COMMENTS ON PROPOSED USP <795>
(CompoundingToday.com)

Comments on selected aspects of the proposed USP <795>. The numbers on the left are the same as those actually in the chapter. Only those items with comments are reproduced.

1. INTRODUCTION AND SCOPE

Defines Nonsterile Compounding: Nonsterile compounding is defined as
5 combining, admixing, diluting, pooling, reconstituting other than as provided
6 in the manufacturer package insert, or otherwise altering a drug or bulk drug
7 substance to create a nonsterile medication. Reconstituting a conventionally
8 manufactured nonsterile product in accordance with the directions contained
9 in the approved labeling provided by the product's manufacturer is not
10 considered compounding as long as the product is prepared for an individual
11 patient and not stored for future use.

+Is it a requirement that the individual reconstituting the manufactured product wear gloves, mask, etc? Oftentimes, antibiotics for reconstitution release powders into the air when opened for reconstitution. Seems potentially problematic…especially if the compounder may have respiratory issues. Even though it is understandable to omit them here, the problem still exists and possibly manufacturers should be required to add a labeling statement.

+…not stored for future use …needs clarification. Is it really necessary? In the antibiotic reconstitution example, it is generally stored and administered over 14 days. The way it reads can be interpreted for immediate use.

12 **1.1 Scope**

13 COMPOUNDED NONSTERILE PREPARATIONS AFFECTED

27 AFFECTED PERSONNEL AND SETTINGS

28 This chapter applies to all persons who prepare CNSPs and all places where
29 CNSPs are prepared. This includes but is not limited to pharmacists,
30 technicians, physicians, veterinarians, dentists, naturopaths, chiropractors,
31 and nurses, in all places including but not limited to pharmacies, hospitals
32 and other healthcare institutions, patient treatment sites, and physicians' or
33 veterinarians' practice sites.

+For non pharmacists/technicians, this is not realistic and most likely will not be implemented in states. Non-pharmacist professionals don't generally fall under the state boards of pharmacy and the specific professional boards of those professions see these standards, as well as those of 800, as problematic and will ignore them, as they have for other pharmacy professional practice standards. Recommend limiting the proposed chapter to pharmacy facilities.

The compounding facility's leadership and all personnel involved in preparing, storing, packaging, and transporting CNSPs are responsible for 1) ensuring that the applicable practices and quality standards in this chapter are continually and consistently applied to their operations, and 2) proactively identifying and remedying potential problems within their operations. Personnel engaged in the compounding of CNSPs must also comply with applicable laws and regulations of the regulatory jurisdiction. The compounding facility must designate one or more individuals (i.e., the designated person) to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CNSPs. The responsibilities of the designated person include but are not limited to:

- Developing and implementing a training program
- Routinely monitoring and observing compounding activities and taking immediate corrective action if deficient practices are observed
- Demonstrating the procedures for personnel and observing and guiding personnel throughout the training process
- Evaluating whether individuals with certain conditions, such as rashes or respiratory illnesses, will be allowed to work in compounding areas

+Difficult to understand where "dry" rashes on the trunk, back, legs, etc. would be problematic here. Needs clarification. Possibly just limit to respiratory conditions, rashes in exposed areas, weeping rashes or those that may be contagious?

before their conditions are resolved because these conditions carry the risk of contaminating the environment and CNSPs

+This last part of the entire sentence is not necessary as it is common knowledge.

+it seems these standards are aimed at large and very large compounding facilities. However, many are small operations and all these standards may involve only one person doing the compounding.

2. PERSONNEL QUALIFICATIONS—TRAINING, EVALUATION, AND REQUALIFICATION

+Seems like a lot of this came from 797, but that is fine….they will be somewhat harmonized.

+There is no discussion or apparent allowance for training variances as to the type and extent of training for different sites. If only doing minimal "low-risk" compounding, why is it necessary to be trained in more technical and detailed compounding. The type and extent of training should be commensurate with the type and extent of compounding being done.

