, dispensing, quantity, lot number, medication transfer, undispensed medication disposition)
- Initials and date of recorder
- Unused, patient returns

Policy Development

IDS should develop policies for the following:

- Tracking expiration dates of investigational drugs
- Use of computer software for investigational drugs management
- Audits
- Establishing if an investigational drug warrants hazardous drug handling precaution
- Investigational drug storage, returns and disposal
- Continuous temperature monitoring and reporting
- Establishing IDS study fees to investigators/sponsors
- Coordinating studies across multiple sites
- Mailing investigational drugs
- Use of an investigational drug from another institution
- Study closeout procedures

IDS Best Practices for Prescribing Investigational Drugs

Ensure that protocol information is sufficient for pharmacy staff at the time of prescribing

- Study protocol
- Investigator drug brochure
- Pharmacy manual
- Safety data sheets

IDS to train pharmacy and other personnel on the study team

- Training should be documented

Compile and maintain a list of qualified prescribers

Create a template of protocol-specific (including all study arms) medication order sets

- With CPOE – utilize clinical decision support when feasible
- Participate in investigational order set development
- Review and approve investigational drug order sets as part of a multi-disciplinary team

Best Practices for Dispensing and Administering Investigational Drugs

IDS facilitates the dissemination of study drug information which should include:

- Medication designation and common synonyms
- Dosage form and strength
- Pharmacology and pharmacokinetics
- Dosing range and schedule
- Preparation information
- Route of administration
- Storage information
- Dispensing information
- Administration instructions
- Monitoring parameters
- Expected therapeutic effect and adverse event profile
- Supportive care for toxicity of the study drug regimen
- Drug-drug and food-drug interactions
- Contraindications
- Special precautions for handling
- Disposal methods

Proper order review and verification by pharmacy staff

Process for verification that informed consent was obtained

Labeling procedures for IV and oral medications

Procedures for dispensing single- or double-blind studies

Administration:

- IDS should identify administration required by sponsors

Pharmacist Role in the Protocol Life Cycle for Investigational Drugs

Pharmacists should develop the medication information section of the protocol

Pharmacist should provide recommendation for supportive care in the protocol that are consistent with institutional standards

Pharmacists should participate in Scientific Review Committees

- Define who will be supplying study and commercial drug stock
- IND requirements
- Appropriateness and completeness of medication information in the protocol
- Assure clarity in the treatment and medication administration section of the protocol
- Assure clarity in the dose modification section of the protocol
- REMS is followed (if applicable)
- Reporting requirements for adverse events
- Protocol-specific order sets
- Multicenter studies – drug distribution model clearly defined

Pharmacists should participate in IRB protocol review

- Review all medication information
- Informed consent review – risks related to drug therapy – investigational or otherwise
- Risks are reasonable in relation to anticipated benefits
- Guidelines for reporting adverse events are clear
- Pharmacists serving on IRBs serve as a liaison to the pharmacy department/IDS following protocol approval

Pharmacist Best Practices for Counseling and Monitoring Investigational Drugs

Pharmacists provide medication counseling to patients receiving investigational drugs

Pharmacist should assess adherence to study drug

Pharmacists should participate in reporting of unanticipated events/adverse events

Pharmacy Technician Role

Institutions should precisely define the role of an IDS pharmacy technician

Minimum qualifications should be established for pharmacy technicians working in IDS

Pharmacy technicians' roles should be established to facilitate IDS operations

- Investigational drug preparation
- Assist with investigational drug accountability
- Monitor storage condition of study drugs
- Ordering of investigational drug supplies and manage the return process
- Assistance with monitoring visits and audit preparation

Expanded Access Study Drugs

IDS pharmacists should familiarize themselves with gaining access to expanded access study drugs

- www.clinicaltrials.gov
- NCI's Physician Desk Query (www.cancer.gov)
- NCI's Treatment Referral Center (http://ctep.cancer.gov/branches/pmb/referral_center.htm)
- Company-specific websites

IDS pharmacist should determine whether the manufacturer will make study drug available through a single-patient IND

IDS pharmacist should verify FDA and local IRB approval for use of study drug through non-emergency expanded access

IDS pharmacist should be familiar with the FDA and NCI websites regarding expanded access

