USP <795> & <797> 2021 REVISIONS: A QUALITY UPGRADE OR AN UNDUE BURDEN?

PART I USP <795> REVISIONS

With the revisions of both major USP compounding chapters comes much potential change for how compounding and health system pharmacies operate when it comes to both non-sterile and sterile compounding. Given the history of the most recent revisions, with the appeals and formal meetings between USP Compounding Expert Committee Members and key stakeholders, this newly appointed cycle of committee members had a lot of time to think about and come up with rationale for the changes to these chapters. The main question that must be answered is this: do these changes increase the quality of compounding and lower the risk of potential harm to the patients receiving compounded medications? In this article series we're going to look at some of the changes made to each of the chapters and use this question as a means for measuring their purported intention.

USP CHAPTER <795>

Since 2012, with the New England Compounding Center's nationwide meningitis outbreak, industry regulators have shifted their focus and attention to compounding pharmacies. The revisions to both chapters reflect priorities that have changed and a drive toward building quality into the compounding process rather than trying to test our way to quality. What exactly do I mean by that? Personnel training and competency evaluation are put front and center in the newest revision to USP <795>. Training, quality assurance and quality control in the current version of <795> are almost an afterthought that gets rearranged to the beginning of the chapter and expanded upon in the latest revision.

As a side note, the USP Committee also released scientific rationale document for changes to the chapters and a separate document specifically for the rationale of the beyond use dates (BUDs) for each chapter. The last document released is a reference guide for what USP considers to be a stability study. For now, this remains a reference. However, there has been talk in USP Committee meetings that this document itself could eventually become an informational chapter.

<795> PERSONNEL TRAINING & EVALUATION

Knowledge of core competencies must be evaluated by operator demonstration at least every 12 months. These core competencies include:

- Hand hygiene
- Garbing
- Cleaning and sanitizing
- Handling and transporting components and CNSPs
- Measuring and mixing
- Proper use of equipment and devices selected to compound CNSPs
- Documentation of the compounding process (e.g., Master Formulation and Compounding Records)

The revised chapter continues, "Steps in the training procedure must include the following:

- Read and understand this chapter, other applicable standards and other relevant literature
- Understand and interpret safety data sheets (SDSs) and, if applicable, certificates of analysis (COA)
- Read and understand procedures related to their compounding duties"

All of this is to be overseen by a "designated person(s)" that is responsible for maintaining

training records among many other responsibilities. You can think of the designated person almost as your quality control/quality assurance manager; they

hold many of the same responsibilities if compared side-by-side.

<795> CLEANING & SANITIZING

Table 1. Minimum Frequency for Cleaning and Sanitizing in Nonsterile Compounding Area(s)-Surfaces

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Between compounding CNSPs with different components
Floors	• Daily, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Walls	• Every 3 months, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Ceilings	• When visibly soiled and when surface contamination (e.g., from splashes) is known or suspected
Storage shelving	• Every 3 months, after spills, and when surface contamination (e.g., from splashes) is known or suspected

In the revision to USP <795> there are minimum frequencies for cleaning and sanitizing non-sterile compounding area surfaces and equipment.

Table 1. Minimum Frequency for Cleaning and Sanitizing in Nonsterile Compounding Area(s)-Equipment

Site	Minimum Frequency
CVE	• At the beginning and end of each shift, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Clean and sanitize all horizontal work surfaces of the CVE between compounding CNSPs with different components
BSC	• At the beginning and end of each shift, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Clean and sanitize all horizontal work surfaces of the CVE between compounding CNSPs with different components • Clean and sanitize under the work surface at least monthly
Other devices and equipment used in compounding operations	• Before first use and thereafter in accordance with the manufacturer's recommendations • If no recommendation is available, between compounding CNSPs with different components

DOCUMENTATION FOR <795>

Documentation has a large part in USP Chapter <795>. As I'm sure you've heard this saying before, "if you don't document it, it didn't happen." It's the last section in the revision of <795> but really documentation of various compounding activities and other events (e.g., recalls, customer complaints, investigations and corrective actions), is sprinkled throughout the chapter. In section 15 of the revision it states, "documentation must include, but is not limited to, the following:

- Personnel training, competency assessments and qualification records including corrective actions for any failures

- Equipment records (e.g. calibration, verification and maintenance reports)
- COAs and all documentation required for components not conventionally manufactured
- Receipt of components
- SOPs, MFRs, and compounding records
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigations and corrective actions
- Records of cleaning and sanitizing the designated compounding area
- Temperature logs
- Accommodations to personnel compounding CNSPs
- Any required routine review (e.g., yearly review of QA and QC programs, yearly review of chemical hazard and disposal information)

One key part of the documentation is the retention of records which "must be readily retrievable for at least 3 years after preparation or as required by the laws and regulations of the applicable regulatory jurisdiction, whichever is longer."

