

Compounding Essentials: The “NEW” USP <795> :

Pharmaceutical Compounding - Non-Sterile Preparations

NYSCHP – Compounding Mini Series
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Web/Live Session (1 CEU)



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DISCLOSURES -

- Lou Diorio is a shareholder of **LDT Health Solutions, Inc.**, an International Medication Safety and & Quality Management Consultancy.
- The opinions expressed are that of the presenter and based upon the information provided by USP & FDA at the time of the presentation.
 - For the latest USP compendial references go to; **www.USP.org**
 - The latest FDA information and resources can be found at; **www.FDA.gov**

Session Objectives-

• **PHARMACISTS-**

- Categorize the "Aw" (Activity of Water) of CNSPs and its impact on the calculation of proper determination of BUDs.
- Outline the attributes of a compliant non-sterile compounding training program.
- Describe the proper establishment of QA & QC programs in the compounding of non-sterile dosage forms.
- Outline the attributes of a compliant non-sterile master formula record (MFR).

• **Technicians-**

- Describe the functioning of the QA & QC programs as an essential part of the total quality improvement efforts of your compounding program.
- Be able to describe the complete and proper garbing when compounding CNSPs.
- Discuss the physical attributes of a properly designed non-sterile compounding area.
- List five (5) tangible take-aways from compounding operations (compounders) to add to their USP <795> compliance plan.

GROUND RULES -

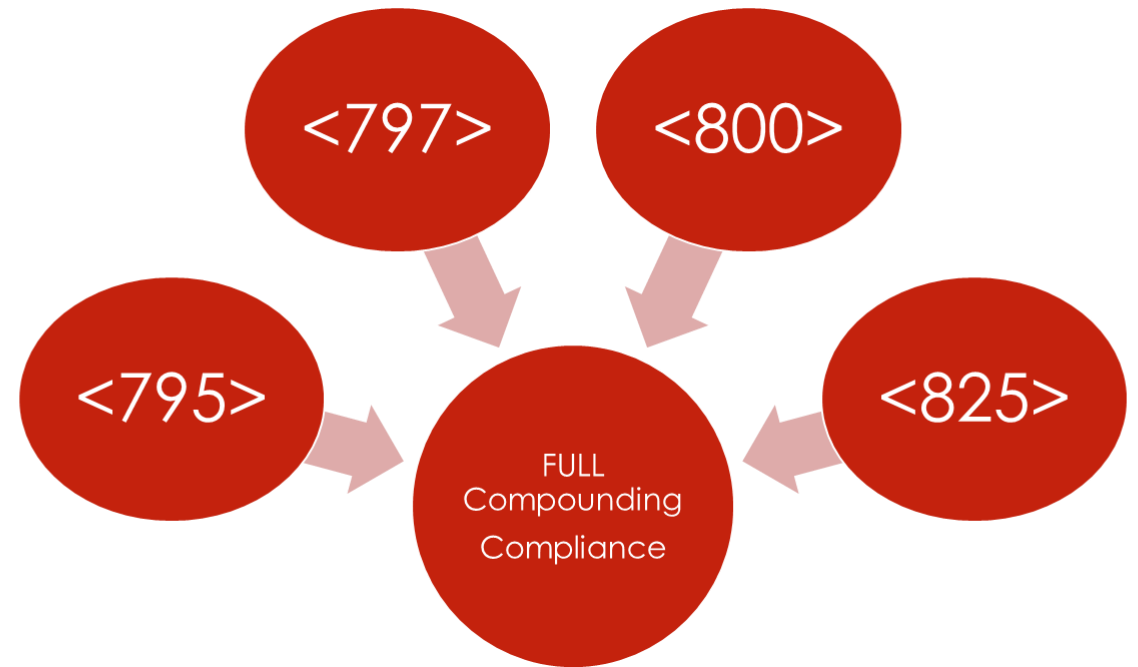
- Please ask questions at any time !
- The “management” reserves the right to defer any questions to the end of the session.



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Be aware of the changes to the structure of the USP compounding chapters -

- The Revised Chapters are both Descriptive and Prescriptive....but could be incomplete if you refer to only one General Chapter, if required.
- Be careful of the “should” “shalls” and the “musts.”
- There are concepts and language that has been harmonized between Chapters.



The road to compounding compliance...