3. PERSONAL HYGIENE AND GARBING

Compounding personnel must maintain personal hygiene. Individuals that may have a higher risk of contaminating the CNSP and the environment

(e.g., due to rashes, sunburn, recent tattoos or oozing sores, conjunctivitis, active respiratory infection) must report these conditions to the designated person. The designated person must evaluate whether these individuals will be allowed to work in compounding areas before their conditions are resolved because of the risk of contaminating the environment and CNSPs.

+See previous discussion in Section 1.1, Lines 50-53.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain hand hygiene and wear clean clothing required for the type of compounding performed. Before entering a designated compounding area, compounding staff must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:

- Remove personal outer garments (e.g., bandanas, coats, hats, jackets, scarves, sweaters, vests)
- Remove all hand, wrist, and other exposed jewelry or piercing that can interfere with the effectiveness of the garb or hand hygiene (e.g., watches, rings that may tear gloves)
- Remove headphones and earphones
- Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures

+Some of the above may not be necessary for low numbers of simple nonsterile compounding and lead to excessive costs with no reasonable benefit.

3.2 Hand Hygiene

Box 3-1. Hand Hygiene Procedures

3.3 Garb and Glove Requirements

Gloves are required to be worn for all compounding activities. Other garb (e.g., shoe covers, head and facial hair covers, face masks, gowns) must be appropriate for the type of compounding performed as needed for the protection of personnel from chemical exposures and for prevention of preparation contamination. Garb must be stored to prevent contamination (e.g., away from sinks to avoid splashing onto garb). Visibly soiled garb or garb with tears or punctures must be changed immediately.

+If understood correctly, the only required item to be worn is gloves; other items must be appropriate for the compounding situation. That sounds appropriate and reasonable.

4. BUILDINGS AND FACILITIES

Compounding facilities must have a space that is specifically designated for compounding. Areas related to nonsterile compounding must be separated from areas not directly related to compounding. Areas intended for nonsterile compounding must be separated and distinct from the areas intended for sterile compounding (see *Pharmaceutical Compounding—Sterile*

171 *Preparations* □797□), except where permitted as described in □800□.
172 Compounding areas used to compound hazardous CNSPs must not be used
173 for compounding nonhazardous CNSPs (see □800□).

+It is not clear what level of "separation" is required. If a separate room with its own HVAC, etc., this is not reasonable for many small scale compounders servicing patients throughout the US doing only simple, occasional compounding. It would be fine for the large scale compounders but it is important to maintain patient access in all geographical areas. For many situations, it is not necessary to have a separate room, etc. It is too costly to build out, operate and the return on investment is not there.... so patients will be without access to their compounded medications. This is true of both small hospital pharmacies and independent pharmacies.

174 Compounding facilities must be designed and controlled to provide a well
175 lighted working environment, with temperature and humidity controls for the
176 comfort of compounding personnel wearing the required garb. Heating,
177 ventilation, and air conditioning systems must be designed and controlled to
178 prevent decomposition and contamination of chemicals, components, and
179 CNSPs (see also *12. CNSP Handling, Packaging, Storage, and Transport*).
180 Temperature and humidity must be maintained as required for components
181 and compounded preparations.

+Humidity control is not necessarily required in USP APIs or USP Product Monographs except where it states to store in a Dry Place.

A Dry Place is a place that does not exceed 40% average relative humidity at 20° (68° F) or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place. Determination is based on NLT 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value does not exceed 40% relative humidity. Storage in a Container validated to protect the article from moisture vapor, including storage in bulk, is considered a Dry Place.

The geographical variations in the US from coastal, gulf, desert, etc. results in pharmacies with low and some with high humidities. Once a door is opened, the humidity inside the facility changes. The reference to humidity probably should be removed.

One must also consider that when ingredients and finished preparations are in "Tight Containers", room humidity is generally a moot point unless the container is repeatedly opened.

5. CLEANING AND SANITIZING

213 **Table 1. Minimum Frequency for Cleaning and Sanitizing Surfaces in**
214 **Nonsterile Compounding Areas**

Site	**Minimum Frequency**

Ceilings Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected

+Is it really necessary to clean ceilings every 3 months in a nonsterile compounding area? Possibly necessary if compounding large numbers/volumes of preparations and using a lot of powders but not necessary for others. Every 6 months should be sufficient, especially for low numbers/volumes of preparations.

