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The Latest and Greatest on USP 797/800 - An Update

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Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.

Objectives

- Review the scope and purpose of USP <797> and USP <800> and identify key differences between the two chapters
- Describe proposed changes to USP <797> and USP <800> as well as timelines for implementation
- Identify challenges that pharmacies may face in implementing the new standards

USP <797> Scope

- Applies to compounded sterile preparations in all settings
- Describes conditions and practices to prevent harm from:
  - Microbial contamination (non-sterility)
  - Excessive bacterial endotoxins
  - Variability in the intended strength of ingredients
  - Unintended physical and chemical contaminants
  - Ingredients of inappropriate quality in compounded sterile products (CSPs)

USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. 2008.

USP <797> Proposed Major Changes

2008 Version	Proposed 2019 Update
Three risk levels for CSPs • **Low risk**: aseptic manipulations within ISO 5 or better hoods; combining 3 or less sterile products into a single bag/vial • **Medium risk**: combining > 3 commercial sterile drug products and those requiring complex manipulations • **High risk**: non-sterile ingredients, lack effective antimicrobial preservatives, sterile surfaces	Simplified compounded sterile preparation (CSP) microbial risk levels • **Category 1 CSPs**: *shorter* beyond-use date (BUD), may be prepared in an unclassified segregated compounding area (SCA) • **Category 2 CSPs**: *longer* BUD, must be prepared in a cleanroom suite (buffer room with ante-room)
N/A	Guidance on use of opened or punctured manufactured products and CSPs

USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. 2008. https://www.usp.org/sites/default/files/usp/document/our-work/compounding/proposed-revisions-gc-797.pdf

USP <797> Proposed Major Changes

2008 Version	Proposed 2019 Update
Section on "readying for administration"	Scope of chapter *excludes administration* of medications
Investigation in the event of: •Sterility test failure •Recovery of colony-forming units during environmental monitoring	Emphasis on conducting investigations and implementing corrective actions in specific situations such as: •Media fill failure •Personnel qualification failure •Facility certification failure •Out-of-specification results on lab tests •Quality-control check failures •Complaints indicating CSP quality issue •Adverse events
Radiopharmaceuticals as CSPs	Removal of section on radiopharmaceuticals – *Refer to General Chapter <825>*

USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. 2008. https://www.usp.org/sites/default/files/usp/document/our-work/compounding/proposed-revisions-gc-797.pdf

USP <797> Proposed Major Changes

2008 Version	Proposed 2019 Update
• Anti-neoplastics shall not be prepared as immediate-use CSPs • All personnel who compound hazardous drugs shall be fully trained in the storage, handling, and disposal of these drugs – annual verification • Storage ***preferably*** within a containment area such as a negative pressure • Facilities that prepare a "low volume" of HDs may compound in a non-negative pressure room with "two tiers of containment"	Removal of information related to handling of hazardous drugs –*Refer to General Chapter <800>*

USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. 2008. https://www.usp.org/sites/default/files/usp/document/our-work/compounding/proposed-revisions-gc-797.pdf

USP <800> Scope

- **Purpose**:
  - Describe practice and quality standards for handling hazardous drugs in healthcare settings and help promote patient safety, worker safety, and environmental protection
- Applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs
- Applies to both sterile and nonsterile products

Who is at Risk?

Anyone handling hazardous drugs is at risk of exposure[1]

- Pharmacists
- Pharmacy Technicians
- Nurses
- Physicians
- Surgeons
- Physician Assistants
- Respiratory Therapists
- Home Health Aides
- Nurses' Aides
- Housekeeping
- Janitorial Services
- Environmental Services
- Veterinarians
- Veterinarian Technicians
- Veterinarian Assistants

http://www.usp.org/sites/default/files/usp/document/our-work/healthcare-quality-safety/800-know-your-exposure-to-hazardous-drugs.pdf

Hazardous Drug Definitions

NIOSH	ASHP
Carcinogenicity	Carcinogenicity in animal models, in the patient population, or in both
Teratogenicity or 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 in 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 by hazardous criteria above	

Power LA, Coyne JW. ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm Oct 2018.

