2022 USP Revisions
Chapters <795> & <797>

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Disclosures

- No conflicts to declare
- No ELDU or antimicrobial discussion

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Objectives

Pharmacists

- To outline the newest revisions to USP <795>, <797>
- To apply the newest revisions of USP <795> and <797> to your pharmacy practice
- To understand and be able to restate the newest revisions to USP <795> and <797>, as well as some of the reasoning to these changes

Pharmacy Technicians

- To recognize USP guidelines and their role in your pharmacy practice
- To employ the newest guidelines outlined in USP chapter revisions related to beyond-use dating
- To explain the importance of following USP guidelines in a veterinary setting

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Outline

1 USP <795>

Pharmaceutical Compounding – Nonsterile Preparations

2 USP <797>

Pharmaceutical Compounding – Sterile Preparations

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USP <795>

Pharmaceutical Compounding – Nonsterile Preparations

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Overview for <795> Revisions

1 Brief History

2 Training

3 Beyond-Use Dating

4 Documentation

5 Facility & Equipment

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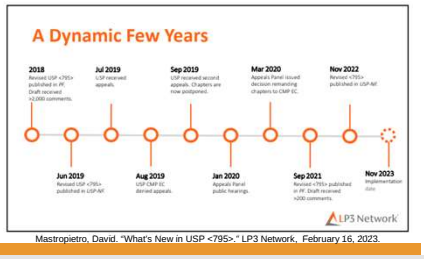
Brief History of USP <795>



Mastropietro, David. "What's New in USP <795>." LP3 Network, February 16, 2023.

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Training

- Previous versions stated:
  - Individual compounders are responsible for ensuring that each compounding incidence meets criteria for a finished preparation
  - Personnel should be appropriately trained, capable and qualified
    - Responsibility of each individual
    - Annual evaluation

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Training – 2022 Revision

(1) Designated Person(s): the person *responsible* and *accountable* for the performance and operations **of the facility and personnel**

(2) Personnel *must be* initially trained and demonstrate competency
- Training must include: understanding of USP chapter; understanding & interpreting safety data sheets and certificates of analysis; procedures related to compounding duties
- Mandatory annual refresher training and competency
- All training and competency must be documented!

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Training - Core Competencies

- Personnel *must* be proficient in:
  - Hand hygiene
  - Garbing
  - Cleaning & sanitizing
  - Handling & transporting components and preparations
  - Measuring & mixing
  - Proper selection & use of equipment and devices
  - Documentation

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Beyond-Use Dating

2014 Version

BUD recommendations based on water presence and route of delivery, *in the absence of stability information*.

2022 Revision

BUD limits are decided based on water activity and presence of preservative, *in the absence of a USP-NF monograph or stability information*.

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Water Activity

$$Water\ Activity\ (a_w) = \frac{Vapor\ pressure\ of\ test\ product}{Vapor\ pressure\ of\ pure\ water}$$

a_w of pure water = 1.0

The lower the a_w, the lower amount of free water and lower likelihood of API degradation or rate of microbial proliferation

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Determining Water Activity

No requirement to measure a_w of each product

- BUT, must compare to most similar dosage form of manufactured products in Table 2 of USP <1112> and Table 3 of USP <795>

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USP <795> Table 3

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Preservative

Compounded products with a_w > 0.6 should have adequate antimicrobial protection against bacteria, yeast and mold

→ If unable to add preservatives, *a lower BUD and refrigeration are required*

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Beyond-Use Date Limits

Type of Preparation	BUD (days)	Storage Temperature
Aqueous Dosage Forms ($a_w \geq 0.6$)		
Non-preserved	14	Refrigerated
Preserved	35	Room temperature or refrigerated
Non-aqueous Dosage Forms ($a_w < 0.6$)		
Oral liquids (non-aqueous)	90	Room temperature or refrigerated
Other	Up to 180	Room temperature or refrigerated

These BUDs are only in the absence of a USP-NF Compounded Preparation Monograph or CNSP-Specific Stability Information

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Extending BUDs

2014 Version

Compounders may extend a BUD with specific information on stability, compatibility and degradation of ingredients

2022 Revision

A BUD may only be extended with:

