INTRODUCTION

On March 30 a newly revised draft of USP 795 concerning nonsterile compounding was made available for download and review. At 24 pages, the proposed new draft of USP 795 is somewhat longer than the 16 pages of the existing chapter. The draft is significantly better organized and easier to read. Information concerning hazardous drug compounding and sterile compounding is removed, replaced with references to chapters 800 and 797, respectively.

The compounder is strongly encouraged to carefully read the proposed draft, which may be downloaded free at http://www.usp.org/compounding/general-chapter-795.

Below are a series of comments concerning the proposed chapter agreed upon by the Nonsterile Compounding Consensus Group (NCCG), a diverse collection of highly respected experts with decades of experience in this area. At the end of this document is a listing of the names, credentials and background of each contributing member.

Each set of comments begins with the corresponding line number found in the draft of 795. **Bolded** comments are simply summaries of what the proposed new chapter contains. They are not present for all sections, and mainly focus on significant additions, deletions or edits of the existing version of the chapter. *Italicized* comments represent observations and recommendations by the NCCG.

The hyperlink shown above also allows one to register for an Open Microphone session to take place on April 20.

This link also allows for comments to be submitted to USP concerning the draft. All such comments must be submitted by July 31.

The NCCG strongly urges all nonsterile compounders and other interested parties to submit comments in this manner should they agree with those presented below, or have their own observations concerning the draft.

The final version of the chapter will be published on June 1, 2019, and will become effective, along with chapters 797 and 800, on December 1, 2019.

COMMENTS OF THE NONSTERILE COMPOUNDING CONSENSUS GROUP

3 **- The new term compounded nonsterile preparations (CNSPs) is introduced.**

7 - The definition of compounding is modified to specifically exclude the reconstituting a manufactured product as per manufacturer instructions.

> *We recommend that the use of marketed "kits" that are simply packaged ingredients still requiring combination and mixing be specifically included within the definition of compounding.*

12 - Since ophthalmic and respiratory preparations are not included in 1.1 Scope because, as sterile preparations, they fall under the scope of USP 797, we recommend that this fact should be mentioned here.

27 - The section "Affected Personnel and Settings" USP 795 is declared to apply to "pharmacists, technicians, physicians, veterinarians, dentists, naturopaths, chiropractors, and nurses, in all places including but not limited to pharmacies, hospitals" and other healthcare institutions, patient treatment sites, and physicians' or veterinarians' practice sites."

24 - All content concerning hazardous drugs is removed; the reader is referred to USP 800.

41 - Following precedent set in USP 800, a "designated person (DP) is required who bears overall responsibility and accountability for "the performance and operation of the facility and personnel in the preparation of CNSPs." A detailed list of responsibilities is included.

> *While an admirable concept, this list does not include all duties and responsibilities described in subsequent sections of the chapter. We therefore suggest that this list be expanded to include these additional elements.*
>
> *Since the chapter allows these duties to be distributed among more than one individual, we recommend that in such cases the chapter stipulates that a "lead" DP must be identified.*

66 - An excellent addition would be a "box" describing minimal aspects of compounding technique, including equipment use, as there is no standardization in this regard currently available.

83 - An actual list of some eight topics to be covered in mandatory compounder training is provided in the new revision. The list of nine training steps present in the existing version is streamlined and reorganized into four in the new version.

> *This change is admirable in that it will standardize and improve the quality of training programs.*

113 - The draft stipulates that if a compounder is the only such employee within an organization that he/she must obtain "appropriate" documented external training and competency assessment.

> *We recommend that the chapter stipulate whether this requirement applies only to initial training and competency assessment, or for ongoing training and competency as well. We recommend that latter.*

We think that this requirement is too restrictive in that such training and assessment could be performed on site by an external third party, and therefore recommends changing Line 114 to read: "person must document that they have obtained appropriate training and competency assessment either at another facility, or on site from a visiting preceptor with appropriate credentials."

118 - The section devoted to personal hygiene and garbing is significantly expanded, resulting in useful detail based upon widely held best practices.

In Lines 129 and 350 the term "designated" is added to the phrase "compounding area."

We recommend that this word is either dropped from these two lines since it does not appear in the 12 other instances of "compounding area," and does not appear to add useful additional meaning.