- Expanded access and charging for expanded access ~~(https://www.fda.gov/news-events/public-health-focus/expanded-access~~(https://www.fda.gov/news-events/public-health-focus/expanded-access
- Treatment use: (www.fda.gov/RegulatoryInformation/Guidances/ucm126495.htm)
- Individual patient IND requests:) https://www.fda.gov/drugs/investigational-new-drug-ind-application/physicians-how-request-single-patient-expanded-access-compassionate-use)
- NCI treatment center referral: (http://ctep.cancer.gov/branches/pmb/referral_center.htm)

Question #12:

Which of the following time points is recommended for follow-up by a pharmacist for patients starting a new oral oncolytic therapy?

a. Prior to first refill
b. At consistent 6-month intervals
c. With first report of patient toxicity
d. Within 7 to 14 days following starting the drug

VII. Specialty Pharmacy

A. ASHP Specialty Resource Guide[46]

B. Definitions for Specialty Pharmacy and Specialty Pharmaceuticals:

1. Specialty pharmacy practice encompasses the provision of specialty pharmaceuticals requiring unique fulfillment and patient care support services

Elements for Specialty Pharmacy:

Fulfillment:
• Coordination of care and facilitating drug access to limited distribution specialty pharmaceuticals • Facilitating mail order delivery logistics • Negotiating payer contracts • Maintaining cold-chain distribution • Dispensing and tracking REMS drugs • Accounts receivable support/management • Program accreditation
Technical and Clinical Patient Care Support:
• Benefits investigation, prior authorization, and patient assistance program (PAP) • Call-center development, staffing, and monitoring • Case management, which may include development of protocols and disease state management at a minimum • Product device training • Data management of technical and clinical patient care services
Characteristics of Specialty Pharmacy:
• High-cost medications • Complex treatment regimens involving intensive patient education and follow-up • Special handling, storage, and delivery requirements for medications • Need for companion correlative testing for specific medications • Limited or exclusive distribution networks • Medications that treat rare diseases that may require long-term treatment and have severe symptoms • Medications defined by payers as specialty pharmaceuticals

C. Care Models

1. Traditional Patient Care:
    a. Specialty medication filled at a retail pharmacy
    b. Patient education and interaction screening provided on-site by pharmacist
    c. No use of standardized case management or education protocol
    d. No programmatic approach to ensuring adherence
2. Coordinated Care
    a. Pharmacies that focus primarily on specialty pharmaceuticals
    b. These pharmacies provide reimbursement assistance, patient care coordination, and ongoing monitoring of the patients
    c. Pharmacy is responsible for obtaining necessary and accurate paperwork from the physician office to start work on financial coverage
    d. Assistance for prior authorizations is generally offered
    e. Pharmacy likely does **not** have access to the patient medical record
    f. Pharmacy may offer help for patient assistance programs sponsored by the drug manufacturer
    g. Requires coordination between pharmacists and reimbursement specialists

3. Integrated Care
    a. Requires pharmacists deployed in a comprehensive medication management system and integrated into the primary medical care team
    b. Pharmacists are often residency trained and board-certified
    c. Collaborative practice agreement with physician groups is common
    d. Pharmacist often has a physical presence in the clinic with high-volume specialty pharmacy medications
    e. Pharmacy team collaborates to manage transitions of care between inpatient and outpatient settings
    f. Pharmacists have full access to the patient's medical record

Success Factors for integrated care model:

- Complete and timely information about the patient and services they are receiving
- Access to EMR
- Adequate resources for patient education and self-management support
- Ability to measure and report on quality of care
- Culture of teamwork between physicians and pharmacy staff

D. Specialty Pharmacy Business Models:

1. Build – development from within an organization for the entirety of special pharmacy services
2. Partner – fulfillment and patient care services provided by the entity; other services may be contracted out – e.g., call center, prior authorizations, case management, etc.
3. Outsource – contracting with a vendor to provide all or most of specialty pharmacy services
4. Manage individual patient risk – no formal specialty pharmacy program, utilization of white and or brown bagging

Specialty Pharmacy Accreditation Agencies (only 1 is required)

- ACHC (www.achc.org)
- URAC (www.urac.org) –provides accreditation services to multiple health care services including specialty pharmacy

E. HOPA Best Practices for the Management of Oral Oncolytic Therapy (2018)[47]

Prescribing:

