UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

An Overview of USP <795> and Updates in Nonsterile Compounding Standards

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Disclosure

- **Relevant Financial Conflicts of Interest**
  - **CE Presenter, Travis Miller:**
    - No relevant conflicts of interest exist
  - **CE Mentors, Ashley Bowden, Stephen Andrews, Amanda Woods:**
    - No relevant conflicts of interest exist
- **Off-Label Uses of Medications**
  - This presentation will not include off-label uses of medications

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Learning Objectives – Pharmacists

At the conclusion of this activity, participants should be able to successfully:

- Apply USP <795> standards for an appropriate nonsterile compounding environment
- Identify compounding ingredients that are acceptable for use in nonsterile preparation, as well as common ingredients that can have adverse effects in certain patients
- Use new stability and beyond-use dating requirements for nonsterile compounding products

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Learning Objectives – Technicians

At the conclusion of this activity, participants should be able to successfully:

- Classify the different categories of nonsterile compounding
- Compare the types of equipment used for nonsterile compounding
- Outline documentation requirements for nonsterile compounding

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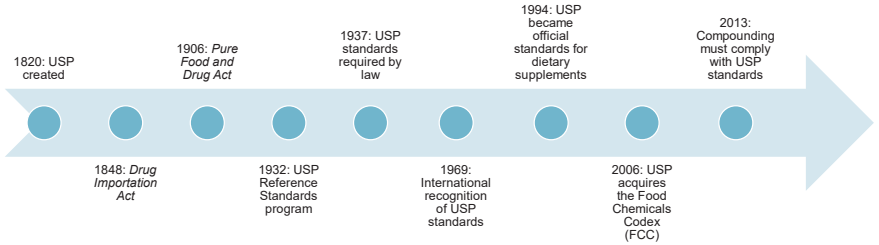
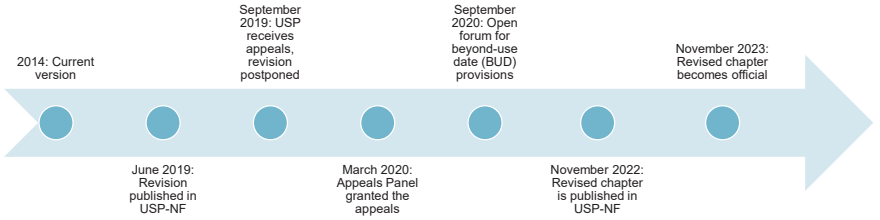
Timeline of United States Pharmacopeia (USP)



USP Timeline. Accessed January 31, 2023. https://www.usp.org/200-anniversary/usp-timeline. 6

Timeline of USP <795>



USP General Chapter 795 | USP. Accessed February 15, 2023. https://www.usp.org/compounding/general-chapter-795. 7

What is USP <795>?

- Standards for compounding quality nonsterile preparations
- Applies to formulations for humans and animals
- Focused on acceptable strength, quality, and purity
- Those engaged in compounding should comply with state and federal laws and regulations

General Chapter: USP. <795> Pharmaceutical Compounding—Nonsterile Preparations. In: USP–NF. May 1, 2020. DOI: https://doi.org/10.31003/USPNF_M99595_05_01. 8

Scope of <795>

- Required:
  - Solid oral preparations
  - Liquid oral preparations
  - Rectal preparations
  - Vaginal preparations
  - Topical preparations
  - Nasal and sinus preparations
  - Otic preparations
  - Reconstitution
- Not Required:
  - Nonsterile radiopharmaceuticals
  - Reconstitution
  - Repackaging
  - Splitting tablets
  - Administration

General Chapter: USP. <795> Pharmaceutical Compounding—Nonsterile Preparations. In: USP–NF. Nov 1, 2023. DOI: https://doi.org/10.31003/USPNF_M99595_06_01. 9

Personnel Training

Demonstrate knowledge and competency initially and every 12 months:

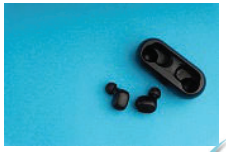
- Hand hygiene
- Garbing
- Cleaning and sanitizing
- Handling and transporting components and preparations
- Measuring and mixing
- Proper use of equipment and devices
- Documentation

Personnel Preparation

Remove outer garments

Remove hand, wrist, or other exposed jewelry

Remove earbuds or headphones



Hand Hygiene

Wash hands with soap and water for at least 30 seconds

Dry hands completely with disposable towels or wipers

Don gloves

Garb and Glove Requirements

Gloves must be worn for all compounding activities

For hazardous items, appropriate personal protective equipment (PPE) must be worn and disposed of according to USP <800>

Garb must be replaced immediately if visibly soiled or integrity is compromised

Garb should be removed when leaving the compounding area

- Gowns may be reused if not damaged or soiled

Inspect gloves for holes, punctures, or tears

Categories

Simple

- Preparation that has a USP compounding monograph
- Products that require addition of ingredients directed by the manufacturer