History of Hazardous Drug Guidance

- **1983-84** - ASHP Practice Spotlight: safe handling of cytotoxic drugs
- **2004** - NIOSH Alert
- **2006** - ASHP Guidelines on Handling Hazardous Drugs
- **2008** - USP 797 revision in 2008 to harmonize with NIOSH 2004 alert
- **2010** - NIOSH list of antineoplastic and hazardous drugs
- **2016 - USP Chapter 800 Hazardous Drugs—Handling in Healthcare Settings**

NIOSH List

- National Institute for Occupational Safety and Health
- 3 groups of drugs:
  - **Group 1:** *Antineoplastic* drugs
  - **Group 2:** Non-antineoplastic drugs that meet *one or more of the NIOSH criteria* for a hazardous drug
  - **Group 3:** *Reproductive risk*
- Updated every 2 years

NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2016.

Hazardous Drugs List

- Institution-specific HD list must be maintained and reviewed **annually**
- Assessment of new drugs
- Classify investigational agents based on mechanism of action
- Re-categorization as new toxicologic information becomes available
- Consider dosage form

Exposure Risk Points

http://www.usp.org/sites/default/files/usp/document/our-work/healthcare-quality-safety/800-know-your-exposure-to-hazardous-drugs.pdf

HD Receipt

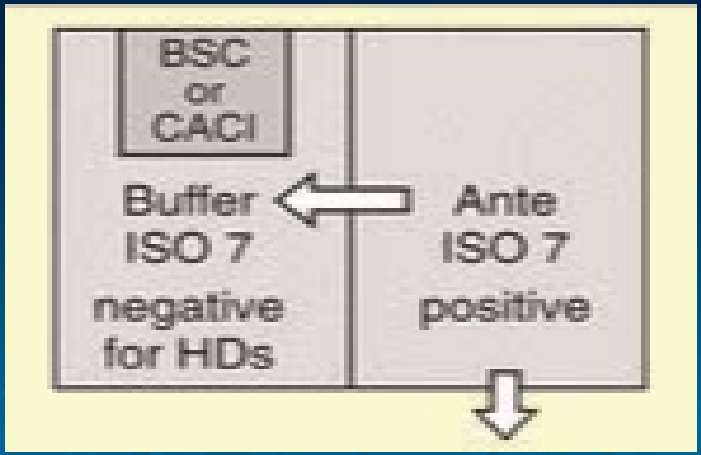
- Receive HD in sealed, impervious plastic wrap
- Handle with chemotherapy gloves
- Open in neutral or negative-pressure non-sterile area
- Immediately deliver to HD storage area

HD Storage

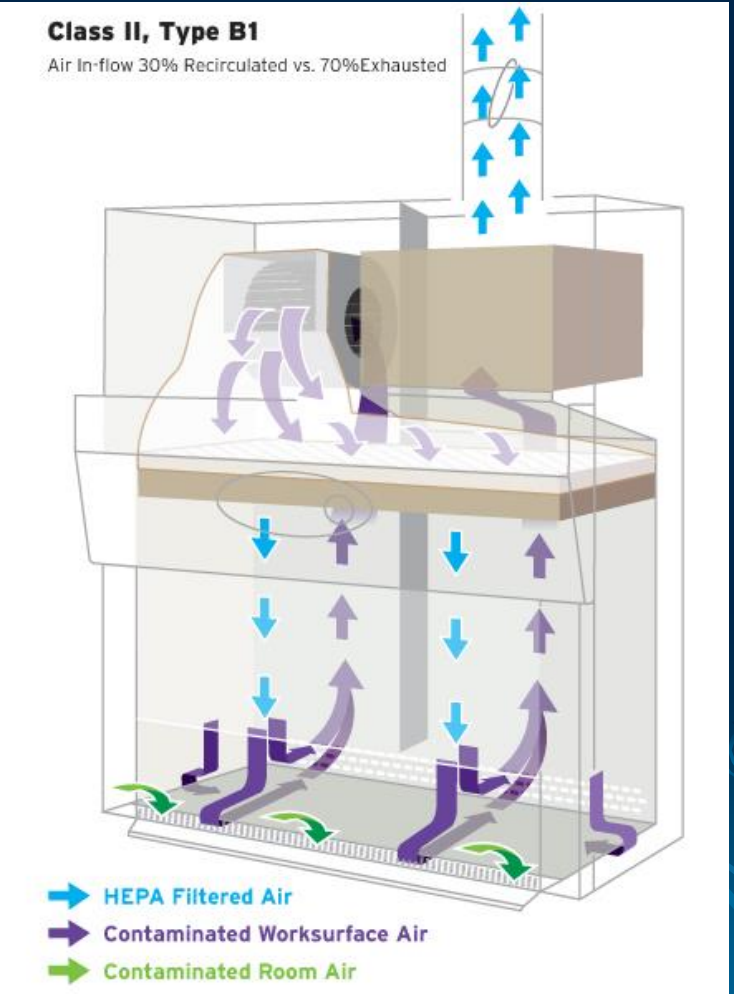
- HDs ***must*** be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH)
- Designated hazardous drug sign displayed
- Restricted access
- Antineoplastic HD requiring further manipulation stored separately
  - Dedicated storage refrigerator
- Sterile and non-sterile HD can be stored together