- Patient consent, including intent of therapy should be obtained for oral oncolytic therapy.
- Pharmacists should provide a comprehensive review of new oral oncolytics and determine their place in therapy via an interprofessional formulary committee.
- When feasible, pharmacists should support oral oncolytic prescribing on an individual patient level, taking into consideration both patient- and medication-specific characteristics.
- Pharmacists should be involved in the creation of oral oncolytic templates for electronic prescribing that include all required components and any standard supportive care measures or monitoring

- Pharmacists should perform a comprehensive medication review at the time of prescription
- Oral oncolytic safety and quality standards should be consistent with intravenous treatment standards
- The oncology team should communicate the intent of oral oncolytic therapy, pertinent drug-drug interactions, and potential implications for the patient's comorbidities and management strategies to the patients' primary care provider

Education:

- Pharmacists should be involved in the development or endorsement of standardized education materials and education should be consistent across the oncology care team
- A separate education visit- in person or over the phone (virtually) should occur after the oncologist's initial prescribing visit and before the start of oral oncolytic therapy to supplement and reiterate information provided during the oncologist visit
- Education should be comprehensive and focus on patient self-care management of oral oncolytic adverse events and the importance of medication adherence
- An assessment of patient knowledge, confidence to manage adverse effects and need for follow-up should occur during the education session
- Patient and caregiver attendance at the education session is encouraged

Dispensing/Distribution:

- A dedicated medication assistance team (a non-pharmacist) should prospectively screen and provide financial support for oral oncolytic medications
- The dispensing pharmacy should have access to necessary information for safely filling the oral oncolytic medication, including laboratory values and progress notes
- The dispensing pharmacy should have access to necessary information for safely filling the oral oncolytic medication, including laboratory values and progress notes
- The dispensing pharmacy should have a dedicated liaison for the clinic and provide information that includes financial toxicities, refills, medication adherence and any identified medication adverse events
- Specialty pharmacists and oncology pharmacy organizations should partner to promote the education of oncology pharmacists and optimize oncology patient care

Monitoring/Follow-up:

- A consistent process with standardized tools should be used in the oncology clinic setting for monitoring and follow-up
- An oncology pharmacist should be involved in the creation of monitoring and follow-up materials and ideally in the assessment and monitoring of a patient's symptoms and medication adherence
- Initial monitoring of symptoms and adherence, including patent-reported outcomes (PROs), should occur between 7 and 14 days after the start of treatment
- Ongoing monitoring of symptoms and adherence including PROs should occur at each clinical encounter or at least before each refill
- Medication reconciliation should occur at each assessment point above, ideally by a pharmacist
- Adherence assessment should be user friendly, reliable, cost effective and practical

- Collaborative practice agreements, including laboratory and symptom monitoring, should exist in settings in which clinical oncology pharmacists are part of the interdisciplinary team
- Communication within the oncology team and with the patient's primary care provider should be ongoing

Practice Management:

- Oncology practices should have an oral oncolytic program with pharmacist involvement where possible
- Before oral oncolytic program development, a baseline gap assessment should be performed to assess areas for improvement and baseline performance on oral oncolytic quality measures
- Pre- and post-financial, clinical quality measures including interprofessional and patients experience should be assessed for continuous quality improvement
- Sufficient resources should be provided to meet the above quality measures

F. ASCO NCODA Patient-Centered Standards for Medically Integrated Dispensing (MID) - 2019[48]

Patient Relationships:

- Communications related to the dispensing process, whether directly with the patient or on the patient's behalf should be documented in the patient record
- Direct access for patients to the MID team is required. Patients should have access to direct phone lines and after-hours phone numbers should be available. All calls left on voicemail must be returned by the next business day.

Education:

- Prior to initiation of an oral anticancer drug, a formalized patient education session should occur with an experienced clinical educator such as a nurse, physician, pharmacist, nurse practitioner or physician's assistant. The discussion should include drug name (generic and brand), dose, schedule, potential adverse effects, and how to properly manage them, fertility (where applicable), treatment goal, duration of therapy and financial and affordability considerations.
- An informed consent form (or assent if applicable) that includes the intent of patient therapy should be reviewed by the patient (and caregiver, if applicable) with a patient educator. After signing the informed consent, the patient will receive a copy and the original document will be included in the patient record. The patient should sign the form after all questions are answered with the patient retaining a copy.
- Patient education will include review of the clinical treatment-related parameters for which the patient and/or caregiver should contact the oncology team. Emergency and secondary (non-emergent) points of contact for the patient should be established and documented in the patient record.
- At the time of initiation of any new therapy initiation, written patient education should be provided. This information should be provided in the language of preference, wherever possible and the provider should ensure that the patient understands the information contained in the written materials.
- Prescribing information required by law must be given to patients.