6. EQUIPMENT AND COMPONENTS

6.1 Equipment

Automated, mechanical, electronic, and other types of equipment used in the compounding or testing of compounded preparations must be inspected prior to use and verified for accuracy at the frequency recommended by the manufacturer, and at least annually. Immediately after compounding, the equipment must be cleaned to prevent cross-contamination of the next preparation.

+Confusing. Equipment also includes hot plates, stirriers, mixers, etc…..must these be verified for accuracy? Possibly change to, "As appropriate, automated, mechanical, electronic…etc)

Any weighing, measuring, or other manipulation of an active pharmaceutical ingredient (API) or added substance in powder form that could generate airborne contamination from drug particles must occur inside a containment device such as a containment ventilated enclosure (CVE) (i.e., powder containment hood). The CVE must be cleaned as described in *Table 2*. The CVE must be certified annually. If the CVE is not equipped with an exhaust alarm, the device should be certified every 6 months according to requirements such as the current Controlled Environment Testing Association (CETA) or American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRE) guidelines, or other jurisdictional standards.

+This will be quite costly and one wonders if ALL powders, both APIs and excipients, is too broad. There are numerous powders that are safe, have higher densities and less likely to become airborne that could be considered to be manipulated outside a CVE. Also, if only doing 1 or 2 a day, this may be cost-prohibitive with little demonstrated need.

6.2 Components

Compounding personnel must establish, maintain, and follow written SOPs for the selection and inventory control of all components, including all ingredients (i.e., APIs, inactive ingredients), containers, and closures, from receipt to use in a CNSP.

+Does this mean an ongoing inventory requiring a lot of time without a lot of return on investment of time; also, what is involved in "…from receipt to use in a CNSP?". This appears to

be unnecessary to keep track of ingredients, containers and closures as they progress through the process from receiving, storage, usage, dispensing, etc..

252 COMPONENT SELECTION

266 All ingredients other than APIs should be obtained from an FDA-registered
267 facility.

+"Should" is appropriate here as excipients may or may not be available from FDA-registered facilities.

Outside of the US, the facility must comply with applicable laws and
268 regulations of the regulatory jurisdiction. These ingredients should be
269 accompanied by a valid COA that verifies that the ingredient meets an
270 official monograph, if one exists, and any additional specifications for the
271 ingredient. If ingredients other than APIs cannot be obtained from an FDA
272 registered facility, the designated person must select a material that is
273 suitable for the intended use. The designated person must establish the
274 identity, strength, purity, and quality of the API by reasonable means. These
275 means may include visual inspections, evaluation of the COAs, and/or
276 verification by analytically testing a sample to determine conformance with
277 the COA.

+Line 276-Analytically testing excipients can be very costly.

278 *Purified Water*, or an equivalent quality of water, must be used to
279 reconstitute conventionally manufactured nonsterile products when water
280 quality is not stated in the manufacturer's labeling (see *Water for*
281 *Pharmaceutical Purposes* □1231□).

+If "reconstitution of conventionally manufactured nonsterile products" is not in the definition of compounding, why is this here? It should be in the FDA-approved labeling of the product.

282 COMPONENT RECEIPT

289 ……If there is a compendial monograph
290 for any ingredient received, the COA for the ingredient must be verified to
291 ensure that the ingredient has met the acceptance criteria of all specified
292 monograph tests for that lot and includes the test results.

+If the provider of the ingredients is FDA registered and must provide a valid COA, then why must the pharmacy take the time to verify it to ensure that the ingredient has met the acceptance criteria of **all specified monograph tests** for that lot and include the test results? This should be the responsibility of the provider and the pharmacy just spot checking to confirm the COA.