1. Stability information
2. Specification of the material of composition of the container closure
3. Testing for antimicrobial effectiveness

→ only up to a MAXIMUM of 180 days

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Documentation

Written or electronic documentation to demonstrate compliance with this chapter must:

- Comply with all laws & regulations of the applicable regulatory jurisdiction
- Be readily retrievable for 2 years or as required by local laws (whichever is longer)

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Required Documentation Items

- Training, competency assessments, and qualification records (including corrective action)
- Equipment records
- COAs & all documentation for components
- SOPs, master formulation records, compounding records
  - Release inspection and any testing records
- Adverse events, complaints or any corrective action
  - Results of investigations
- Cleaning records, temperature logs
- Accommodations to personnel compounding
- Any required routine review (e.g. annual review of QA/QC, hazard information, etc)

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Facility & Equipment

Compounding Area

- Non-sterile area separated from both sterile and hazardous areas
- Well-lighted, NO CARPETS
- Temperature monitored and documented at least once a day

Minimum Cleaning Frequency

- Work Surfaces: beginning & end of each shift, after spills, or known/suspected contamination
- Floors: daily, after spills, or known/suspected contamination
- Shelves: every 3 months, after spills, or known/suspected contamination
- Walls/Ceilings: when visibly soiled or known contamination

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Facility & Equipment

Closed System Processing Device (CSPD)

- *Not* carved out in previous revisions
- For activities resulting in powder generation, a CSPD that includes a containment ventilated enclosure (CVE) and biological safety cabinet (BSC) is recommended
  - → The pharmacy must perform a powder generation assessment to determine the need for CSPD

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Facility & Equipment

Compounding Components

- Upon receipt:
  - Perform visual inspection
  - Verify COA
  - Document date, quantity, supplier name, lot number, expiration, results or testing
  - Reject components of unacceptable quality

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Learning Assessment

Who is responsible for ensuring the performance and operations of the compounding facility and personnel?

a. The designated person.
b. Each individual is responsible for their own training and performance.
c. The pharmacist in charge.
d. The hospital administration.

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Learning Assessment

Who is responsible for ensuring the performance and operations of the compounding facility and personnel?

a. **The designated person.**
b. Each individual is responsible for their own training and performance.
c. The pharmacist in charge.
d. The hospital administration.

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Learning Assessment

According to the 2022 Revision of USP <795>, beyond-use dates are determined based on water activity and the presence of preservative. In the absence of a USP-NF monograph or stability information, assign the appropriate beyond-use date for each item below:

a. Capsules:
b. Non-preserved, aqueous dosage form (a_w > 0.6):
c. Preserved, aqueous dosage form (a_w > 0.6):
d. Non-aqueous (a_w < 0.6) oral liquid:

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Learning Assessment

According to the 2022 Revision of USP <795>, beyond-use dates are determined based on water activity and the presence of preservative. In the absence of a USP-NF monograph or stability information, assign the appropriate beyond-use date for each item below:

a. Capsules: up to 180 days
b. Non-preserved, aqueous dosage form (a_w > 0.6): 14 days
c. Preserved, aqueous dosage form (a_w > 0.6): 35 days
d. Non-aqueous (a_w < 0.6) oral liquid: 90 days

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USP <797>

Pharmaceutical Compounding – Sterile Preparations

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Overview for <797> Revisions

1 Brief History
2 Basics
3 Product Classification
4 Requirements
5 Facility & Equipment
6 Beyond-Use Dating
7 Quality Assurance & Control
8 Documentation
9 Allergenic Extracts

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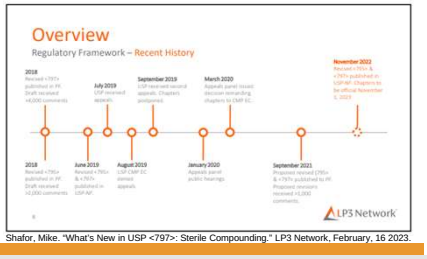
Brief History of USP <797>



Shafor, Mike. "What's New in USP <797>: Sterile Compounding." LP3 Network, February, 16 2023.