129 - While in most cases recognized best practices, we feel that the list of items not permissible in a designated compounding area is overly prescriptive, and suggest the following alternate language:

"Before entering a designated compounding area, compounding staff must remove any items that are not easily cleanable, that might interfere with garbing or compounding, or that might compromise the cleanliness of the compounded product. This may include head cover, piercings, jewelry, and long or ornate fingernails."

140 - Detailed requirements for hand hygiene are introduced.

141 - We suggest editing Lines 141 - 146 as follows to more clearly differentiate the cleaning of hands versus gloves:

"Hand hygiene is required whenever entering and reentering the compounding area. Gloves should be washed with soap and water or preferably replaced prior to initiating any compounding activity related to a new CNSP. Gloves must be changed in the event of known or suspected holes or tears."

159 - Unsoiled gowns may be reused, but only during the same "work shift."

We feel that while this is an acceptable requirement for high volume compounders, it will result in the wastage of significant quantities of gowns for small compounders. We suggest that a qualifier to this effect be added, e.g. “at least weekly.”

160 - The draft stipulates that "Gloves, shoe covers, hair covers, facial hair covers, face masks, or head coverings, coverings, if used, may not be reused and must be replaced with new ones.

Lines 166-168 state that "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.

While we see this as a useful requirement, it seems that such a vague definition will lead to extremes of interpretation. Additional clarifying language is recommended.

178 - We suggest changing "prevent" to "minimize"

187 - We suggest moving this "See Also" to the end of line 181.

189 - Compounding area walls, ceilings, storage areas and work surfaces are specifically required to be "cleanable." Carpet is specifically forbidden in the compounding area.

> *We believe that ceilings should be removed from this sentence and given separate attention. While ceilings should be kept free of visible dust and other particulate, and should be free of cracks or stains, "cleaning" need not require the use of liquids.*
>
> *We recommend adding language that floors, and walls "should" be smooth and nonporous to be easily cleanable.*

210 - We believe that further guidance concerning the selection of cleaning and sanitizing agents would be helpful. For example, isopropyl alcohol, while a disinfectant, is not a detergent or deactivating agent. Hypochlorite and peroxide-containing products on the other hand can combine disinfecting, detergent and deactivating activity.

214 - A specific schedule for cleaning compounding walls, ceilings and storage areas is presented in Table 1.

> *We see this as a helpful addition.*

224 - We suggest that this long sentence should be divided as follows:

> *"Automated, mechanical, electronic, and other types of equipment used in the compounding or testing of compounded preparations must be inspected prior to use."*
>
> *"The accuracy of this equipment must be verified at the frequency recommended by the manufacturer, and at least annually."*

However, this second sentence then has some issues. At the very least it should be rewritten as follows:

- *The accuracy of this equipment must be verified at the frequency recommended by the manufacturer or annually, whichever is less.*
- *Yet "annual" seems arbitrary: what is the rationale for this frequency? We suggest that manufacturer recommendations be followed "under normal operating conditions."*
- *Also, what equipment is included here? Ointment mills? Capsule machines? Who is to do this, and how? We recommend the following rewrite of this sentence:*
- *"The accuracy of equipment must be verified as per manufacturer recommendations or more frequently based upon conditions of use."*

243 - A new Table 2 presents minimum required cleaning frequencies for equipment, CVEs and work surfaces.

> *We recommend stipulating that equipment should also be cleaned "between compounding of different drugs" if appropriate - e.g. ointment mills, capsule machines.*
>
> *We recommend that when Table 2 requires the cleaning of compounding equipment "before first use" that this wording be clarified to "before first use each day (or shift) to avoid ambiguity.*

249 - We suggest stating that electronic versions of SDSs are acceptable if properly reviewed and stored in a readily retrievable manner.

253 - While we agree that someone should be responsible for component selection, requiring this of the DP is unnecessarily restrictive. However, if this language remains, this duty should be added to the other DP duties found in Section 1.1.

254 - As written the chapter requires the compounder to "qualify" vendors.

> *We believe that "qualification" is a duplicative and burdensome step as long as FDA-approved suppliers are used. This section should be edited to reflect this interpretation.*

289 - This line seems to imply that the compounder must compare each COA to the monograph; the use of FDA-registered suppliers makes this a redundant and time-consuming process.