309 COMPONENT EVALUATION BEFORE USE

323 COMPONENT HANDLING AND STORAGE
324 All ingredients used to prepare CNSPs must be handled and stored in
325 accordance with the manufacturer's instructions or per applicable laws and
326 regulations of the regulatory jurisdiction. The handing and storage must
327 prevent contamination, mix-ups, and deterioration (e.g., loss of identity,
328 strength, purity, and quality). If specific instructions are not available,
329 ingredients must be stored in tightly closed containers under controlled
330 temperature, humidity, and lighting conditions as detailed in this chapter.
331 Moisture-sensitive ingredients must be stored in tight, well-closed
332 containers.

+Many excipients only require "well-closed" containers. Does this mean they will need to be repackaged into "tight containers"? USP definitions are as follows:

- **Well-Closed container:** A container-closure system that protects the contents from contamination by extraneous solids and from loss of the article under ordinary or customary conditions of handling, shipment, storage and distribution.
- **Tight Container:**A container-closure system that protects the contents from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure.

+Humidity control is not necessarily required in USP APIs or USP Product Monographs except where it states to store in a Dry Place.

- A Dry Place is a place that does not exceed 40% average relative humidity at 20° (68° F) or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place. Determination is based on NLT 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value does not exceed 40% relative humidity. Storage in a Container validated to protect the article from moisture vapor, including storage in bulk, is considered a Dry Place.

The geographical variations in the US from coastal, gulf, desert, etc. results in pharmacies with low and some with high humidities. Once a door is opened, the humidity inside the facility changes. The reference to humidity should possibly be removed.

333 Packages of ingredients that lack a vendor's expiration date must not be
334 used after 1 year from the date of receipt by the compounding facility.

+This can be quite wasteful. Not aware that the current chapter "3 years" has been a problem over the years. Recommend 3 years be maintained unless documentation shows it is a problem.

343 COMPONENT SPILL AND DISPOSAL

7. SOPS AND MASTER FORMULATION AND COMPOUNDING RECORDS

385 **7.2 Creating Master Formulation Records**

394 **Box 7-1. Master Formulation Record**
A Master Formulation Record must include at least the following information:
 Name, strength, and dosage form of the CNSP
 Physical description of the final CNSP
 Ingredient identities and amounts, and container–closure systems, including necessary
characteristics of components (e.g., particle size, salt form, purity grade, solubility)

+Particle size is not always available on a C of A and nothing is provided here concerning how it is to be expressed. Terms such as

- "fine powder", etc. vs
- 100-200 mesh, vs
- 50-100 micron vs
- nlt 90% less than 500 microns, etc.

If the components are to be used in preparing solutions, it may not be necessary to know the particle size. Would suggest adding (e.g., particle size **as necessary and appropriate**, salt form….etc.)

395 **7.3 Creating Compounding Records**

409 **Box 7-2. Compounding Records**
 Name, vendor or manufacturer, lot number, and expiration date of each ingredient and container–closure system

+Expiration date of container-closure systems are not usually available.

411 **8. RELEASE TESTING**
418 ……All checks and inspections, and any
419 other tests necessary to ensure the quality of the CNSP (e.g., pH, assays),
420 must be detailed in the facility's SOPs and completed before release.

+If a compounded preparation is sent out for assay, the results may not be back before the patient needs the medication and the BUD is being used up. Recommend dispensing and following up if the assay is OOS. The loss of a few days therapy is potentially more problematic than any clinical significance of a compounded preparation assaying at 89% or 111% and needing to be recalled.

9. LABELING

470 **10. ESTABLISHING BEYOND-USE DATES**
471 Each CNSP label must state the date beyond which the preparation cannot

be used and must be discarded (i.e., the BUD). The parameters described in this section must be considered before establishing these dates.

+Suggest inserting the word “appropriately” prior to “discarded”.

10.1 Terminology

10.2 Parameters to Consider in Establishing a BUD

10.3 Establishing a BUD for a CNSP

The BUDs indicate the days after the CNSP is prepared and beyond which the CNSP cannot be used. The day that the preparation is compounded is considered Day 1.

+The day on which the preparation is compounded should be Day 0 (zero), not Day 1. With short BUDs, the loss of a day can be important. A theoretical 1 day BUD would be 24 hours after it was compounded; 2 days 48 hours; 3 days 72 hours, etc.

