Association of Professors of Dermatology

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Compounding Medication Regulations

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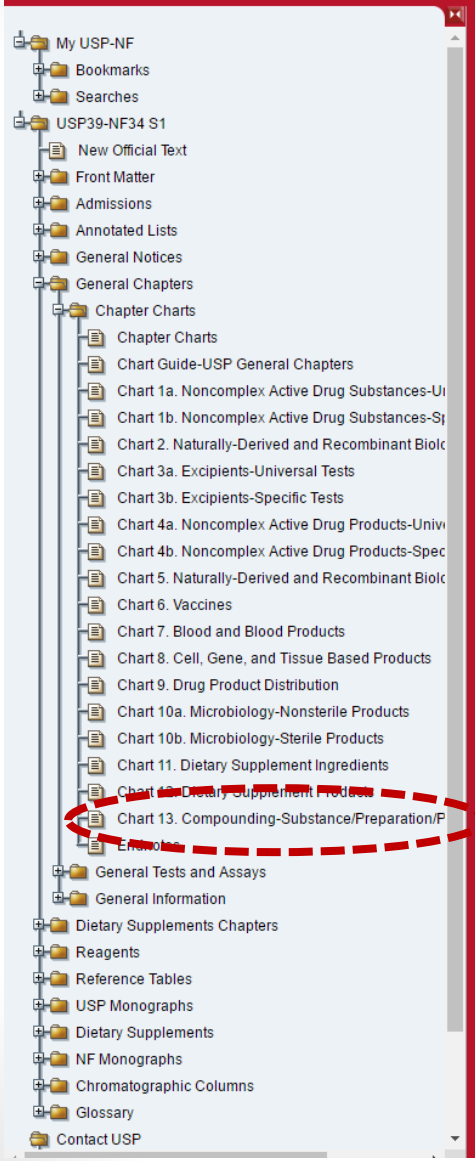
United States Pharmacopeial Convention (USP)

- Scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide.
- Created in 1820 by a group of 11 physicians who recognized an essential need for a national lexicon of drug names and formulas in the United States.
- USP's drug standards are enforceable in the United States by the Food and Drug Administration, and are used in more than 140 countries.

United States Pharmacopeia and National Formulary (US-NF)

- Combination of two compendia
  - Unites States Pharmacopeia (USP)
  - National Formulary (NF)
- Book of public pharmacopeial standards for chemical and biological drug substances, dosage forms, compounded preparations, excipients, medical devices, and dietary supplements.
  - Monographs – name, definition, packaging/storage/labeling, specification of ingredient or preparation
  - General chapters – tests and procedures referred to in multiple monographs are described in detail
  - General notices – provide definitions for terms in monographs



(541) Titrimetry				✦		
(621) Chromatography			✦	✦		✦
(659) Packaging and Storage Requirements					✦	
(660) Containers—Glass					✦	
(661) Plastic Packaging Systems and Their Materials of Construction					✦	
(661.1) Plastic Materials of Construction					✦	
(661.2) Plastic Packaging Systems for Pharmaceutical Use					✦	
(671) Containers—Performance Testing					✦	
(730) Plasma Spectrochemistry						
(731) Loss on Drying						
(736) Mass Spectrometry			✦	✦		✦
(761) Nuclear Magnetic Resonance Spectroscopy			✦	✦		✦
(781) Optical Rotation				✦		
(786) Particle Size Distribution Estimation by Analytical Sieving						✦
(795) Pharmaceutical Compounding—Nonsterile Preparations	✦	✦			✦	
(797) Pharmaceutical Compounding—Sterile Preparations	✦	✦			✦	
(800) Hazardous Drugs—Handling in Healthcare Settings	✦				✦	
(823) Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses	✦					
(831) Refractive Index						✦
(852) Atomic Absorption Spectroscopy			✦	✦		✦
(853) Fluorescence Spectroscopy			✦	✦		✦
(854) Mid-Infrared Spectroscopy			✦	✦		✦
(855) Nephelometry, Turbidimetry, and Visual Comparison				✦		✦

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- First published in 2004, last revised in 2008.
- Compounding Expert Committee began latest revision in 2010, completed in 2015.
- Proposed revision published for public comments, due on January 31, 2016.
- Compounding Expert Committee currently reviewing more than 8,000 comments from over 2,500 stakeholders.

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- Currently **3 contamination categories** for Compounded Sterile Preparations (CSPs)

- Assigned primarily according to the potential for microbial contamination during the compounding of low or medium risk level CSPs or the potential for not sterilizing high risk level CSPs, any of which would subject patients to risk of harm, including death.

- High risk level CSPs must be sterilized before being administered to patients.