HD Sterile Compounding

- **Containment Primary Engineering Control (C-PEC)**
  - Externally vented
  - ISO Class 5 or better air quality
  - Biological safety cabinet (BSC)
    - Class II
    - Lined with plastic-backed mat
  - Compounding Aseptic Containment Isolator (CACI)

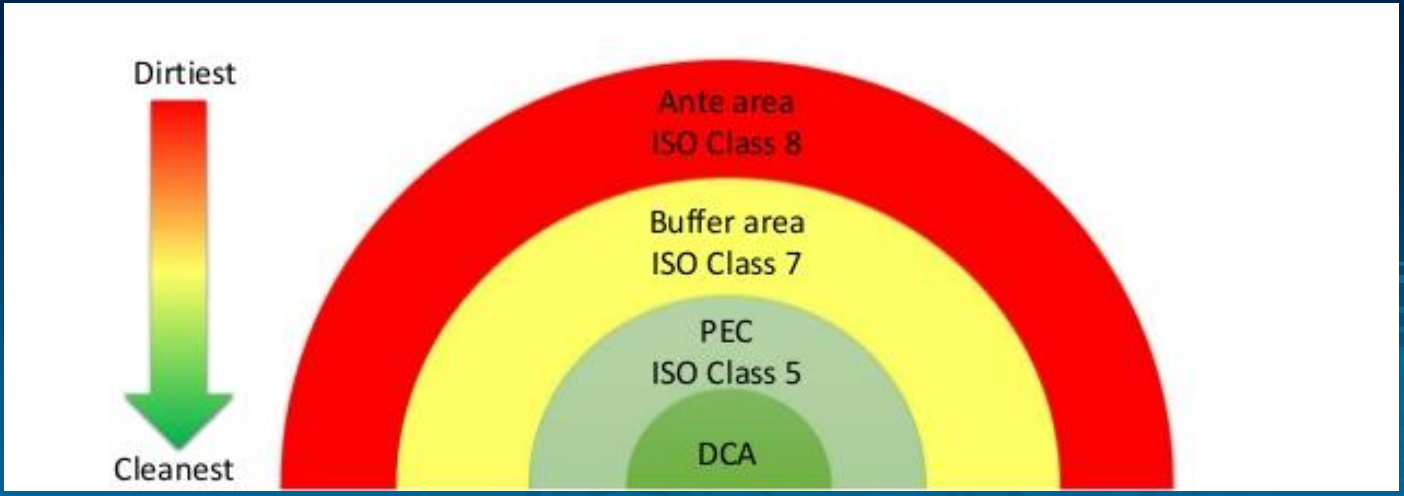


Biological safety cabinet (BSC) II



HD Sterile Compounding

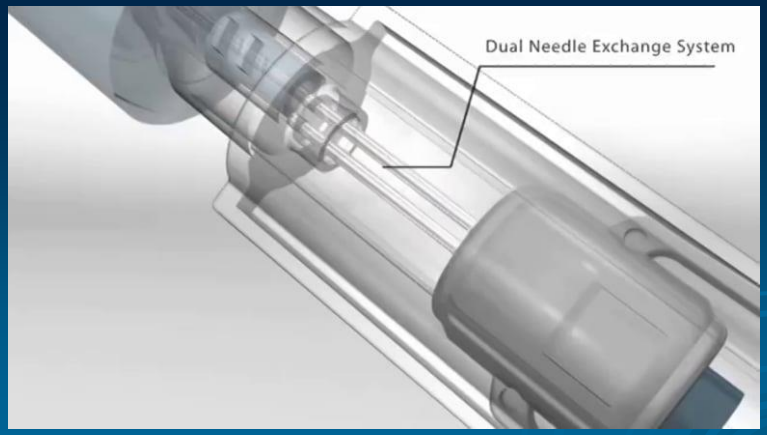
- **Containment Secondary Engineering Control (C-SEC)**
  - Externally vented
  - ISO Class 7 or better air quality
  - Negative pressure
  - HEPA filter
    - 12 or 30 ACPH



USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings

HD Sterile Compounding

- Closed-System Transfer Devices (CSTD)



HD Non-sterile Compounding

- **Containment Primary Engineering Control (C-PEC)**
  - Externally vented or redundant HEPA filtered
  - Biological safety cabinet (BSC) class I or II
  - CACI
  - Containment ventilated enclosure (CVE)
- **Containment Secondary Engineering Control (C-SEC)**
  - Externally vented
  - Negative pressure
  - HEPA filter - 12 ACPH

Environmental Quality and Control

- Environmental wipe studies for HDs *should* be performed routinely at least every 6 months
- Surface wipe sampling should include:
  - C-PEC and equipment
  - Staging or work areas near C-PEC/pass-through
  - Areas adjacent to C-PECs (floors)
  - Areas outside of buffer room and patient administration areas

Personal Protective Equipment (PPE)

- **Protection, reduce exposure to HDs aerosolization and drug residue**
- Handling all HDs: gloves
- Compounding HDs: gowns, gloves, head, hair, and double shoe covers
  - Double gloves for sterile compounding
- Administering injectable HDs: gloves and gowns

Personal Protective Equipment (PPE)

- Spills, cleaning under C-PEC work surface, suspected airborne HD exposure:
  - Chemical cartridge type respirator or powered air-purifying respirator (PAPR)