Moderate

- Preparation that requires special calculations or procedures
- Preparation for which stability data is not available

Complex

- Preparation that requires special training, environment, facilities, equipment, and procedures

Environment

- Adequate space designated for compounding (separate from sterile compounding area, no carpet)
- Source of hot and cold water and an easily accessible sink
- Potable water for hand washing
- Purified water (or better quality) for compounding nonsterile preparations
- Purified water, distilled water, or reverse osmosis water for rinsing equipment and utensils
- Well lit
- Appropriate temperature (monitor once daily or continuously with device)
- Equipment and containers stored off the floor

Cleaning and Sanitizing

Location	Frequency (minimum)
Work surfaces	• Beginning and end of each shift on compounding days • After spills and surface contamination • Between compounding products with different components
Floors	• Daily on compounding days • After spills and surface contamination
Walls	• Visibly soiled, after spills, and surface contamination
Ceilings	• Visibly soiled and surface contamination
Storage shelving	• Every 3 months, after spills, and surface contamination

Closed-System Processing Devices

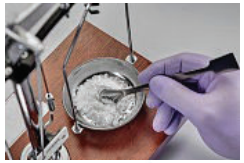
- Compounding components that can generate airborne chemical particles

Site	Frequency (minimum)
Containment ventilated enclosures (CVE)	• Beginning and end of each shift, after spills, and after surface contamination • Between compounding preparations with different components
Biological safety cabinets (BSC)	• Beginning and end of each shift, after spills, and after surface contamination • Between compounding preparations with different components • Under the work surface at least monthly
Other devices and equipment	• Before first use and thereafter according to manufacturer's recommendations • If no recommendation, between compounding with different components

- CVEs and BSCs must be certified at least every 12 months

Compounding Equipment

- Types of mortars and pestles
  - Glass: liquids, staining, oily
  - Wedgwood: reducing size of dry crystals
  - Porcelain: blending powders, pulverizing soft crystals
- Sizes and types of spatulas
  - Small spatula blades → dry chemicals
  - Large spatula blades → ointments, creams, blended powder for capsules
  - Stainless steel and plastic spatulas
- Do not use parchment paper when preparing creams



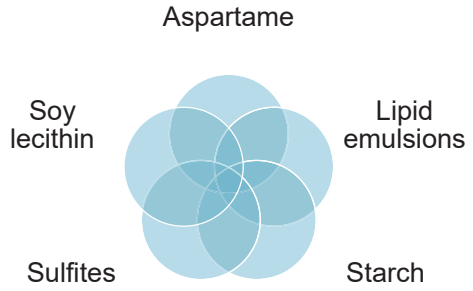
Compounding Ingredients

- A USP, National Formulary (NF), or FCC substance is the recommended source for all ingredients
- Manufactured by an FDA-registered facility
- Certificate of Analysis (COA) to show the ingredient meets expected quality
- Ingredients that lack an expiration date must be assigned an expiration of no more than 3 years from the date of receipt
- Once removed from the original container, excess ingredient should be discarded
- All containers should be labeled
- Rotate so that oldest stock is used first

Active Pharmaceutical Ingredient (API) vs Excipient

API	Excipient
• any substance with pharmacological activity or direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals or affecting the structure and function of the body	• any substance that is necessary to compound a preparation but is not intended to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation

Ingredients with Common Adverse Effects



Receiving Products

Document

- Receipt date
- Quantity received
- Supplier name
- Lot number
- Expiration date
- Results of any in-house or third-party testing performed

Evaluation Before Use

Visually re-inspect all components for:

- Container breakage
- Looseness of cap or closure
- Deviation from expected appearance or texture

Any component found to be unacceptable must be rejected, labeled as rejected, and removed from active stock

Spill and Disposal

- Maintain current chemical hazard and disposal information
- Management and documentation described in standard operating procedures (SOPs)
- Readily accessible spill kit in the compounding area
- Training in spill management of chemicals
- Waste disposed of according to laws and regulations of jurisdiction

Documentation Requirements

Master Formulation Record:
detailed record of procedures that describe how the product is prepared

- Created for each unique formulation
- Changes approved and documented according to standard procedures

Compounding Record:
documents the compounding of each individual product preparation

- Created for each preparation
- Reviewed for completeness before preparation is released
- Reviewer name and date of review
- Traceability of all components

Master Formulation Record (MFR)

- Name, strength, and dosage form
- Identities and amounts of components
- Container closure system(s)
- Complete instructions including equipment, supplies, and description of compounding steps
- Physical description
- BUD and storage requirements
- Reference source to support assigned BUD
- Calculations for quantities and concentrations
- Labeling requirements
- Quality control procedures and expected results
- Other information needed to describe the compounding process and ensure repeatability

Compounding Record (CR)

- Name, strength, and dosage form
- Date of preparation
- Prescription number and MFR reference
- Person that prepared and verified the preparation
- Name, manufacturer, lot number, and expiration date of each component
- Quantity of components and total quantity
- BUD and storage requirements
- Calculations for quantities and concentrations
- Physical description
- Quality control procedure results
- Labeling requirements
- Documentation of adverse reactions