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- For the purposes of chapter 797, CSPs include any of the following:
  - Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that must be sterile when they are administered to patients.
  - Manufactured sterile products that are either prepared strictly according to the package insert or prepared differently than published in such labeling.
  - ***Note***: The FDA states that "Compounding does NOT include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in the package insert." However, the package insert rarely describes environmental quality (e.g. ISO class air designation, exposure duration, personnel garbing/gloving, and other aseptic precautions.)

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- High risk compounding examples:
  - Dissolving nonsterile bulk drug and nutrient powders to make solutions that will be terminally sterilized,
  - Measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.

- Medium risk compounding examples:
  - Compounding of total parenteral nutrition fluids using manual or automated devices,
  - Filling of reservoirs of injection and infusion devices with more than three sterile drug products,
  - Transfer of volumes from multiple ampuls or vials into one or more final sterile containers.

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- Low risk compounding examples:
  - Single volume transfers of sterile dosage forms from ampuls, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers.
  - Simple aseptic measuring and transferring with not more than three packages of manufactured sterile products, including an infusion of diluent solution to compound drug admixtures and nutritional solutions.

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- **Examples relevant to dermatologic surgery**:
  - Buffering/compounding aseptically prepared, commercially purchased, preservative-containing lidocaine with epinephrine, with aseptically prepared, commercially purchased sodium bicarbonate.
  - Compounding Kenalog with lidocaine
  - Reconstituting Botox??

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- Proposed revisions
  - Collapse compounded sterile preparations (CSP) microbial risk categories from **three to two** and change terminology.
  - No sterile compounding is inherently “low risk” and preparation of all CSPs must be done carefully.
  - Rename categories neutrally as **Category 1 and 2 CSPs**, which are distinguished primarily by the conditions under which they are made and time within which they are used.

Chapter 797 Pharmaceutical Compounding – Sterile Preparations

- Proposed revisions
  - Category 1 CSPs have shorter beyond use date (BUD) and may be prepared in a segregated compounding area,
  - Category 2 CSPs have a longer BUD and must be prepared in a cleanroom environment.

BUDs for Category 1 CSPs

	Storage Conditions	
	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)
BUD	≤12 hours	≤24 hours

[a] The BUDs specified in the table indicate the hours after the Category 1 CSP is prepared beyond which the CSP cannot be used. The BUD is determined from the time the CSP is compounded.

CSP Processing Environment

Segregated Compounding Area

Cleanroom

Table 9. In-Use Times for Conventionally Manufactured Products and CSPs Opened, Stored, and Used for Sterile Compounding in ISO Class 5 or Better Air Quality

Components	In-Use Time
Conventionally Manufactured Sterile Product	
Ampuls	Use *immediately* after opening and passing through a sterile particulate filter
Pharmacy Bulk Package	As specified by the manufacturer
Single-dose container (e.g., bag, bottle, syringe, or vial)	6 hours
Multiple-dose container	28 days, unless otherwise specified by the manufacturer
CSP	
Compounded single-dose container	6 hours
Compounded stock solutions	6 hours
Compounded multiple-dose container[a]	28 days, unless otherwise specified by the original compounder

[a] The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with (51) at

Table 10. In-Use Times for Conventionally Manufactured Products and CSPs Opened and/or Stored in Worse than ISO Class 5 Air[a]

Components	In-Use Time
Conventionally Manufactured Sterile Product	
Ampuls	Use *immediately* after opening and passing through a sterile particulate filter
Pharmacy Bulk Package	Not applicable. Contents of pharmacy bulk packages must be used only in an ISO Class 5 or better environment.
Single-dose container (e.g., bag, bottle, syringe, vial)	Use for a single patient within the time specified by the manufacturer, or by the end of the case or procedure, whichever comes first. Discard remainder.
Multiple-dose container	28 days, unless otherwise specified by the manufacturer
CSP	
Compounded single-dose container	Use for a single patient immediately. Discard remainder
Compounded multiple-dose container[b]	28 days, unless otherwise specified by the original compounder

Summary Comparison of Minimum Requirements for Category 1 and Category 2 Compounded Sterile Preparations

	Category 1 CSPs	Category 2 CSPs
Personnel Qualifications		
Visual observation of hand hygiene and garbing	Quarterly	Quarterly
Gloved fingertip sampling	Quarterly	Quarterly
Media fill testing	Quarterly	Quarterly
Personal Protective Equipment		
See *Table 2*.		
Buildings and Facilities		
Primary engineering control (PEC)	Not required to be placed in a classified area	Required to be placed in a classified area
Recertification	Every 6 months	Every 6 months
Environmental Monitoring		
Nonviable airborne monitoring	Every 6 months	Every 6 months
Viable airborne monitoring	Monthly	Monthly
Surface sampling	Monthly	Monthly
Release Testing		
Physical inspection	Required	Required
Sterility testing	Not required	Based on assigned BUD
Endotoxin testing	Not required	Required if prepared from nonsterile ingredient(s)[b]
BUD		
BUD assignment	≤12 hours at controlled room temperature or ≤24 hours if refrigerated	>12 hours at controlled room temperature or >24 hours if refrigerated

[a] This table summarizes the requirements that apply specifically to Category 1 and Category 2 CSPs. There are numerous requirements in the chapter that are not summarized in this table because they apply to all CSPs, regardless of whether they are Category 1 or Category 2.