If there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD specified in the monograph must be used, unless a shorter BUD is required as described below. If there is no *USP–NF* compounded preparation monograph for the CNSP, *Table 3* represents the maximum BUDs for CNSPs that are packaged in tight, light-resistant containers unless there is a CNSP specific stability study as described below. The BUDs in *Table 3* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. APIs or ingredients known to be susceptible to decomposition will require shorter BUDs (see *10.3 Establishing a BUD for a CNSP, Shorter Buds May Be Required*).

Table 3. Maximum BUD by Type of Preparation in the Absence of
+Comments on Table 3:

+30 days for preserved aqueous dosage forms is good.

+The reduction for Nonaqueous dosage forms from 180 days to 90 days is very problematic and I’m not sure that there is any justification for this. It should remain at 180 days.
Also, USP Chapter <1112> states that “**Nonaqueous liquids or dry solid dosage forms will not support spore germination or microbial growth due to their low water activity.”**
Again, what basis was used to drop from 180 days to 90 days for nonaqueous dosage forms?

The BUDs specified in *Table 3* for aqueous dosage forms and nonaqueous dosage forms may be extended up to maximum of 180 days if there is a stability study (published or unpublished) using a stability-indicating assay for the specific API, CNSP, and container–closure that will be used.

+Allowance should be made if the compounded preparation is being used in a clinical study and can be assayed periodically to extend the BUD past 180 days. Some studies may go on for a year or two and it is preferable to use the same lot of drug product throughout the study.

561 If the BUD of the CNSP is extended beyond the BUDs in *Table 3*, an
562 aqueous CNSP must first be tested for antimicrobial effectiveness (see
563 *Antimicrobial Effectiveness Testing* □51□) at the end of the proposed BUD
564 unless such testing was done as part of the referenced stability study. The
565 test must be conducted once for a particular CNSP. If changes are made to
566 the ingredients or storage conditions of the CNSP, the test must be
567 conducted for the new preparation. When a range of API concentrations are
568 compounded in the same CNSP formulation and stored under the same
569 conditions, the antimicrobial effectiveness test can be conducted for the
570 highest and lowest concentrations, and the results can be similarly
571 extrapolated for the concentrations within the range studied (e.g., bracketed
572 study design).

+Just to be clear, if there are published studies using stability-indicating analytical methods that provide a BUD for a Preserved aqueous dosage forms that shows the API is stable for 90 days, then the Antimicrobial Effectiveness Testing <51> must be done before using that 90 day date? If there has been NO reported instance of microbial growth in compounded oral preparations using commercial preserved vehicles, this does not seem necessary. Commercial oral liquid vehicles contain preservatives and have already been tested. Why address a problem that does not seem to exist?

573 SHORTER BUDS MAY BE REQUIRED

11. QUALITY ASSURANCE AND QUALITY CONTROL

12. CNSP HANDLING, PACKAGING, STORAGE, AND TRANSPORT

619 **12.1 Handling of CNSPs**

625 **12.2 Packaging of CNSPs**

635 **12.3 Storing CNSPs within the Compounding Facility**

647 The humidity of the storage room temperature area should be maintained
648 at or below 60%.

+Source of this requirement? As previously mentioned, this may be extremely difficult or impossible to obtain in coastal areas, especially in the south.
Or, does this simply apply to CNSPs that are ready to dispense that could be stored in a “cabinet” and not a “room”? If they are properly packaged in “Tight-Containers”, then there is no need for this requirement as a Tight-Container is impervious to moisture.

The compounding facility must adhere to SOPs to detect and prevent temperature excursions within the controlled temperature area. When it is known that a CNSP has been exposed to temperatures either below or above the storage temperature limits for the CNSP, personnel must determine whether the CNSP integrity or quality has been compromised and, if so, the CNSP must be discarded.

+The definition of "Controlled Room Temperature" should be mentioned here where excursions are allowed as per the definition. There should be very few instances where the CNSP must be discarded as per that definition.

12.4 Shipping and Transporting CNSPs

13. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

13.1 Complaint Handling

13.2 Adverse Event Reporting

14. DOCUMENTATION