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>.

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

PART II USP <797> 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 <797>: A CRITICAL BALANCE

In part II of this series, we're going to talk about some of the major changes to USP <797> or what may be required for sterile compounding if it is finalized. As previously stated in the first article of the series, the New England Compounding Center's nationwide meningitis outbreak really changed the way regulatory bodies have looked at compounding pharmacies, especially if they're performing sterile compounding. The Food and Drug Administration (FDA) have dedicated a lot of time and effort toward putting more focus on compounding pharmacies prioritizing their efforts by risk. This means that if your pharmacy performs what's considered high risk sterile compounding or those procedures that start with non-sterile ingredients, have been at the top of their priority list. The days of the FDA only showing up at your pharmacy door if they received a complaint are long gone. The FDA wants to have eyes on the operations that are performing high risk sterile compounding to see that they have processes, procedures and quality systems that can guarantee quality and detect when something may not be going as it should be by having the proper quality controls in place.

It's no secret that the FDA has a seat at the table at the United States Pharmacopeia expert committee member meetings as a government liaison. Usually, several people from the FDA are in attendance and have a large part in how the chapter has evolved. The FDA has experts in several areas including microbiology, quality assurance and control that usually have input on what goes into the chapter. As a counterbalance, one of the major pharmacy organizations, the Alliance for Pharmacy Compounding (A4PC, which is largely composed of compounders), usually will contend some areas of the proposed chapter revision to keep the chapter in balance so compounding won't be made cost prohibitive to patients or worse, not allow patients access to some of the life-saving treatments that compounding pharmacies make and those medications that traditional manufacturers and 503B pharmacies don't produce.

The changes found in the most recent revision of USP Chapter <797> are really a compromise between A4PC and the FDA and some of the contentions A4PC had with the original 2019 revision. The USP Expert Committee has for the most part, in my opinion, done an excellent job in striking a balance between trying to increase the expectations of compounders when it comes to quality assurance and control while also keeping in mind that patients are really the focus, we should all be paying attention to. That is, patient safety and access to critical medications that only 503A compounding pharmacies provide.

<797> COMPOUND CATEGORIES

At the center of USP Chapter <797> is really the compounded sterile preparation (CSP) categories. Depending on the category of the CSP being prepared will dictate how and where it is compounded, meaning what environmental controls will be in place, how much post-compounding testing, if any, will be performed as well as the beyond use date (BUD) that compounders will be able to label their compound with. In the revised chapter there are several tables that illustrate what BUDs can be used given certain parameters. Let's first mention that there are 3 categories in this revision as opposed to 2 in the 2019 version.

Category 1 CSPs have the least number of requirements imposed on them meaning they're expected to at least be compounded under controlled environmental conditions in a segregated compounding area or a cleanroom.

Table 10. BUD Limits for Category 1 CSPs

Storage Conditions	
Controlled Room Temperature (20°-25°C)	Refrigerator (2°-8°C)
≤ 12 h	≤ 24 h

In the revision, Category 2 CSPs have a table (table 11) that illustrates the BUD limits for those compounded according to Category 2 requirements.

As you can see from table 11., Category 2 CSPs BUDs depend on a few critical factors:

- Compounding method (aseptically processed vs terminally sterilized)
- Whether sterility testing was performed and passed
- Storage conditions

With Category 3 CSPs, the opportunity to extend BUDs up to 180 days is possible. However, there are several requirements that must be met. First, any BUD must be supported by stability data, "using a stability indicating analytical method that is able to distinguish the active ingredient from its degradants and impurities (e.g., by forced degradation studies) and quantify the amount of the active ingredient."