[b] See exemptions in *10.3 Bacterial Endotoxins Testing*.

Minimum Garb and Glove Requirements

CSP Category	PEC type	Minimum Requirement
Category 1	Any	• Non-cotton, low-lint, disposable gown or coveralls • Low-lint, disposable covers for shoes • Low-lint, disposable covers for head and facial hair that cover the ears and forehead • Sterile gloves and sterile sleeves[a]
Category 2	Laminar airflow system (LAFS) and biological safety cabinet (BSC)	• Non-cotton, low-lint, disposable gowns or coveralls • Low-lint, disposable covers for shoes • Low-lint, disposable covers for head and facial hair that cover the ears and forehead • Mask • Sterile gloves and sterile sleeves[a] • Eye shield is optional
Category 2	RABS (CAI or CACI) or isolator	• Non-cotton, low-lint, disposable gowns or coveralls • Low-lint, disposable covers for shoes and hair • Sterile gloves

[a] If a sterile gown is used, the use of sterile sleeves is optional.

Summary of Proposed Changes Relevant to Dermatologic Surgery

Categories of Risk	Collapse 3 into 2 categories
Environment	No significant change. All compounding to be done in Primary Engineering Control (PEC) with ISO Class 5 environment.
Garb/Glove	No significant change.
Testing	More frequent (gloved fingertip sampling/media fill testing)
BUD	Shortened to max 12-24 hrs; labeling required
In-time use	New; labeling required
Reconstituting	Unclear whether still excluded

State Boards Currently Requiring Compliance with USP Chapter <797>

Alabama	Yes	D
Alaska	No	
Arizona	No	
Arkansas	Yes	
California	Yes	L
Colorado	Yes	A, C
Connecticut	Yes	D
Delaware	Yes	
District of Columbia	No	
Florida	Yes	†
Georgia	Yes	
Guam	Yes	
Hawaii	No	B
Idaho	No	
Illinois	No	K
Indiana	Yes	
Iowa	No	C
Kansas	Yes	C
Kentucky	Yes	
Louisiana	Yes	†
Maine	Yes	
Maryland	Yes	E †
Massachusetts	Yes	D
Michigan	Yes	J
Minnesota	Yes	
Mississippi	No	
Missouri	Yes	A
Montana	No	
Nebraska	Yes	N
Nevada	No	I
New Hampshire	Yes	D
New Jersey	Yes	C
New Mexico	Yes	
New York	No	A
North Carolina	Yes	
North Dakota	No	I
Ohio	No	G
Oklahoma	Yes	B
Oregon	Yes	A
Pennsylvania	F	
Puerto Rico	Yes	D
Rhode Island	Yes	
South Carolina	No	H
South Dakota	Yes	C
Tennessee	Yes	
Texas	C	
Utah	Yes	
Vermont	Yes	
Virgin Islands	—	
Virginia	Yes	
Washington	Yes	M
West Virginia	Yes	
Wisconsin	Yes	
Wyoming	Yes	

Current Situation and Next Steps

- USP Compounding Expert Committee is planning stakeholder roundtable for early 2017
- USP anticipates that proposed standard will NOT be finalized in 2017
- FDA has released "Insanitary Conditions at Compounding Facilities" Draft Guidance
  - Examples of insanitary conditions:
    - Putting on gowning apparal improperly
    - Engaging in aseptic manipulations with exposed hands, wrists, legs, hair, or mouth
    - Performing aseptic manipulations outside of and ISO 5 area
  - *"If a compounding facility produces drugs under insanitary conditions, the facility and responsible individuals may be subject to Federal regulatory actions…"*

My humble opinion…

- Stop compounding lidocaine with sodium bicarbonate.
- Not worth the regulatory risks.
- Painless anesthesia can be easily achieved without buffering lidocaine:
  - 1 cc syringes
  - 30-gauge needles
  - INJECT SLOWLY!
  - In highly sensitive locations (lip, nasal tip, palms/soles), first inject 0.5-1 ml plain lidocaine; no epi = no preservative = neutral pH
  - We have done it for years – it works!