- Other activities requiring respiratory protection:
  - N95 respirator
  - No protection vs. gases/vapors and little protection vs. direct liquid splashes

Hazard Communication Plan

- Institutions must establish policies and procedures for **all aspects** of HD handling
- Elements of the plan:
  - Written plan on how the standard will be implemented
  - All containers of hazardous chemicals shall be labeled, tagged, or marked with identity of the material and appropriate hazard warnings
  - Safety Data Sheets (SDS) must be maintained for all hazardous chemical used and accessible to staff
  - Training program for staff with potential for exposure
  - Personnel of reproductive capability confirm in writing that they understand risks of handling HDs

Personnel Training

- Training prior to employee independently handling HDs and reassessed annually
- Must include:
  - Overview of the institution's list of HDs
  - Review of SOPs related to handling of HDs
  - Proper use of PPE and equipment/devices
  - Spill management
  - Response to known or suspected HD exposure
  - Proper disposal of HDs

Labeling/Packaging/Transport

- Labeling: HDs must be labeled as such
- Packaging: Use containers to maintain physical integrity, stability and sterility during transport
- Transport:
  - Use containers that minimize the risk of breakage/leakage
  - Never use pneumatic tubes to transport antineoplastic HDs

HD Dispensing

- HDs not requiring further manipulation may be dispensed without further requirements for containment, *unless*:
  - Required by manufacturer
  - Visual indicators of HD exposure
- Segregate equipment used for dispensing activities for HD

HD Administration

- HDs must be administered safely using protective medical devices and techniques
- Appropriate PPE worn when administering HDs and disposed properly
- CSTDs must be used for administration of antineoplastic HDs when dosage form allows
- Avoid manipulating HD dosage forms when possible

