

Compounding of Sterile Medications in the Pharmacy —

USP Chapter <797> Provides Guidance

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The USP has recently published a revised version of general chapter <797> Pharmacy Compounding — Sterile Preparations addressing sterile compounding.¹ This chapter provides guidance on requirements for the compounding of safe, sterile pharmaceutical dosage forms in the pharmacy, as opposed to the controlled pharmaceutical manufacturing environment.

This chapter was prompted by concerns over the quality of drugs produced in the growing arena of pharmacy compounding laboratories.² This was not the first USP chapter to provide guidance in this area. Previously, USP published chapter <1074>, Dispensing Practices for Sterile Drug Products Intended for Home Use in an attempt to address this concern. This chapter was not as effective as originally hoped.³ To this end, USP <797> was created. While the FDA is charged with enforcing USP, there is some leeway in enforcement practice at the pharmacy level. However, many state boards and professional associations have adopted the provisions of the USP chapter in their expectations.⁴

This chapter has generated a great deal of interest in the compounding pharmacy. Among the provisions of the chapter, the compounding pharmacy is expected to:

- Have written quality procedures with allowance for in-process checks on compounding,
- Establish accuracy and precision of measuring and weighing,
- Observe the requirement for sterility,
- Qualify methods of sterilization and purification,
- Establish safe limits and ranges for strength of ingredients, bacterial endotoxins, particulate matter, and pH,
- Ensure labeling accuracy and completeness,
- Ensure beyond-use date assignment, and
- Establish packaging and storage requirements

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To help with the microbial risk level, there are three categories of products described in the current <797>:

1. Low Risk Medications –

“The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 (see Table 1 [in Guidance Document]) or better air quality using only sterile ingredients, products, components, and devices. The compounding involves only transfer, measuring, and mixing manipulations with closed or sealed packaging systems that are performed promptly and attentively. Manipulations are limited to aseptically opening ampoules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices and packages of other sterile products. For a low-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 48 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 14 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20 °C or colder.”

2. Medium Risk Conditions exist when the medication is compound under aseptic conditions as above, and any of the following additional conditions exists –

- a. “Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP (compounded sterile product) that will be administered either to multiple patients or to one patient on multiple occasions.
- b. The compounding process includes complex aseptic manipulations other than the single-volume transfer.
- c. The compounding process requires unusually long duration, such as that required to complete dissolution or homogeneous mixing.
- d. The sterile CSPs do not contain broad-spectrum bacteriostatic substances, and they are administered over several days (e.g., an externally worn or implanted infusion device).
- e. For a medium-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods:
 - i. before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature (see *General Notices and Requirements*),
 - ii. for not more than 7 days at a cold temperature (see *General Notices and Requirements*), and
 - iii. for 45 days in solid frozen state at –20 °C or colder.”

3. High Risk Conditions –

- a. “Nonsterile ingredients, including manufactured products for routes of administration — other than those listed under c. in the Introduction — are incorporated or a nonsterile device is employed before terminal sterilization.
- b. Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see Table 1 [in Guidance Document]). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.
- c. Nonsterile preparations are exposed for at least 6 hours before being sterilized.
- d. It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients (see Ingredient Selection under *Pharmaceutical Compounding — Nonsterile Preparations <795>*).
- e. For a high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods:
 - i. before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature (see *General Notices and Requirements*),
 - ii. for not more than 3 days at a cold temperature (see *General Notices and Requirements*), and
 - iii. for 45 days in solid frozen state at –20 °C or colder.

All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk CSP solutions subjected to terminal steam sterilization are passed through a filter with a nominal porosity not larger than 1.2 µm preceding or during filling into their final containers. Sterilization of high-risk level CSPs by filtration is conducted entirely with an ISO Class 5 or superior air quality environment...”

In addition, all fill procedures are expected to be qualified by a media fill (process simulation) under worst case conditions.

The requirement for ISO Class 5 fill conditions is new to the compounding pharmacy, as are the contamination control, facility, environmental monitoring, personnel gowning, and training requirements. In addition, there is a clear expectation for a series of Standard Operating Procedures (SOPs) to document practice and provide internal guidance to the pharmacy in compounding practice.

In particular, this expectation extends to a written environmental monitoring plan for at least the critical area.

Finished product release tests for high risk fill conditions include a Sterility Test and a Bacterial Endotoxin test in addition to chemical tests for strength and accuracy of compounding practices.

All in all, <797> provides a great deal of guidance to ensure that medications made in the pharmacy are prepared under conditions that approach those of the manufacturing community. In addition, it begins to bring the expectations of a GMP-like Quality System to the compounding pharmacy.

References

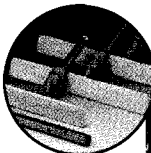
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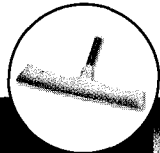
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