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USP <797>– Purpose

- To prevent harm resulting from:
  - Microbial contaminants
  - Excessive endotoxins
  - Variability in intended strength of correct ingredients
  - Unintended contaminants
  - Ingredients of inappropriate quality
  - Physical or chemical incompatibilities
- Proviso for other non-inferior methods

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USP <797>– Basics

Dosage forms that MUST be sterile:

- Injections
- Irrigations for internal body cavities (except mouth, rectal, sinus)
- Ophthalmics
- For pulmonary inhalation (except local application to nasal area)
- Baths and soaks for live organs and tissues
- Implants

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Personnel & Settings Affected

Previous Version	2022 Revision
Personnel = Pharmacists, nurses, pharmacy technicians, physicians • All who prepare, store and transport CSPs	→ Personnel Added: **Veterinarians**, dentists, naturopaths, chiropractors • Anyone who enters a sterile compounding area
Settings = Hospitals, other healthcare institutions, patient treatment clinics, pharmacies, physicians' practice facilities	→ Settings Added: Infusion facilities, **veterinarian's practice sites**

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Compounded Sterile Product Categories

Previous Version

Low-, medium-, high-risk, and immediate use

- Dependent on microbial risk level
  - Dependent on the components and difficulty of procedures involved

2022 Revision

Category 1, 2, 3 + an exception for immediate-use

- Category determined by location where compounding occurs & probability of microbial growth
- Dictates testing (surface & environmental, particulate-matter & stability & release), beyond-use dating, and frequency of competency assessments

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Immediate-Use CSP Criteria

1. Aseptic technique must be followed with sterile SOPs in place
2. Preparation according to evidence-based information for physical & chemical compatibility
3. Involves ≤ 3 different sterile products
4. Components from single-use containers are only used for 1 patient
   a. Any unused portion MUST be discarded
5. Administration MUST begin within 4 hours of starting preparation
6. Must be labeled unless the CSP is administered or administration witness by person who prepared it

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Category Breakdown

Category 1	Category 2	Category 3
Least controlled environmental conditions	More environmental controls & testing than Category 1	Sterility Testing Supplemented by endotoxin testing (when applicable) More qualification, garbing, cleaning & monitoring requirements than Category 2

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Beyond-Use Dating

Stability Factors

- Chemical and physical properties of the drug and/or its formulation
- Compatibility of the container-closure system with the finished preparation

Sterility Factors

- Preparation environment
- Aseptic preparation
- Sterilization method
- Components and ingredients
- Sterility testing
- Storage conditions (packaging, temperature)

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Beyond-Use Dating

Type of Container	Time within which product MUST be used
Single-dose	Up to 12 hours (if opened in ISO Class 5)
Multiple-dose (preserved)	Up to 28 days (if supported by <51> testing)
Multiple-dose (non-preserved, aqueous topical, and topical ophthalmics)	After first opening = • 24 hours (room temperature) • 72 hours (refrigerated)
Pharmacy Bulk Package	As specified by manufacturer

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Category 1

Facility Configuration		Type of Compounding	Controlled Room Temp. (20-25°C)	Refrigerated (2-8°C)
Unclassified SCA	PEC	Non-HD	≤ 12 hours	≤ 24 hours
Unclassified C-SCR	C-PEC	HD	≤ 12 hours	≤ 24 hours

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Category 2

Preparation Characteristics		Storage Conditions		
Method	Sterility Test Performed and Passed?	Controlled Room Temp. (20-25°C)	Refrigerated (2-8°C)	Frozen (-25 - -10°C)
Aseptically Processed	Test not performed	1 Day	4 Days	45 Days
		4 Days	10 Days	45 Days
	Yes	30 Days	45 Days	60 Days
Terminally Sterilized	Test not performed	14 Days	28 Days	45 Days
	Yes	45 Days	60 Days	90 Days

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Category 3

Compounding Method	Controlled Room Temp. (20-25°C)	Refrigerated (2-8°C)	Frozen (-25 - -10°C)
Aseptically processed	60 Days	90 Days	120 Days
Terminally sterilized	90 Days	120 Days	180 Days