Deactivating, Decontaminating, Cleaning, Disinfecting

Process	Description	Agents
Deactivation	Inactivation of HD compounds	Sodium hypochlorite (Bleach) Peroxide
Decontamination	Physically remove inactivated particles	Sodium hypochlorite (Bleach) Peroxide Alcohol Water
Cleaning	Removal of organic/inorganic material	Germicidal detergent
Disinfection	Inhibit/destroy microorganisms	Sterile alcohol Disinfectant

HD Spills

- Training about proper spill kit use
- SOPs required for spill prevention and cleanup procedures (including use of PPE and respirators)
- Document circumstances of spill
- Immediate medical evaluation for potentially exposed personnel
- Non-employees exposed should report to ED for evaluation

HD Disposal

- Bulk Hazardous Drug Waste
  - >3% of the capacity of the container
  - Chemotherapy vials (empty or partially full), syringes, materials used to clean
- Trace-Contaminated Waste
  - Minimal drug (<3% total capacity)
  - Gowns, gloves, gauze, masks
  - May be incinerated at medical regulated waste facility
- Sharps
  - Needles, ampules, syringes

Medical Surveillance Program

- Should have the following elements:
  - Baseline assessment of worker's health and medical history
  - Estimate of workers HD exposure over time
  - Monitoring of organ function at risk for toxicity from HD exposure
  - Follow-up plan for acute and long-term exposure to HDs

Old vs. New HD Standards

2008 Version USP <797>	USP <800>
Storage ***preferably*** within a containment area such as a negative pressure	HDs ***must*** be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH)
Facilities that prepare a *"low volume"* of HDs may compound in a non-negative pressure room with "two tiers of containment"	All facilities that prepare HDs must have a containment secondary engineering control (C-SEC) •Must be externally vented, physically separated, have appropriate air exchange, and have a negative pressure

USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. 2008.
USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings

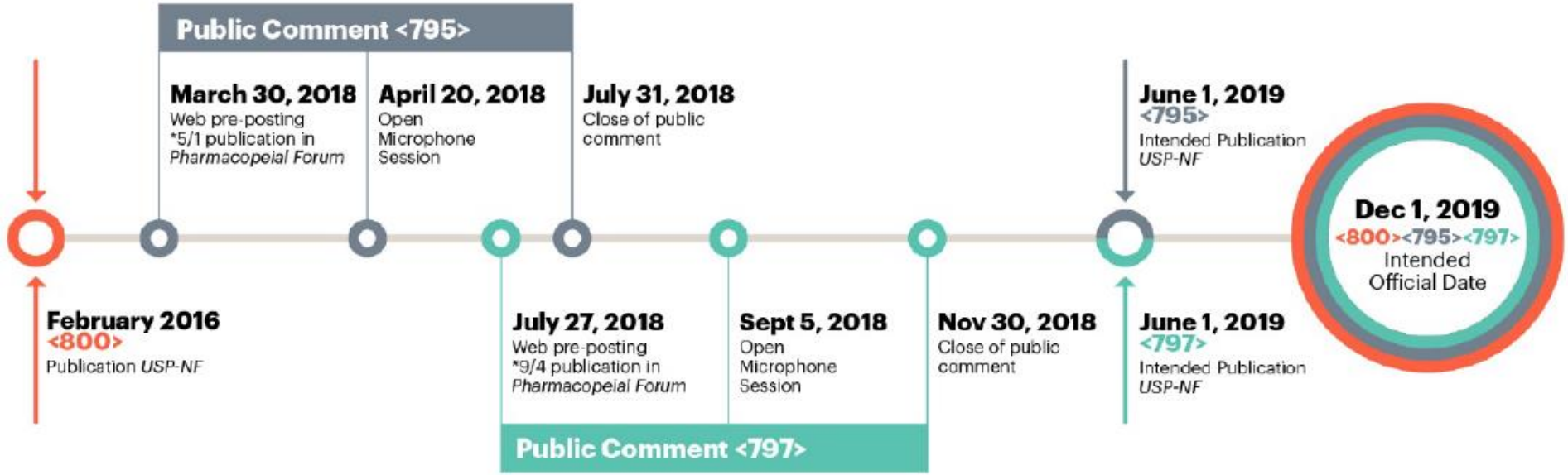
Old vs. New HD Standards

2008 Version USP <797>	USP <800>
Only allows low-risk non-HD Compounded Sterile Preparations (CSPs) with 12 hour or less beyond-use date (BUD) to be prepared in an unclassified segregated compounding area (SCA)	Allows low and medium risk HD CSPs to be prepared in an unclassified containment segregated compounding area (C-SCA) • C-SCA required to have fixed walls, be externally vented with 30 ACPH and have negative pressure