Additional requirements for Category 3 CSPs are:

Facility and Personnel Requirements for Category 3 CSPs

- Personnel must pass garbing, hand hygiene and media fill every 3 months – media fill with surface monitoring (all done together)
- Garbing must be sterile and not allow any exposed skin in buffer room (face and neck
- must be covered), disposable garb may not be re-used…
- Environmental monitoring: Viable Air – at least monthly, viable surface – at least weekly and after compounding procedures

Table 11. BUD Limits for Category 2 CSPs

Preparation Characteristics		Storage Conditions		
Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20°-25°C)	Refrigerator (2°-8°C)	Freezer (-25° to -10°C)
Aseptically processed CSPs	No	Prepared from one or more nonsterile starting component(s): 1 day	Prepared from one or more nonsterile starting components(s): 4 days	Prepared from one or more nonsterile starting components(s): 45 days
		Prepared from only sterile starting components: 4 days	Prepared from only sterile starting components: 10 days	Prepared from only sterile starting components: 45 days
	Yes	30 days	45 days	60 days
Terminally sterilized	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

- Sporicidal use increased to weekly for Category 3 CSPs

Stability Data Requirements for Category 3 CSPs

- Stability indicating methods must be used
- CSPs must be prepared according to exact formulation from which the stability data is derived
- CSP must use same packaging and container closure as used in the study
- Stability study documentation must be available including description of methodology (e.g., number of samples taken, storage conditions), validation of the method, the stability-indicating analytical method, and all of the result of the study

Release Testing for Category 3 CSPs

- Test according to USP <71> or validated alternative method that is not inferior to <71> testing, with acceptable results
- Must test for bacterial endotoxins when indicated by dosage form.

Table 12: BUD Limits for Category 3 CSPs

Preparation Characteristics	Storage Conditions		
Compounding Method	Controlled Room Temperature (20°-25°C)	Refrigerator (2°-8°C)	Freezer (-25° to -10°C)
Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs	60 days	90 days	120 days
Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs	90 days	120 days	180 days

<797> PERSONNEL TRAINING & COMPETENCY

In the revision to USP <797> there's now a requirement for a designated person who is responsible for overseeing training of personnel involved in sterile compounding. This is just one of the many responsibilities of the designated person(s); more to follow.

As you might already be able to tell, the compounding categories are the dividing line for the frequency with which many tasks are to be performed. Training and competency evaluation is no different. At minimum, for the *core skills of compounding*, "competency must be **demonstrated, and written or electronic testing** must be completed initially and at least every 12 months." (emphasis added)

According to the revision of <797> the core skills of compounding include:

- Hand hygiene
- Garbing
- Cleaning and disinfection
- Calculations, measuring, and mixing
- Aseptic technique
- Achieving and or maintaining sterility and apyrogenicity
- Use of equipment
- Documentation of the compounding process (e.g., master formulation and compounding records)
- Principles of high-efficiency particulate air (HEPA)-filtered unidirectional airflow within the ISO Class 5 area
- Proper use of primary engineering controls

- Principles of movement of materials and personnel within the compounding area

<797> ASEPTIC MANIPULATION COMPETENCY

The competency evaluation for garbing has been modified to include not just hand hygiene and donning garb with a glove fingertip and thumb sampling, but also includes performing a media fill test in conjunction with the garbing competency. To clarify, how exactly this would be accomplished is an operator would perform hand hygiene and garbing, then perform a media fill test then have their gloved fingertips and thumbs (of each hand) sampled using growth media.

For hand hygiene specifically, the revision makes note that, "brushes must not be used for hand hygiene. Hand dryers must not be used. A closed system of soap (i.e., nonrefillable container) to minimize the risk of extrinsic contamination must be readily available or in close proximity to the sink."

For Category 1 and 2 CSPs this evaluation would be done initially and then every 6 months thereafter. For Category 3 CSPs, operators must complete initially and then every 3 months thereafter.

One additional important change is the **collection of a surface sample after the media fill** of the direct compounding area. USP <797> states, "a failure in the media fill, gloved fingertip and thumb sampling, or surface sample constitutes an overall failure of the aseptic manipulation competency."

A couple important notes that you should take about media fills that the revision points out are:

- Media fills simulate the most difficult and challenging compounding procedure
- The simulation MUST capture elements that could affect sterility including the length of the procedure, number of and complexity of aseptic manipulations and the number of personnel in the cleanroom during the procedure.