Label vs Labeling

Label: on immediate container	Labeling: on immediate container or inside the packaging system
• Prescription number • Amount and concentration of active ingredients • Storage conditions • BUD • Dosage form • Total amount or volume	• Route of administration • Indication that preparation is compounded • Special handling instructions • Warning statements • Compounding facility name and contact information

Current BUD Guidelines

1. Refer to manufacturer for stability information on specific preparation
2. In the absence of stability information, follow the table below

Formulation	BUD
Nonaqueous	6 months or earliest expiration of any active ingredient (whichever is earlier)
Water-containing (oral)	14 days (stored at cold temperatures)
Water-containing (topical)	30 days

Updates to BUDs

- Becomes “official” on November 1 , 2023
- Introduces the concept of water activity (a_w)
  - Used to assess the susceptibility to microbial contamination and potential for degradation due to hydrolysis
  - Reduced a_w helps prevent microbial growth
  - Compounders are not required to measure a_w
  - Preparations with an $a_w \geq 0.6$ should contain an antimicrobial preservative
    - If contraindicated, store the preparation in a refrigerator

Water Activity of Aqueous Dosage Forms ($a_w \geq 0.6$)

Dosage Form	a_w
Oral Suspension (water based)	0.992
Nasal Spray	0.991
Gel (water based)	0.990
Lotion	0.986
Foam	0.983
Cream (oil in water emulsion)	0.968
Oral Solution (water based)	0.906

Water Activity of Nonaqueous Dosage Forms ($a_w < 0.6$)

Dosage Form	a_w
Tablet (compressed)	0.465
Capsule (powder filled)	0.435
Powder (for inhalation)	0.402
Ointment (hydrophilic petrolatum)	0.396
Suppository (polyethylene glycol base)	0.374
Troche/lozenge (gelatin base)	0.332

Updated BUD Limits

Preparation	BUD	Storage
Nonpreserved aqueous ($a_w \geq 0.6$) dosage forms	14 days	Refrigerator
Preserved aqueous ($a_w \geq 0.6$) dosage forms	35 days	Room temperature or refrigerator
Nonaqueous ($a_w < 0.6$) oral liquids	90 days	Room temperature or refrigerator
Other nonaqueous ($a_w < 0.6$) dosage forms	180 days	Room temperature or refrigerator

Preparations Requiring Shorter BUDs

Existing stability data

Expiration date of any of the components occurs before assigned BUD

Extending BUDs

- Preparations with a USP-NF monograph
- Preparations with stability information

- If extended, an aqueous preparation must be tested for antimicrobial effectiveness
  - Conducted once for each formulation in the container
  - May rely on results provided by an FDA facility or published in peer-reviewed literature

Maximum of 180 days

Quality Assurance and Control

- Quality Assurance (QA): system of procedures, activities, and oversight to ensure the compounding process meets quality standards
- Quality Control (QC): sampling, testing, and documentation of results
- Programs must be established and documented in the SOPs
- SOPs describe roles, duties, and training of personnel
- Reviewed at least once every 12 months

Designated Person Responsibilities
Adherence to procedures
Prevention and detection or errors
Evaluation of complaints and adverse effects
Appropriate investigations and corrective actions

Recalls of Dispensed Compounds

Notify prescriber immediately of a failure of specifications with the potential to cause patient harm

Recall unused dispensed products and quarantine stock in the pharmacy

Investigate other lots affected and recall if necessary

Handling Complaints

Keep record of each complaint

- Name of complainant
- Date complaint was received
- Nature of the complaint
- Response to the complaint
- Name, strength, and prescription number of product
- Findings of any investigation and follow-up

Compound Packaging

Packaging materials must:

- Maintain physical and chemical integrity and stability of the product
- Protect against damage, leakage, contamination, and degradation
- Protect personnel from exposure

What do I Need to Document?

- Personnel training, competency assessments, and qualification records
- Equipment records
- COAs for components not conventionally manufactured
- Receipt of components
- SOPs, MFRs, and CRs
- Inspection and testing records
- Complaints and adverse events
- Results of investigations and corrective actions taken
- Cleaning and sanitizing records
- Temperature logs
- Accommodations to personnel compounding preparations
- Required routine review

How Long do I Keep Documentation?

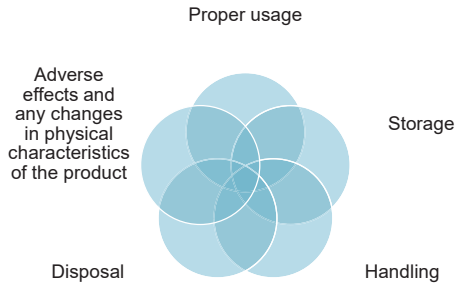
At least 2 years

OR

Whichever is longer!

Whatever time is required by laws and regulations in your jurisdiction or internal policies

Patient Counseling



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