**Note differences in terminology and requirements in the SCA in USP <797> and C-SCA in <800>*

USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. 2008.
USP General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings

USP Timeline for General Chapter Revisions



Note: The current version of General Chapters <795> and <797> published in USP-NF are official.

Potential Challenges

- Financial/physical plant
  - New equipment
  - Facility design changes
  - Separation of hazardous/non-hazardous compounding
  - Storage
- Time
  - Documentation
  - More frequent environmental sampling

Potential Challenges

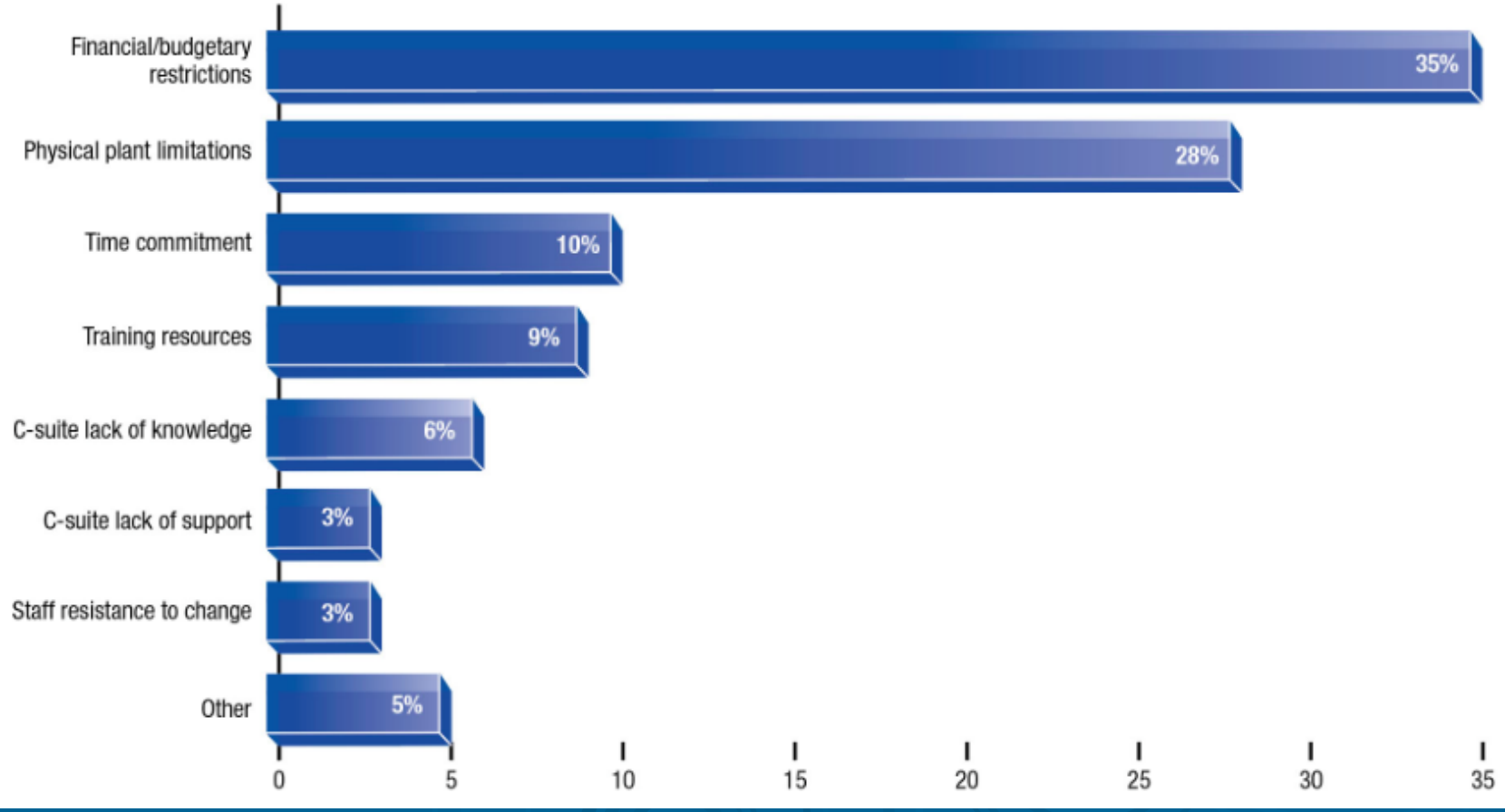
- Staff training/education
- Lack of evidence
  - Recommendations based on expert panel opinions
- Impact on low volume sites
  - Outpatient clinics, physician offices, etc.