<797> GARBING REQUIREMENTS

The minimum requirements for garbing for Category 1 & 2 CSPs include:

- Low-lint garment with sleeves that fit snugly around wrists and an enclosed neck
- Low-lint shoe covers
- Low-lint cover for head that covers the hair and ears, and if applicable, cover for facial hair
- Low-lint face mask
- Sterile powder-free gloves

Gowns may be reused within the same shift for category 1 & 2 CSPs as long as the gown is, "maintained in a classified area or inside the perimeter of a segregated compounding area (SCA).

As previously mentioned, with Category 3 CSPs, all garb must be low-lint and sterile, single use (if disposable) and cover 100% of the skin.

<797> FACILITY DESIGN & ENVIRONMENTAL CONTROLS

The designated person(s) is mentioned for being responsible, "for ensuring that each area related to CSP preparation meets the classified air quality standard appropriate for the activities to be conducted in that area. The designated person(s) must also ensure that the ISO Class 5 areas are located, operated, maintained, monitored, and certified to have appropriate air quality."

Having a designated person or team of people that are responsible for many of the quality aspects of a compounding pharmacy's operation is not a new idea. In fact, it's standard operation to have a quality assurance team for pharmaceutical manufacturing. Keeping track of quality controls and maintaining an operation that performs either sterile or non-sterile compounding is not necessarily easy if you don't have dedicated personnel devoted to those tasks.

Some other changes in facility design seen in the revision is the prohibition of free-standing

humidifiers, dehumidifiers and air conditioners within classified areas.

Another major change that the revision brings about is the idea of having 2 distinct anterooms; a "dirty" and "clean" anteroom. The first anteroom that would be entered by personnel would be considered the dirty anteroom where hand hygiene and initial garbing would take place. This leads to a change in where the sink may or may not be located. The revision also gives the option of having the sink used for hand hygiene located either inside or outside of the anteroom. This honestly makes a lot of sense given that water can not only be a source of contamination but can allow for the growth of microorganisms in the cleanroom.

Another addition to <797> engineering controls includes requirements for how Category 2 & 3 CSPs that are prepared from non-sterile ingredients. It specifies that, "presterilization procedures, such as weighing and mixing, must be completed in an ISO Class 8 or better environment (e.g., anteroom or buffer room). Presterilization procedures must be performed in single-use containment glove bags, containment ventilated enclosures (CVEs), BSCs, or CACIs to minimize the risk of airborne contamination."

<797> ENVIRONMENTAL MONITORING

Environmental monitoring is a critical component to the quality assurance program to of a suitable environment for sterile compounding or aseptic processing. There are several changes and new requirements to what environmental monitoring must be performed. Of course, like many other aspects of the chapter, it is dependent upon the Category which you are compounding. See the table below for a summary of the types of sampling and frequency for each compounding Category.

USP <797> Revision Environmental Monitoring Requirements

Category	Type of Sampling	Minimum Frequency & Location
Category 1	Air: Total Particle Count	Under dynamic operating conditions at least every 6 months
	Air: Viable Sampling	All Classified Areas under dynamic operating conditions at least every 6 Months
	Surface Sampling	All Classified Areas and Pass-through Chambers at least MONTHLY
Category 2	Air: Total Particle Count	Under dynamic operating conditions at least every 6 months
	Air: Viable Sampling	All Classified Areas under dynamic operating conditions at least every 6 Months
	Surface Sampling	All Classified Areas and Pass-through Chambers at least MONTHLY
Category 3	Air: Total Particle Count	Under dynamic operating conditions at least every 6 months
	Air: Viable Sampling	At least 30 days prior to commencement of compounding and at least monthly
	Surface Sampling	At least WEEKLY & within PEC at the end of every batch (before cleaning and disinfection occurs)

It should also be pointed out that there are changes to the incubation times and temperatures of the various viable sampling that is required. Let's talk first a little bit about the different types of media used for the sampling types. Tryptic soy agar (TSA) is a general growth media that can be used for the promotion of growth of both bacteria and fungi. Malt Extract Agar (MEA) and Sabouraud Dextrose Agar (SDA) are growth media that are typically used to isolate fungi.