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Personnel

Competency Objectives

- Hand hygiene & garbing
- Cleaning & disinfection
- Calculations, measuring, admixing
- Aseptic technique
- Equipment use
- Documentation
- Proper use of PECs
- Principles of HEPA-filtered unidirectional airflow and movement of materials/personnel within compounding area

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Personnel Training

Previous Version

- All training must be completed and documented
- Training completed by skilled personnel
- Should include: didactic training, written competence assessment, observed skill assessment, media-fill testing

2022 Revision

- Training must be completed and demonstrated before preparing CSPs independently
- Requalification every 12 months
  - All core competencies
  - Via written testing
- Training program must be developed
  - Required training & frequency, as well as evaluation processes

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Practical Skills Competency Evaluations

Hand Hygiene & Garbing

- Successful 3 times in succession
- Requalification
  - Category 1 & 2: every 6 months
  - Category 3: every 2 months
- Incubation using TSA media with neutralizing additives
  - 30-35°C ≥ 48 hours
  - 20-25°C ≥ 5 additional days
  - *Failure = presence of turbidity or growth
- Must be documented

Aseptic Manipulation

- Requalification
  - Category 1 & 2: every 6 months
  - Category 3: every 3 months
- Incubation using SCDM
  - 20-25°C for 7 days
  - 30-35°C for 7 additional days
  - *Failure = presence of turbidity or growth
- Must be documented

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Personnel Requirements

Hygiene

- Self-report conditions that may increase risk of contamination
- Before entering compounding area, must:
  - Remove outer garments, cosmetics, jewelry, electronics & accessories
  - Wipe glasses
- No air dryers for hand hygiene

Garbing

- Facility determines order of garbing (documented in SOP)
- Sterile gloves donned in classified room or SCA, sanitized with sterile 70% isopropyl alcohol before entering ISO class 5 PEC
- *Donning & doffing garb in the anteroom or SCA must NOT occur at the same time!

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Facility Requirements

Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD CSPs

PEC Type	Device Type	Placement for Compounding Category 1 CSPs	Placement for Compounding Category 2 & Category 3 CSPs
LAFS	LAFW	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure anteroom
	IVLFZ	CANNOT BE USED in an unclassified area	
	BSC	Unclassified SCA	
RABS	CAI or CACI	Unclassified SCA	
Isolator	Isolator	Unclassified SCA	ISO Class 8 positive pressure room

Shafor, Mike. "What's New in USP <797>: Sterile Compounding." LP3 Network, February, 16 2023.

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Cleanroom Layouts

Shafor, Mike. "What's New in USP <797>: Sterile Compounding." LP3 Network, February, 16 2023.

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Facility Requirements

- Minimum differential pressure between each ISO classified area: 0.02-inch water column
- ACPH requirements (ante- & buffer room HVAC contributes ≥ 15 ACPH each)
  - ISO Class 8 (anteroom): ≥ 20 ACPH
  - ISO Class 7 (buffer room): ≥ 30 ACPH
  - SCA: no requirement
- Pre-sterilization activities must be completed in an ISO Class 8 or better
- Monitor temperature & humidity on days when compounding is completed
  - Temperature: ≤ 20°C
  - Humidity: ≤ 60% relative humidity
  - *Devices verified for accuracy at least every 12 months
- Designated person ensures ISO Class 5 areas appropriately certified

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Facility Certification

- Frequency:
  - Initially
  - At least every 6 months
  - Upon redesign, construction, replacement or relocation, etc.
- What:
  - Airflow and pressures
  - HEPA filter integrity
  - Total airborne particle count
  - Smoke visualization
- Corrective action to be implemented and documented if required

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Equipment & Supplies

- Standards for equipment are similar to previous revision
  - However, accuracy must be assessed before first use and for each day the equipment will be used
- Supplies were not mentioned in previous versions
  - New revision states that supplies should be non-reactive, non-sorptive, sterile and de-pyrogenated
  - If re-usable, must be disinfected and de-pyrogenated before re-use

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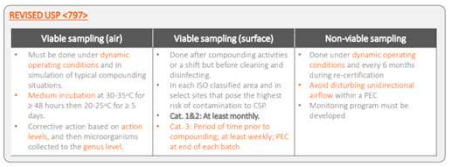
Environmental Sampling