2017 USP 797 Compliance Study

FIGURE 7

Primary Challenge to Achieving USP Compliance

Once again, hospitals find financial restrictions and physical plant limitations to be the top challenges to achieving compliance with the USP compounding chapters.



Douglass K, Kastango E, Cantor P. Pharmacy Purchasing and Products. 2017;14(10):16.

2017 USP 797 Compliance Study

TABLE 6

Compliance Rates for General Facility Design

While pharmacy has had some success in eliminating nonessential items and personnel from the compounding area, a variety of design challenges remain.

	Compliance Rate
Ceiling panels are impervious and hydrophobic; caulked around the perimeter of each to seal to frame	44%
Sink in anteroom (AR) is equipped with hands-free controls for water and soap dispensing	56%
A line of demarcation in the ante-area or SCA separates the dirty area from the clean area*	56%
Furniture, equipment, and plant surfaces are smooth and cleanable	68%
Walls are solid surface or locking panels and are impervious, cleanable, and nonshedding	74%
Floors are cleanable (heat-sealed wide sheet vinyl or other solid surface) and molding is coved	74%
Climate of buffer and anterooms is conducive to comfort (ie, 68°+/-)	83%
No sink drain or water in the buffer room	84%
Furniture, equipment, and supplies in the buffer room, AR, or SCA are limited to those essential for compounding-related activities	85%
Access to compounding areas is limited to those performing compounding-related activities	88%

*SCA=segregated compounding area

Douglass K, Kastango E, Cantor P. Pharmacy Purchasing and Products. 2017;14(10):16.

2017 USP 797 Compliance Study

TABLE 7

Environmental Sampling Compliance Rates

While overall environmental sampling is at 80%, rates for surface sampling are particularly low.

	Compliance Rates
Surface Sampling	74%
General Viable Air Sampling and Surface Sampling Considerations	75%
Environmental Sampling Program	77%
Incubation	77%
Viable Air Sampling	85%
Non-Viable Particle Testing	96%
Total Environmental Monitoring Compliance	**80%**

Douglass K, Kastango E, Cantor P. Pharmacy Purchasing and Products. 2017;14(10):16.

2017 USP 797 Compliance Study

TABLE 8

Personnel Garbing and Sampling Compliance Rates

Compliance with gloved fingertip sampling requirements has yet to pass the three-quarter mark.

	Compliance Rates
Gloved Fingertip Sampling	73%
Hand Washing and Garbing	83%
Personnel Media-Fill Challenge Testing	86%
Total Garbing and Sampling Compliance	**82%**