Adherence and Persistence:

- Calendars or other scheduling communications are helpful to maximize adherence. If provided, the calendar should include refill dates and medication schedules, clearly outlining specific dates to take medication. Include documentation of calendar information in the patient record.
- A systematic comprehensive follow-up process that is documented in the patient record within 7 days of dispensing the oral oncolytic is required. Communication to patients is an essential element of patient education to assess adherence and toxicities. Communication to patients is an essential element of patient education to assess adherence and toxicities. Communications should be tailored to presentation, specific medications, and patient comorbidities. Subsequent calls to the patient should be based on individual patient requirement and assessment of patient risk factors (education comprehension, performance status, tolerance to previous therapies, etc.). The prescriber must be notified directly when issues related to compliance are identified by the MID team.
- Pill caddies may be appropriate and helpful for patient adherence.
- Continually evaluate electronic and manual tools that may be helpful in advancing patient adherence.
- Establish a plan for assessment of adherence of patient and toxicity at each clinical encounter. Variances should be documented in the patient record.
- Adherence assessment and documentation should include (1) confirmation patient received the prescription (2) start date for the medication (3) verification that the patient understands how to take the medication, including with/without food, taking whole/crushed tablets, safe handling, etc.
- Monitoring of drug toxicity, laboratory testing and any prescription, OTC, or herbal medication changes. Contact prescriber in a timely manner to address potential problems/issues.
- Discussion of any financial issues that may be affecting adherence by the patient and assessment of the need for increased assistance.

Safety:

- Patient identity should be verified using two patient identifiers (e.g., name, date of birth, address) at the time of entering the prescription and at the time of dispensing.
- Appropriate diagnosis, allergy, correct drug/dose, and directions must be verified. The most recent provider note should be reviewed to validate treatment plan.
- Prescriptions for an oral oncolytic, either retained internally for processing or referred to an external pharmacy will be reviewed by the MID personnel for potential drug interactions or toxicity risks.
- If a patient does not pick up a prescription or accept delivery for an oncolytic, the pharmacist will notify the prescriber and verify therapy status.
- Patient profile is reviewed for duplicate therapies.
- The prescriptions should only be filled after patient education and consent forms have been completed.
- Drug interactions must be actively reviewed at each patient encounter. This includes a review of the patient record as well as a conversation with the patient about recent medication changes including OTC and/or herbal therapies.
- Do not refill medications unless verified with the prescriber and the patient.

- The MID team will verify that a toxicity evaluation and management visit with a provider has been scheduled for approximately 2 weeks after initiation of new oncolytic therapy.
- Labeling of prescriptions should follow legal labeling requirements.

Refilling of Prescriptions:

- Prior to refilling an oral anticancer drug, the MID team will review patient records for clinically relevant information (laboratory data, prescription changes, latest progress note, and cycle of therapy).
- Interventions involving a patient's refill of medication should be documented in the patient record (e.g., coordination with intravenous chemotherapy and new medications prescribed). The MID team may need to clarify this intervention with the patient and be prepared to respond to any questions the patient may ask.

Documentation:

- Every clinical encounter with a patient will be documented in the patient record. In most cases this would be an electronic medical record and questions posed by the patient will be documented as well.

Benefits Investigation:

- All aspects of benefit investigation and patient assistance will be coordinated by the MID team including prescription coverage and copay determination, copay assistance and foundation/pharmaceutical industry patient assistance programs. All patients will receive evaluation for financial support.
- Results of benefit investigation information should be documented in the patient medical record.

Medication Disposal:

- The MID will have a standard operating procedure in place to ensure the proper disposal of patients' unused medication and expired drugs.
- Patient education will include directions to ensure proper disposal of unwanted or expired medications.
- Brochures addressing proper disposal may be helpful in providing locations and addresses of local sites that accept unwanted/unused medications.

Patient Satisfaction:

- Practices are encouraged to solicit feedback from patients using surveys such as the National Community Oncology Dispensing Association patient satisfaction survey to identify and address continuous improvement opportunities at MID practices.