<795> QUALITY ASSURANCE & QUALITY CONTROL

Just to make sure everyone is on the same page, let's discuss the difference between quality assurance and quality control. The revision says quality assurance is "a system of procedures, activities, and oversight that ensure that the compounding process consistently meets quality standards." However, quality control, "is the sampling, testing and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP."

To oversimplify this point: QC is all of the data collected to prove your facility and processes are under a state of control and QA is the system that puts all of the QC activities in place in order to "assure" quality.

Any task that is critical to the overall quality of the product, that is anything that can affect the quality, safety, ingredient, purity and potency (QSIPP) of the final preparation, should be measured. In other words, you should have a quality control check in place to ensure the compound is meeting specifications.

To walk through a simplified QA/QC process from beginning to end as an example let's look at the receipt and use of an active pharmaceutical ingredient (API). The revision to <795> would have you:

1. Document the receipt of the API
2. Document you verified critical attributes on the COA (i.e. potency, purity etc.)
3. If the potency is less than 100%, perform calculations to get the final concentration to as close to 100% as possible
4. Document the calibration of the scale
5. Document the weight of the API used, show calculations on the batch required if applicable
6. Document the accuracy and other quality attributes of the preparation on the compounding record (i.e., visual inspection, appearance, smell etc.)
7. Document whether final release testing was performed
8. Attach any analytical testing documentation to the batch record.

The backbone of your quality assurance and quality control systems are your Standard Operating Procedures (SOPs). All of the records and data that you're collecting should be dictated by your SOPs. While buying a bundle of SOPs can save you time to some degree, quite a bit of customization will need to be done in order to make the SOPs work for your facility.

ESTABLISHING BEYOND USE DATES

Last but certainly not least, establishing beyond use dates for CNSPs. The controversial topic that delayed the revisions has been made much clearer in the 2021 revision. As previously stated, there are even scientific rationale documents for why the standards are written as is.

The chapter clarifies what parameters must be considered when establishing a BUD for a CNSP. The chapter says, "when establishing a BUD for a CNSP, compounders must consider parameters that may affect stability including but not limited to:

- Chemical and physical stability properties of the API and any added substances in the preparation (e.g., if the API and added substances in the preparation are known to rapidly degrade over time and/or under certain storage conditions, reduce the strength of the preparation, or produce harmful impurities)
- Compatibility of the container closure system with the finished preparation (e.g., leachables, interactions, adsorption, and storage conditions)
- Degradation of the container closure system, which can lead to a reduction in integrity of the CNSP
- Potential for microbial proliferation in the CNSP
- Significant deviations from essential compounding steps and procedures; changes to essential compounding steps may have an impact on the stability of the formulation"

Table 4. BUD Limit by Type of Preparation in the Absence of a USP-NF Compounded Preparation Monograph or CNSP-Specific Stability Information

Type of Preparation	BUD (days)	Storage Temperature[a]
Aqueous Dosage Forms ($a_w \geq 0.60$)		
Non-preserved aqueous dosage form[b]	14	Refrigerator
Preserved aqueous dosage form[b]	35	Controlled room temperature or refrigerator
Nonaqueous Dosage Forms ($a_w < 0.60$)		
Oral liquids (nonaqueous)[c]	90	Controlled room temperature or refrigerator
Other nonaqueous dosage forms[d]	180	Controlled room temperature or refrigerator

a See *Packaging and Storage Requirements* ⟨659⟩

b An aqueous preparation is one that has an $a_w \geq 0.6$ (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).

c A nonaqueous oral liquid is one that has an $a_w < 0.6$.

d Capsules, tablets, granules, powders, nonaqueous topicals, suppositories, and troches.