294 - This line seems to imply that every time an MFR is used the COAs of all products used would require review. As this would be a pointless and time-consuming requirement, we feel that this language should be edited.

301 - The requirement of the current version that an expiration date be placed on any received API that does not already have one has been dropped.

> *We believe that the required posting of an expiration date on APIs lacking one already should be retained as this provides a rapid and easy way for employees to check inventory for expired items.*

306 - the requirement that "The compounding facility must keep a written record of each shipment of components received in accordance with the recordkeeping requirements described in 14. Documentation" should in the opinion of the NCCG be clarified to allow existing documents such as invoices or packing slips to serve this function.

331 - we recommend deleting this line, which states that "Moisture-sensitive ingredients must be stored in tight, well-closed containers," since leaving this sentence would imply that some ingredients are <u>not</u> moisture-sensitive.

334 - The maximum expiration date that may be assigned to ingredients received without expiration dates is one year, versus three years in the current version.

> *We believe that such an arbitrary change, one that will markedly increase product costs due to more frequent turnover, must either be returned to the current three-year limit or supported by sound rationale.*

346 - Information on any new chemical, e.g. its SDS, must be "made accessible" to workers prior to the initial use of the chemical.

350 - At least one spill kit must be available in the compounding area. It must be inspected at least annually for suitability and expiration date. Employees who might need to handle spills must receive documented training. This documented training must be repeated annually.

366 - The section on SOPs no longer provides a list of minimal topics that must be covered. The section also specifies that employees must be able to recognize, report and document CNSP defects.

The chapter should follow the precedent begun with 800 of presenting an actual minimum list of SOP topics. Since such topics are mentioned many times throughout the chapter, this would be a convenience to the compounder.

394 - Required elements of the MFR are reorganized and reworded as shown in Box 7-1. The source of BUD information is added as a requirement. Not present in the draft are:

- **compatibility and stability information, including references when available**
- **calculations needed to determine and verify quantities of components and doses of active pharmaceutical ingredients**
- **sample labeling information, which shall contain, in addition to legally required information on:**
- **quality control procedures and expected results.**
- **4. prescription or control number, whichever is applicable.**

We suggest editing text box element "Complete instructions for preparing the CNSP, including equipment, supplies, and a description of the compounding steps" to include "calculations as needed" since this is present as a requirement in the current version, and a required element of the CR in this draft.

394 - We believe that this line, "Quality control procedures (e.g., pH, visual inspection)" should be edited to include "and expected results." This element is present in the existing chapter and is of great importance.

409 - Although rearranged and reworded, all CR elements required in the current version are required in the revision except "duplicate label as described in the Master Formulation Record." Also, "Reference source of the BUD assignment and storage requirements" is added in the draft.

We recommend removing the requirement for the reference source of the BUD, as this is not needed during the compounding process, and is readily available in the MFR.

409 - We suggest changing "Signature or initials of individuals involved in each step" to "Signature or initials of individuals involved in compounding or checking the CNSP. It must be clear which actions each individual performed."

409 - We suggest changing "Total quantity compounded" to "Total quantity compounded, e.g. number of units, volume, or weight"

409 - We suggest adding "Residual amounts should be recorded for controlled drugs."

413 - We recommend adding that this "after completion" step is part of the checking process, and that the results are documented on the CR.

418 - The draft does not require that these "checks and inspections" be documented, or where.

Such detail should be added.

450 - We recommend that explicit language be added stating that "the full names and quantities or concentrations of all active ingredients must be present on the label of any CNSP."

465 - The NCCP recommends that the labeling process be clearly tied into the compounding and checking process.

534 - BUD limits for CNSPs without additional stability studies is presented in Table 3 in the draft. This information is displayed using different preparation types than in the current chapter. Via footnotes, the identities of various preparation types are specified. (see the "BUD Comparison" attachment.)

The most significant changes are (a) the BUD of non-aqueous liquid CNSPs is lowered from 180 to 90 days (b) no BUD, even if supported by full stability, microbial growth and container compatibility studies, may exceed 180 days.

This information is presented in a more usable manner than in the existing chapter. It is helpful to introduce the term "water activity" (Aw) as a means of differentiating aqueous and non-aqueous preparations.