One important note is that, generally speaking, bacteria proliferate at a faster rate than fungi which dictates the length of time you need to incubate the media. The revision states that a sampling device needs to be incubated first at 30-35°C for no less than

48 hours. This incubation time and temperature is to see what, if any, bacteria proliferate on the growth media. Next you have the option of using separate media to isolate fungi, such as MEA or SDA or you can continue to incubate TSA but at a lower temperature (20-25°C) for no less than 5 additional days. Keeping TSA in an incubator at 30-35°C for longer than 72 hours tends to dry out the media and could result in a false negative result, meaning a microorganism was present but didn't grow because conditions weren't optimal for growth promotion.

CLEANING AND DISINFECTION OF COMPOUNDING AREAS

Cleaning and disinfection of the compounding areas has been well defined and can best be summarized in Table 8 of the revision presented below.

Table 8. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Agents in Classified Areas and within the Perimeter of the SCA

Site	Cleaning	Disinfecting	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	• Equipment and all interior surfaces of the PEC on days when compounding occurs and when surface contamination is known or suspected	• Equipment and all interior sur-faces of the PEC daily before compounding and when surface contamination is known or suspected • Apply sterile 70% IPA to the horizontal work surface at least every 30 min if the compounding process takes 30 min or less. If the compounding procedure takes more than 30 min, compounding must not be disrupted and the work surface of the PEC must be disinfected immediately after compounding.	• Monthly for entities compounding Category 1 and/or Category 2 CSPs • Weekly for entities compounding Category 3 CSPs
Removable work tray of the PEC	• Work surface of the tray daily on days when compounding occurs • All surfaces and the area underneath the work tray monthly	• Work surface of the tray be-fore compounding on days when compounding occurs • Apply sterile 70% IPA to the horizontal work surface at least every 30 min if the com-pounding process takes 30 minor less. If the compounding process takes more than 30min, compounding must not be disrupted and the work sur-face of the PEC must be disinfected mmediately after compounding. • All surfaces and the area under the work tray monthly	• Work surface of the tray monthly • All surfaces and the area underneath the work tray monthly
Pass-through(s)	• Daily on days when compounding occurs	• Daily on days when compounding occurs[b]	• Monthly for entities compounding Category 1 and/or Category 2 CSPs

Table 8. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Agents in Classified Areas and within the Perimeter of the SCA

Site	Cleaning	Disinfecting	Applying Sporicidal
			• Weekly for entities compounding Category 3 CSPs
Work Surface(s) outside the PEC	• Daily on days when compounding occurs	• Daily on days when compounding occurs	• Monthly for entities compounding Category 1 and/or Category 2 CSPs • Weekly for entities compounding Category 3 CSPs
Floor(s)	• Daily on days when compounding occurs	• Daily on days when compounding occurs	• Monthly for entities compounding Category 1 and/or Category 2 CSPs • Weekly for entities compounding Category 3 CSPs
Wall(s), door(s) and door frame(s)	• Monthly	• Monthly	• Monthly
Ceilings	• Monthly	• Monthly	• Monthly
Storage shelving and bins	• Monthly	• Monthly	• Monthly
Equipment outside the PEC(s)	• Monthly	• Monthly	• Monthly

STERILITY TESTING

There's been a major change to the standard on sterility testing. In USP Chapter <71> Sterility Tests, the standard that describes how sterility testing needs to be performed, also has a table that states the minimum number of articles that need to be tested out of batch. The revision of USP <797> overrides this table to some degree stating that, "the maximum batch size for all CSPs requiring sterility testing must be limited to 250 final yield units."

This is a departure from what the table in USP <71> states because the standard gives the appropriate number of units to send for batches greater than 500 units. What this change does is put a limit on the number of units in any one batch to be compounded.