BEYOND USE DATING - WHAT IS WATER ACTIVITY?

Chapter <795> describes water activity as the "available water to support microbial growth and hydrolytic reactions." Water activity (a_w) is certainly not a new metric for the preservation of products. In fact, it's been used in the food industry for decades. It even pre-dates modern history when you think about the drying of food. While all the principles of water activity may not have been understood, humans knew that drying food preserved it.

To fully understand what water activity is, let's talk about how water interacts inside food and most importantly for this conversation, your preparations. When we're talking about pure distilled water, it has a water activity of exactly one. However, when measuring the water activity in food or a

pharmaceutical, not all water is free, rather it is bound to ions, surface molecules or cell structures. The amount of free or available water is what is referred to as a substance's water activity.

Preparations or foods that have a water activity of less than 0.6 (or 60% free water) are considered to have "low" water activity. Which, in real terms, means that they do not support the growth of microorganisms and tend to be more stable since water also participates in chemical reactions that can lead to a breakdown in the stability of the compound.

EXTENDING BUDS WITH STABILITY STUDIES

There is a pathway to extend beyond use dates up to a maximum of 180 days. First, if there's a USP monograph that you're following, you're able to use the given beyond use date. If there's no monograph but there's a stability study that's been performed, using a stability indicating analytical method, whether it's published or not, this may be used to extend the BUD; again, up to a maximum of 180 days.

For aqueous CNSPs if you're extending the BUD, antimicrobial effectiveness testing (USP <51>) must be performed to ensure the preservative will adequately maintain stability for the labeled BUD. A compounder may also extend a BUD if there are published antimicrobial effectiveness studies conducted "by an FDA-registered facility or published in peer-reviewed literature as long as the CNSP formulation (including any preservative) and container closure materials of composition are the same as those tested (unless a bracketing study is performed)."

THE ONLY PATH IS FORWARD

While some will take issue with the BUD provisions in the revisions of both <795> and <797>, they have sound, scientifically backed, risk-based rationale. Sterile and non-sterile compounding is coming of age with these much-needed updates. However, just like many things in life, we can do this the easy or the hard way. As I hope I've made clear throughout this summary is that quality and the documentation of is going to be an integral part to compliance with these standards if they become final.

When it comes to documentation, a quality management system is essential for keeping all your records in one place. Even if you're a small operation, the amount of data and records that you'll need to maintain may make your paper-based system obsolete. I highly recommend looking into a quality management system like Compounding360 by PharmacyStars. It is highly customizable, non-destructive (cannot delete or alter records) and easy to use.

Do all these changes make for a safer compounding environment that limits the risk to patients? What these revisions are intending to do is bring a higher level of quality assurance for your compounded preparations. With the emphasis on training and evaluation of operators, there's an increase in assurance that processes and procedures are being followed according to policies. The increased documentation and focus on corrective actions, directs compounders to increase the chances of catching and correcting errors and out of specification results before they reach the patient. There are quite a few changes intended to increase quality and safety for patients in this revision.

A culture change is desperately needed in compounding in general, focusing on increasing the quality of our processes and procedures using quality controls and data collection. A paradigm shift must occur with our thinking centered on a culture that is continuously improving and focused on quality.

If you'd like help with any compliance issues related to USP <795>, <797> or GMPs, always feel free to reach out to me personally, Seth DePasquale, at sdepasquale@visanteinc.com. I'm a board-certified sterile compounding pharmacist and consultant with personal experience in both sterile and non-sterile compounding. It's not that compliance can't be achieved alone but having an experienced guide can make all the difference.

REFERENCES & LINKS

1. United States Pharmacopeial Convention. USP General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations, Proposed revisions 2019 and 2021
2. (2014) Safefood360. White Paper Water Activity (a_w) in Foods. https://safefood360.com/resources/Water-Activity.pdf

You can download all of the documents referenced in this article (and I highly encourage you to) here (https://go.usp.org/Proposed_2021_Revisions_795_797). At the beginning of each of the revised chapter documents there is a link to make comments for the USP Committee, but you can also click here to make comments on USP Chapter <795>. (https://usp.az1.qualtrics.com/jfe/form/SV_3OBK7VUbvver6zs) -

In part 2 of this series, I'm going to provide a summary of the 2021 revision of USP Chapter <797>.