G. Successful Specialty Pharmacy Practice Models

1. Solid Tumor Oncology[49]
2. Hematologic Malignancies[50]

Answers to Question #12:

Choice D is correct because the HOPA best practices for oral oncolytic therapy and the ASCO/NCODA standards for medically integrated dispensing of oral oncolytics recommend 7 to 14 days and within 7 days of therapy initiation, respectively.

Choice A, B, and C are incorrect because the HOPA best practices for oral oncolytic therapy and the ASCO/NCODA standards for medically integrated dispensing of oral oncolytics recommend 7 to 14 days and within 7 days of therapy initiation, respectively.

VIII. **Role of pharmacy technicians in oncology pharmacy – ASHP/HOPA guidelines[51]**

A. Focus: Define the role and scope of the pharmacy technician in the ambulatory setting including education/training, medication compounding, dispensing/distribution, patient care services, revenue cycle optimization, supply chain management, technology/informatics, and quality improvement.

B. Education/training:
   1. Technicians must have appropriate training and credentials for medication preparation and distribution and for the performance of other functions not necessarily requiring a pharmacist's judgement.
   2. Pharmacy Technician Certification Exam (PTCE) established in 1995 but not yet required in a standard fashion
   3. Select State Boards of Pharmacy require pharmacy technicians to be licensed.
   4. A majority of State Boards of Pharmacy (80%) require pharmacy technicians to complete continuing education credits

C. Medication compounding/dispensing/distribution:
   1. USP <797> and <800> compliance and workflow management
   2. Establish best practices per standard references such as ASHP Guidelines for Hazardous Drugs

D. Patient care services:
   1. Technicians may assist in recording medication histories
   2. Assist pharmacists with monitoring patients on oral chemotherapy
   3. Assist with compliance with REMS programs
   4. Record keeping and documentation with investigational drug studies

E. Revenue cycle optimization:
   1. Obtain prior authorizations
   2. Validation of drug claims in revenue cycle
   3. Management of drug denials from insurance companies
   4. Formal program to minimize drug waste
   5. Drug inventory management
   6. Coordinate drug replacement acquisition
   7. Compliance for discarded drug waste billed through JW modifier
   8. Tracking off-label drug use for billing purposes
   9. Assist with patient assistance programs

F. Supply chain management:
   1. Drug purchasing/procurement
   2. Inventory control
   3. Drug shortage management

G. Technology/informatics:
   1. Liaison between clinical staff and informatics team
   2. Roles of technician involvement may include automation/technology systems management, policy/governance, customer service, charge integrity, reporting interface/database management, automation management new technology assessment, workflow management, and education/training

H. Quality ~~improvement:Assessment~~improvement: Assessment (QA)
   1. Environmental monitoring including engineering controls, quality of sterile product preparation and equipment monitoring
   2. Policy development and revision
   3. Training other pharmacy team members on aseptic technique, PPE and HD spill management

IX. Dose rounding – Position Statement from HOPA[52]

A. Developed by HOPA standards committee to promote uniform practice regarding dose rounding with cytotoxic and biologic antineoplastics
B. Monoclonal and biologic agents are to be rounded to the nearest vial size within 10% of the prescribed dose
C. Traditional cytotoxic agents are to be rounded to within 10% of the prescribed dose – NCI Guidelines for Auditing Clinical Trials defines a major deficiency as dose deviations greater or less than 10% which was a rationale for this recommendation. Antibody-drug conjugates are recommended to have dose rounding parameters based on this same convention.
D. The 10% dose rounding allowance is recommended for both curative-intent and palliative-intent treatment.
E. For oral chemotherapy, it is advantageous to use a single strength tablet formulation and round the final dose based on that tablet strength to avoid the risk of medication error and multiple copayments for more than one tablet strength for a single prescription.
F. Institutional standards should develop a policy-driven approach to dose rounding with anticancer agents that is endorsed by a pharmacy and therapeutics committee and/or an oncology practice leadership committee.
G. Exceptions:
   1. Clinical trials where the protocol dictates a rounding procedure that is different from institutional practice.
   2. Pharmacokinetically determined doses of anticancer treatment such as high dose busulfan used in conditioning regimens for hematopoietic stem cell transplant.
   3. Patients with poor performance status, major organ dysfunction, extensive treatment history, relevant enzyme deficiency/genetic polymorphism (e.g., DYPD and fluorouracil) or history of dose reduction for prior toxicity.