The accompanying document that gives the scientific rationale for this change states, "contamination within a batch may not be uniformly distributed across all units. Therefore, the probability of detecting contamination during sterility testing decreases as batch size increases, and risk for unidentified contamination increases. The intent is to reduce the risk of patient harm from undetected contamination of CSPs by introducing a batch size limit."

While the rationale is scientifically sound and logical, it's a departure from the table in USP <71> which allows for batches over 500 units. Perhaps a compromise would be to use the number of units from USP <71> for batches over 500 units but limit it to 1000.

ESTABLISHING BEYOND USE DATES

As stated earlier in this article, there have been some distinct changes to how beyond use dates are established for each of the categories.

In fact, the chapter gives specific considerations and factors upon which BUDs are based. The revision states, "when establishing a BUD for a CSP, compounders must consider parameters that may affect stability including but not limited to:

- "Chemical and physical stability properties of the drug and/or its formulation"
- "Compatibility of the container closure system with the finished preparation (e.g., leachables, interactions, adsorption, and storage conditions"

The revision also states that "BUDs for CSPs are based primarily on factors that affect the achievement and maintenance of sterility, which include but are not limited to the following:

- "Conditions of the environment in which the CSP is prepared"
- "Aseptic processing and sterilization method"
- "Starting components (e.g., sterile or nonsterile ingredients)"
- "Whether or not sterility testing is performed"
- "Storage conditions"

QA, QC & DOCUMENTATION

Quality assurance and quality control are toward the end of the chapter but must not be ignored or overlooked. The revision states, "a facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter and laws and regulations of the applicable regulatory jurisdiction. A designated person(s) must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. "Adherence to procedures"
2. "Prevention and detection of errors and other quality problems"
3. "Evaluation of complaints and adverse events"
4. "Appropriate investigations and corrective actions"

The most important thing to understand here is that quality controls are the individual aspects of compounding procedures and processes that are measured such as using a scale to weigh something and documenting that weight in the compounding record. Another example is final preparation testing. Quality assurance is the program put in place that brings all of the quality controls together to ensure a quality preparation is made. Documentation is key in all of this because if it isn't documented, it didn't happen.

When quality controls are not meeting specifications, this needs to be documented and remediated. Having a system that performs corrective and preventive actions (CAPA) when an out of specification result is detected is truly what separates a compounding operation with a mature quality system and one that is lacking.

A CAPA system is a subject of such importance and depth that it really requires its own article (future forthcoming article?), but the basics are that when something is out of specification, it is thoroughly investigated and corrected. As a follow up, a new policy and procedure may be necessary to be put in place to prevent the out of specification result from recurring.

This isn't the only documentation that is expected from the revision. The chapter states, "documentation must include, but is not limited to the following:

- "Personnel training, competency assessments, and qualification records including corrective actions for any failures"
- "Certification reports, including corrective actions for any failures"
- "Environmental air and surface monitoring procedures and results"
- "Equipment records (e.g., calibration, verification and maintenance reports)"
- "Receipt of components"

- "SOPs, Master Formulation Records (MFRs, if required), and compounding records (if required)"
- "Release inspection and testing records"
- "Information related to complaints and adverse events including corrective actions taken"
- "Results of investigations and corrective actions"

This short list further reinforces the kind of quality program that is expected from the chapter.

THAT'S NOT ALL…

While I've highlighted a lot of the changes in the revision, this is just a summary of the some of the most important parts of the revised chapter. I highly encourage the reader to carefully review the chapter for themselves, particularly if you're in a position of authority within your pharmacy organization.

I'd like to point out that this is in draft form and not finalized which allows people to make comments on any part of the revision.

Finally, I'd like to conclude with the same question I started this series with: do all these changes make for a safer compounding environment that limits the risk to patients? As stated in the previous article on <795>, 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 <797> Pharmaceutical Compounding – Sterile Preparations, Proposed revisions 2019 and 2021

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_81VZpnzjwcQJlZA)