REVISED USP <797>

Viable sampling (air)	Viable sampling (surface)	Non-viable sampling
• Must be done under dynamic operating conditions and in simulation of typical compounding situations. • Medium incubation at 30-35°C for ≥ 48 hours then 20-25°C for ≥ 5 days. • Corrective action based on action levels, and then microorganisms collected to the genus level.	• Done after compounding activities or a shift but before cleaning and disinfecting. • In each ISO classified area and in select sites that pose the highest risk of contamination to CSP. • Cat. 1&2: At least monthly. • Cat. 3: Period of time prior to compounding, at least weekly; PEC at end of each batch	• Done under dynamic operating conditions and every 6 months during re-certification • Avoid disturbing unidirectional airflow within a PEC • Monitoring program must be developed

Shafor, Mike. "What's New in USP <797>: Sterile Compounding." LP3 Network, February, 16 2023.

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Cleaning Schedule

Site	Clean	Disinfect	Sporicidal
ISO Class 5 PEC and equipment inside the PEC	Daily when compounding, and when contaminated.		Category 1 & 2 CSPs = Monthly. Category 3 CSPs = Weekly.
Removable work tray of the PEC, when applicable	-Surface of tray daily. -All surfaces and area under tray monthly.		-Surfaces of tray monthly. -All surfaces and area under tray monthly.
Pass-through(s), work surfaces outside PEC, Floors	Daily on when compounding.		Category 1 & 2 CSPs = Monthly. Category 3 CSPs = Weekly.
Sinks	Each day of use.		At least monthly.
Walls, doors, door frames, ceilings, storage shelving and bins, equipment outside PEC	Monthly		Monthly

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Cleaning Supplies & Agents

Previous Version

- Cleaning tools must be cleanable
- Cleaned before and after use
- Low-linting, preferably synthetic microfiber
- One floor mop may be used for buffer room/area and ante-area is moving from clean to dirty area

2022 Revision

- If reusable, *must* be cleanable
  - Wipers, sponges and mop heads *should* be disposable
- Low lint
  - No reference to material
- One floor mop may be used in both the buffer and anteroom, but only in that order
  - Dedicated mop for HD areas
- Disinfecting agents inside ISO Class 5 PECs must be sterile

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Sourcing Components - Previous

- Preferably complies with official USP-NF monographs, if they exist
- Accompanied by certificate of analysis (COA) from supplier
- Inspect for broken containers, looseness of caps or closures and deviation from appearance
- Mark date of receipt and expiration date
- Maximum 1 year from date of receipt if it is not supplied by the vendor
- Store according to manufacturer in an controlled and monitored environment
- Temperature, humidity and lighting

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Sourcing Components - 2022

- Conventionally manufactured sterile products should be used when appropriate
- All components must comply with USP-NF monograph, if it exists
- APIs must be obtained from FDA-registered facilities (USA)
- Containers and closures must be sterile and de-pyrogenated
- Must be accompanied by COA from supplier
  - Verify labeling and condition of components
  - Temperature sensor and other damages
  - If unacceptable, component is rejected and segregated before appropriate disposal
- Same recommendations for storage and expiration dates

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Component Sterilization

- Terminal sterilization preferred over filtration
  - Steam heat, dry heat, irradiation
- Guidelines for selecting method of sterilization
  - Considerations include physical and chemical stability, packaging integrity
  - Details in performing sterilization (e.g. temperature, duration, indicators)
- Sterilization procedures must be monitored, verified and documented

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Release Testing

Sterility Testing

- Required for:
  - Category 2 CSPs applying maximum BUD limits
  - All Category 3 CSPs
- How:
  - According to USP <71> or non-inferior validated alternative method
  - Method preferred: membrane filtration

Endotoxin Testing

- Required for:
  - Category 2 CSPs (Made from one or more non-sterile component AND assigned BUD requiring sterility testing)
  - All Category 3 CSPs
  - Does not exclude inhalations and topical ophthalmics
  - For injectables: presence of 1 non-sterile component should undergo endotoxin testing (even if it does not require sterility testing according to BUD requirement)