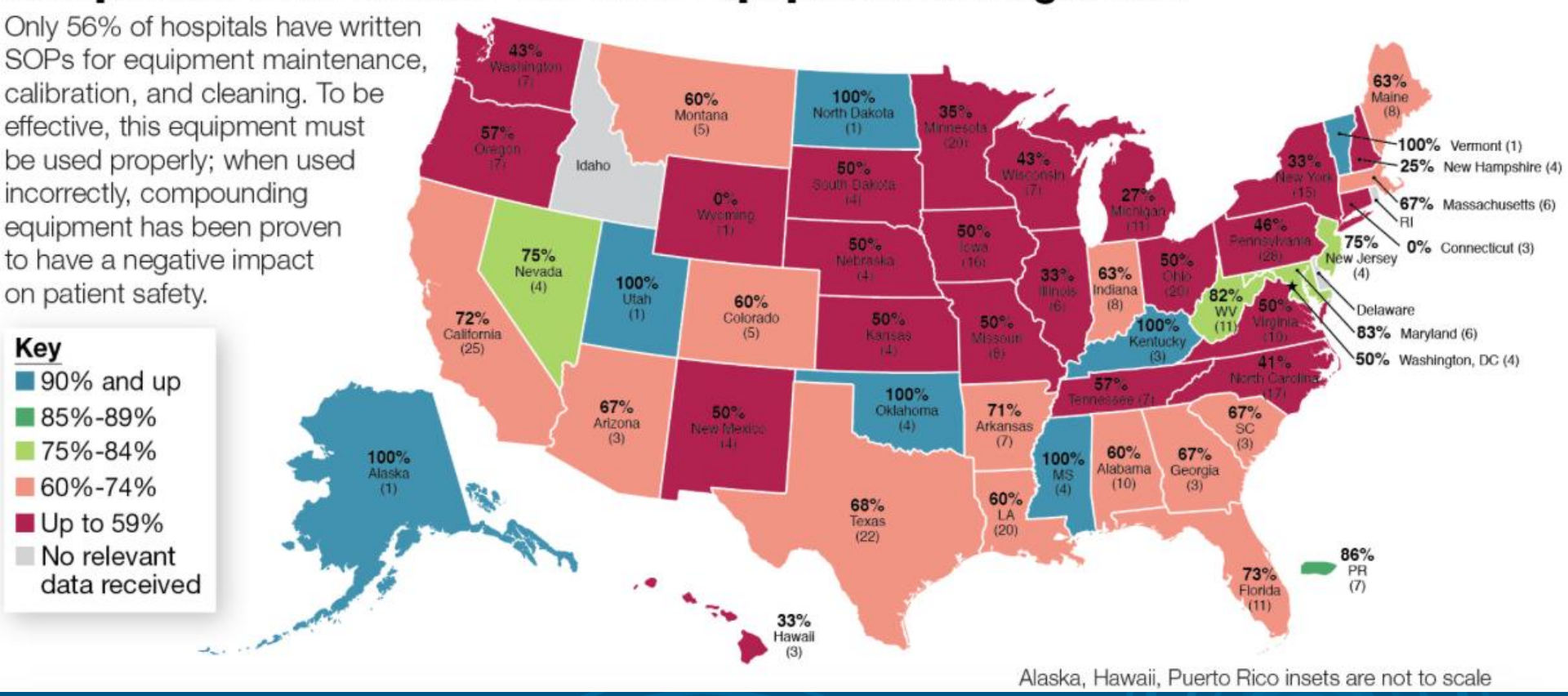
Douglass K, Kastango E, Cantor P. Pharmacy Purchasing and Products. 2017;14(10):16.

2017 USP 797 Compliance Study

FIGURE 10

Compliance with Written SOPs for Equipment Management

Only 56% of hospitals have written SOPs for equipment maintenance, calibration, and cleaning. To be effective, this equipment must be used properly; when used incorrectly, compounding equipment has been proven to have a negative impact on patient safety.



Douglass K, Kastango E, Cantor P. Pharmacy Purchasing and Products. 2017;14(10):16.

Self-Assessment

- **True/False**: USP <800> applies only to the compounding of sterile hazardous drugs
- **True/False**: USP <797> and USP <800> updates are anticipated to become official on December 1, 2019
- **True/False**: The most common challenge to achieving USP compliance has been identified to be financial restrictions

Summary

- USP 797 sets sterile compounding standards vs. USP 800 sets hazardous drug handling standards
- Updated versions will be enforceable **December 1, 2019**
- Institutions should determine readiness to meet standards ***early***
- Some standards will require significant investment of ***time and money***

References

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