> *However, the halving of the BUD for non-aqueous liquids to 90 days is not explained or supported by evidence and will result in significant increases in cost to most compounders and presumably, patients. Hydrolysis is the most common form of chemical degradation and these formulations contain no water. This number should either be returned to 180 days, or the 90 days limit fully explained and supported.*
>
> *Similarly, setting a maximum 180 BUD for CNSPs even if supported by studies is not explained will adversely affect many compounders and their patients. This requirement must be either fully explained or removed.*
>
> *Thought should be given to retaining the topical ("non-oral") category as exists in the current chapter for non-preserved aqueous products with a BUD of 30 days.*

610 - A documented annual "assessment of the QA and QC programs is a new requirement.

> *This seems a prudent and reasonable addition. However, some detailed guidance or examples would be of help.*

635 - Refrigerated and frozen storage requirements are not reviewed in this section, or elsewhere in the draft.

> *We suggest that these topics should be addressed as controlled room temperature storage has been.*

643 - While we are encouraged to see the allowance of electronic monitoring of temperatures, we suggest that if such devices are exclusively used then they must include an automated out-of-range alert feature that is validated periodically, e.g. annually. Otherwise out-of-range conditions might exist for an indefinite period without recognition.

We also suggest stating that the electronic monitoring of humidity (again providing an out-of-range alert system exists) be included.

644 - The draft now requires the calibration or verification of temperature monitoring devices "every 12 months or as recommended by the manufacturer."

While this is seen as a prudent addition, we suggest editing the language to clarify if every 12 months is a minimum frequency. In other words, if manufacturer recommendations state every three years, which frequency is to be followed?

While not specifically required, we recommend that pharmacies document such device calibration / verification.

647 - A humidity target of 60% or less is specified for the first time for areas containing CNSPs.

While we think this is a prudent addition, we recommend that relative humidity (RH) be stipulated in this and other chapters, e.g. USP 797.

We also want to point out that while a careful reading of the chapter finds that the temperature and humidity requirements found in this section apply to all areas where CNSPs or components are found, it would be helpful to state this more clearly in one or more other sections of the chapter.

665 - This section stipulates that a compounder must have an SOP concerning the handling of complaints. It goes on to provide considerable required detail as to the handling of complaints.

This section is an admirable addition and provides useful guidance concerning this important issue.

695 - Detailed requirements concerning the recording, management and reporting of adverse events is also included for the first time.

This section is another admirable addition and provides useful guidance concerning this important issue.

707 - This section has been rewritten to list all the types of documents and records that a compounder must create and maintain. It provides guidance as to how long they must be retained.

While useful, we suggest that COAs be included.

728 - The Glossary is expanded from 11 terms in the current version to 29 in the draft.

838 - A small, non-exhaustive list of acronyms is added to the proposed draft.

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Current Chapter

Preparation Form			Solutions	Suspensions	Emulsions	Semisolids	Ointments	Creams	Pastes	Gels	Manufactured API(s)	USP / NF API(s)
Solid						x		x	x	x	lesser of (6 mo or 1st expiration date)	6 months (180 days)
Liquid	Nonaqueous		x	x		x	x		x			
	Aqueous	Oral	x	x	x					x	14 days at ≤ 5° C	
		Non-Oral	x	x	x					x	lesser of (30 days or duration of therapy)	
All Other												

Table 3 of Draft

.			Capsules	Tablets	Granules	Powders	Suppositories	Ointments	Fixed Oils	Waxes	Emulsions	Gels	Creams	Solutions	Sprays	Suspensions		BUD[1]	
Solid			x	x	x	x												180 days at CRT[2]	
Liquid	Nonaqueous (Aw ≤ 0.6)						x	x	x	x								90 days at CRT[2]	
	Aqueous (Aw > 0.6)	Non-preserved									x	x	x	x	x	x		14 days under refrigeration[3]	≤ 180 days if supported by stability / microbial / container compatibility study
		Preserved																30 at CRT	

1 - In all cases, if the expiration date of any ingredient is less than what is shown in this table, it becomes the the BUD.

2 - Controlled room temperature: 20 to 25° C, 68 to 77° F

3 - 2 to 8° C, 36 to 46° F