X. Patient assistance programs[53]

A. New oncology drugs (oral and IV) have patient assistance programs available through the manufacturer – contact information is typically available on the drug's website

   1. Drug stock provided by the manufacturer for free to a patient who qualifies for coverage through the manufacturer

2. Coverage of off-label use for specialty oncology drugs (e.g., use of a targeted agent for an indication for which is it not approved based on genomic sequencing results)

B. Co-pays can be a formidable cost for many patients receiving high-cost oncology drugs even with insurance; estimates predict that 1 in 4 prescriptions is not filled if the co-pay exceeds $200

C. Commonly used resources:

1. Manufacturer co-pay cards:

a. Not eligible for use for patients with government provided insurance (e.g., Medicare, Medicaid, Tricare)

b. Criticized for shunting prescriptions to higher cost drugs

c. Discount prescription programs/cards widely available (~~i.e~~i.e., Good Rx®)

2. Medicare Part D: Coverage donut hole is 25% for 2022.receding from 50% to 25% by 2020

3. Medicare Part B: 20% out of pocket expense may be picked up by a Medicare supplemental insurance plan or through a charitable foundation

Patient assistance funds

Organization	Website:
Assistance Fund	www.theassistancefund.org
Cancer Care Co-Pay Foundation	www.cancercarecopay.org
Chronic Disease Fund (CDF)	www.cdfund.org
Genentech Access to Care Foundation	www.genentech-access.com/hcp
Healthwell Foundation	www.healthwellfoundation.org
Johnson and Johnson Patient Assistance Fund	www.jjpaf.org
The Lois Merrill Foundation	wwww.thelmf.com
Leukemia and Lymphoma Society	www.lls.org
Medication Assistance Tool	www.medicineassitancetool.org
Novartis Oncology Patient Assistance Fund	www.patientassistancenow.com
National Organization for Rare Disorders (NORD)	www.rarediseases.org
Patient Access Network Foundation	www.panfoundation.org
Patient Advocate Foundation	www.patientadvocate.org/ /

XI. **Drug Shortages**

A. Impact of drug shortages for oncology drugs:[54]
   1. Survey data from HOPA membership (n=243 respondents) indicated that delays in chemotherapy treatment were reported by 93% of survey participants
   2. 85% of respondents noted a drug budget increase secondary to drug shortages
   3. 34% noted at least 1000 hours of additional labor to manage shortages
   4. Increase in near-miss events due to drug substitution (16% of respondents)
   5. Interference in conduct of clinical trials (44% of respondents)

B. Causes of drug shortages:[55]
   1. Economics for generic drug manufacturing
   2. Raw materials shortage
   3. Contaminated drug stock
   4. Stockpiling of drugs in short supply exacerbates the shortage

C. Ongoing management:[56]
   1. FDA Safety and Innovation Act (FDASIA - 2012) – requires reporting of certain drug shortages by manufacturers to the FDA (drugs that are life-supporting, life-sustaining or intended for prevention of a debilitating illness)
   2. FDASIA allows for FDA to expedite review of new or abbreviated drug applications to mitigate the shortage and to maintain an up-to-date list of drugs in short supply; an annual report on drug shortages is provided to Congress
   3. FDA has discretion to:
      a. Release product with quality issues if the issues do not present a risk to public health for drugs in short supply
      b. Work with other manufacturers to increase production
      c. Expedite review of production plant changes and upgrades
      d. Temporary importation
   4. Industry perspective on contributing factors:
      a. Compliance with current good manufacturing practice (cGMP)
      b. Production measures to ensure performance in manufacturing
      c. Resourcing for facilities and equipment
      d. Disruptions in the supply chain
   5. Potential solution for consideration
      a. More favorable reimbursement for generic drugs
      b. Flexible production capacity from manufacturers
      c. Improve efficiencies in regulatory review of manufacturing facilities
      d. Tax incentives for select medications in short supply
      e. Government support of the market to ensure a baseline demand for select drugs
      f. Consideration of market exclusivity for older generic drugs
      g. Contracting – insertion of “failure to supply” clauses that require manufacturers to compensate purchasers for supply interruptions
      h. Increasing availability of unit-of-use packaging

D. Review of current shortages:
   1. FDA - https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm

a. Available as an app for Android or iOS

2. ASHP - https://www.ashp.org/Drug-Shortages/Current-Shortages

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