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Labeling Requirements

- Assigned internal identification number (e.g. order or lot number)
- Active ingredient(s) and their amounts, activities, or concentrations
- Storage conditions if other than controlled room temperature
- BUD
- Route of administration, if not obvious from the container or when necessary for the safe use of the CSP
- Total amount or volume
- If it is a multiple-dose container, a statement indicating so
- Indication that the preparation is compounded

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Quality Assurance & Quality Control

Previous Version

- Mandates QA program formalized in writing with objective, measurable indicators
- Reassessed annually
- States standards for complaint handling

2022 Revision

- Clearly differentiates between quality assurance (QA) and quality control (QC)
  - QA: system of procedures (SOPs)
  - QC: procedures/activities
- Reviewed annually by designated person
- Added for complaint handling
  - CSP recalls to determine severity of problem, distribution and reconciliation

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Documentation: SOPs

Previous Version

- List of 23 recommended SOP topics
- SOPs must be
  - Written
  - Properly approved
  - Designed to ensure quality of environment for preparing CSPs

2022 Revision

- USP 797 provided 32 explicit references to specific facility-related SOPs.
- Two distinct categories of SOPs:
  - Compounding processes
  - Support activities
- Designated person
  - Only one who can make changes
  - Ensure that SOPs are implemented
  - Review SOPs at least annually

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Master Formulation Records

- Required for:
  - All CSPs prepared from nonsterile ingredients
  - CSPs prepared for more than 1 patient

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Master Formulation Records

- Components:
  - Name, strength or activity, and dosage form of CSP
  - Identities and amounts of all ingredients
  - Type and size of container-closure system(s)
  - Complete instructions for preparing the CSP
  - Physical description of the final CSP
  - BUD and storage requirements
  - Reference source(s) to support the stability of CSP
  - Quality control procedures (e.g. pH testing)
  - Sterilization method (e.g. steam, dry heat)
  - Other information needed to ensure repeatability
  - Separate MFRs must be created for each size of batch
  - Must be created before compounding

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Compounding Records

- Required for:
  - All Category 1, 2 and 3 CSPs
  - Immediate-use CSPs prepared for more than 1 patient

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Compounding Records

- Components:
  - Name, strength or activity, and dosage form of CSP
  - Date and time of preparation of the CSP
  - Assigned internal identification number (e.g. prescription, order, or lot number)
  - Method to identify individuals involved in compounding and verifying
  - Each ingredient name, manufacturer, lot number, and expiration date for each ingredient
  - Weight or volume of each ingredient
  - Strength or activity of each component
  - Total quantity compounded
  - Assigned BUD and storage requirements
  - Results of QC procedures
  - If applicable, must also include:
    - Master Formulation Record reference for the CSP
    - Any calculations

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Allergenic Extracts

Previous Version

- Exempted from requirements of sterile compounding if specific conditions are met
- Conditions similar to the preparation of low-risk CSPs

2022 Revision

- Requirements set for facility, personnel, preparation, techniques, labels, shipping and documentation
  - More stringent than existing chapter but less than CSPs
- Requires preparation in ISO Class 5 PEC or AECA (allergen extract compounding area)
- Mandates specific personnel training
- Designated person with expertise in allergen immunotherapy must be trained

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Learning Assessment

When do the updated revisions to USP <795> and <797> go into effect?

a. 6 months after initial publication
b. November 1, 2023
c. January 1, 2024
d. Whenever the regulatory bodies decide

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Learning Assessment

When do the updated revisions to USP <795> and <797> go into effect?

a. 6 months after initial publication
b. **November 1, 2023**
c. January 1, 2024
d. Whenever the regulatory bodies decide

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Implementation date: November 1, 2023

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Resources

- USP Healthcare Quality and Safety Standards
  - Sign up for updates: https://www.usp.org/hqs-signup-form
- Medisca/LP3 Network
  - Database for water activity (of Medisca bases), stability-indicating studies, SOPs; free lectures and seminar trainings (live and asynchronous)
  - Website: https://www.lp3network.com/
- ASHP
  - Helpful resources and training modules
    - *Highly recommend the "Key Changes" documents—short & sweet side-by-side comparison
  - ASHP.org

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Thank you!

Questions?

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