People

Places

Practices



USP <795> Non-Sterile Preparations -

- CNSPs that must comply with this Chapter include but are not limited to the following dosage forms:
 - Solid oral preparations
 - Liquid oral preparations
 - Rectal preparations
 - Vaginal preparations
 - Topical preparations (i.e., creams, gels, and ointments)
 - Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
 - Otic preparations (excluding use in perforated eardrums)

USP <795> Scope -

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

USP <795> Scope *(cont.)* -

- The compounding facility's leadership and all personnel involved in preparing, storing, packaging, dispensing, 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 and dispensing of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

USP <795> Exclusions -

- The following practices are **not** considered compounding and are **not** required to meet the requirements of this chapter. Handling of nonsterile HDs should additionally comply with <800>. Refer to facility SOPs for additional safe practices (e.g., labeling).
- **Nonsterile radiopharmaceuticals**: Compounding of nonsterile radiopharmaceuticals is subject to the requirements in Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging (825).
- **Reconstitution**: Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling
- **Repackaging**: Repackaging of conventionally manufactured drug products (see Good Repackaging Practices <1178> for recommendations)
- **Splitting tablets**: Breaking or cutting a tablet into smaller portions
- **Administration**: Preparation of a single dose for a single patient when administration will begin within 4 h. This includes crushing a tablet(s) or opening a capsule(s) to mix with food or liquids to facilitate patient dosing.

<795> Major Revisions –

- Identification of a “Most Responsible Person” for NS Compounding.
- Harmonization in **language and terminology** from USP <797>.
- Changes in personnel **hygiene and garbing**.
- Addition of **Glove-use** in compounding activities.
- More guidance in relation to the **use of water** in NS preparations.
- Addition of a **formalized training** process and recordkeeping
- More specificity in the **cleaning & sanitizing** of the compounding space(s).
- Changes in **BUD determinations**, with an emphasis on the **Water Activity (A_w)** of the preparation. [ref. USP<1112>]
- Formalization of the **Master Formulation & Compounding Record Documents** used to compound any preparation.
- Refinement in the use of **Quality Assurance & Quality Control**.

NS Compounding Training & Evaluation -

- Training must occur BEFORE beginning to compound.
- Training must occur initially and annually thereafter.
- Training must be documented.
- Training at a minimum must cover the following core competencies:
 - Hand hygiene
 - Garbing
 - Cleaning & sanitizing
 - Handling & transporting of components and CNSPs
 - Measuring & mixing
 - Proper use of equipment & devices selected to compound CNSPs
 - Documentation of the compounding process

NS Compounding Training & Evaluation -

- Training should be formalized, and the process must include:
 - Understanding of requirements in the Chapter.
 - Understand and interpret safety data sheets (SDS) and if applicable certificates of analysis (CoA)
 - Reading and understanding procedures related to their compounding duties



Quality Assurance vs. Quality Control -

- QA is the **SYSTEM** of procedures, activities, and oversight that assures the compounding process consistently meets quality standards.
- QC is the sampling, testing, and **documentation of results** that taken together ensure that all specifications have been met before release of any preparation.



Quality Assurance vs. Quality Control -

- QA systems must establish a system of
 - Adherence to procedures.
 - Prevention and detection of errors and other quality problems.
 - Evaluation of complaints and adverse events.
 - Appropriate investigations and corrective actions.



NS Compounding Training -

- Designated person(s) are responsible for creating and implementing a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel. **This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks.**
- Personnel who compound or have direct oversight of compounding personnel must complete training **initially and at least every 12 months** in appropriate compounding principles and practices as described in this section.
- Other personnel, who do not compound and only perform functions such as in-process checks, final verification, or dispensing of CNSPs, **must undergo training as required** by the facility's SOPs. (*USP <795> sec. 2*)

Physical Plant Attributes for NS Compounding-

- **COMPOUNDING AREA**

- A “designated area” for NS compounding
- Well lit
- Orderly & Sanitary

- **STORAGE AREA**

- Temperature Controlled –Monitored at least DAILY
- Everything must be stored off the floor

- **WATER SOURCES**

- Sink with Hot & Cold must be readily available & cleaned before use in compounding
- Purified Water, Distilled water, or RO water should be used for rinsing equipment & utensils



Establishing a BUD for a CNSP –

- Must be based on chemical & physical stability and the mixture's ability to suppress microbial growth.
- The **water activity** (“a_w”) must be considered.
 - In general, the use of a_w aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. The a_w is different from the water content and may be considered as the available water to support microbial growth and hydrolytic reactions.
 - Nonaqueous dosage forms will not support spore germination or microbial growth due to their low a_w.
 - Reduced a_w greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs.

Establishing Beyond-Use Dates - (from USP <795> Table 4.)

Type of Preparation	Beyond-Use in DAYS	Storage Temperature
<i>Aqueous Dosage Forms ($a_w \geq 0.60$)</i>		
Non-preserved aqueous dosage forms	14	Refrigerator
Preserved aqueous dosage forms	35	Controlled room temperature or refrigerator
<i>Nonaqueous Dosage Forms ($a_w < 0.60$)</i>		
Oral liquids (nonaqueous)	90	Controlled room temperature or refrigerator
Other nonaqueous dosage forms	180	Controlled room temperature or refrigerator

NOTE: For Water Activity Values of Common Compounded Nonsterile Dosage Forms see USP <795> Table 3.

Establishing Beyond-Use Dates -

- BUDs may be extended past the listed maximums dates if one of the following applies:
 - **CNSPs with a USP–NF monograph**: When compounding from a USP–NF compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.
 - **CNSPs with stability information**: If there is a stability study using a stability-indicating analytical method for the API(s), CNSP formulation, and material of composition of the container closure that will be used, then the BUD indicated by the study may be used in lieu of the BUDs specified in Table 4 for aqueous and nonaqueous dosage forms, up to a maximum of 180 days

Minimum Frequency for Cleaning & Sanitization in NS Compounding Areas – *(from USP <795> Table 1.)*

SITE	MINIMUM FREQUENCY
WORK SURFACES	<ul style="list-style-type: none"> - At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected - Between compounding CNSPs with different components
FLOORS	Daily on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspect
WALLS	When visibly soiled, 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

Master Formulation Records - *(from USP <795> Box 2.)*

At a minimum, an MFR must contain the following:

- Name, strength or activity, and dosage form of the CNSP
- Identities and amounts of all components; if applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Container closure system(s)
- Complete instructions for preparing the CNSP including equipment, supplies, and description of compounding steps
- Physical description of the final CNSP
- Beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
- Labeling requirements (e.g., shake well)
- Quality control (QC) procedures (e.g., pH testing, visual inspection) and expected results
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH, temperature)

Tangible take-aways for USP <795> Compliance -

1. Be familiar with USP <795> and the State Pharmacy Practice Act, by reading the documents themselves.
2. Understand the role of FDA Guidance documents especially the guidance with respect to **insanitary conditions**.
3. Be comfortable with the revised chapter for personnel training for non-sterile preparations.
4. Understand the requirements for cleaning & disinfection of all designated compounding spaces.
5. Be mindful of new Beyond-use limits for CSPs and NSCPs

Summary & Conclusions -

- Remember to focus your compliance efforts in terms of the **THREE** key areas of **PEOPLE – PLACES – PRACTICES** in compounding.
- Full Compliance to the 2023 Revised USP Compounding Chapters will require a multi-pronged approach.
 - Including possible physical plant and equipment changes!
- Considerations to FDA Guidance, CETA standards, and Local BOP regulations & requirements will be necessary to assure that compliance gaps are eliminated.
- **Patient Safety is the Primary Objective !**

QUESTIONS

- Many Thanks !
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Reading List / Bibliography -

- General Chapter USP <795> <797> <800> - www.usp.org
- Controlled Environmental Testing Association (CETA) – www.CETAinternational.org
- Pharmacy Purchasing and Products Magazine- www.pppmag.com
- FDA Website – www.FDA.gov
 - Drug Quality & Safety Act -
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376732.htm>
 - Guidance – Pharmacy Compounding -
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf>
- OSHA / NIOSH Resources –
 - HD Drug list - <http://www.cdc.gov/niosh/docs/2016-161/default.html>
 - NIOSH Drug Alert- <http://www.cdc.gov/niosh/docs/2004-165/default.html>
 - Workplace Solutions – PPEs- <http://www.cdc.gov/niosh/docs/wp-solutions/2009-106/pdfs/2009-106.pdf>
 - DONNING & DOFFING – (videos) <http://www.cdc.gov/vhf/ebola/hcp/ppe-training/>
 - CSTD- (Draft for comment) - <http://www.cdc.gov/niosh/docket/review/docket288/default.html>



POST TEST QUESTIONS -

QUESTION ONE -

- TRUE OR FALSE : Gloves must be worn for all compounding activities?
- (a) True
- (b) False

QUESTION TWO -

- TRUE or FALSE: The sink in the compounding area may not be used for any other purpose when compounding is not taking place.
- (a) True
- (b) False

QUESTION THREE -

- Which of the following compounding areas are part of a proper non-sterile compounding area cleaning & sanitation program:
 - (a) Cleanable surfaces (Walls, Ceilings, Floors, etc.)
 - (b) Storage shelving
 - (c) Controlled ventilated enclosures (CVEs) aka “powder hoods”
 - (d) ALL of the above should be included in your plan.

QUESTION FOUR -

- What conditions should be considered when establishing a beyond –use date for a CNSP?
- (a) Chemical stability of the mixture.
- (b) Physical stability of the mixture.
- (c) The water activity of the components.
- (d) All must be considered.

QUESTION FIVE -

- Which of following regulatory bodies have statutes, rules, or regulations, which have jurisdiction over the compounding of non-sterile drugs for “human use”?
- (a) State Board of Pharmacy
- (b) FDA
- (c) Drug Enforcement Administration (DEA)
- (d) ALL of the above

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