COMMENTARY

The Potential Impact of USP General Chapter <797> on Procedures and Requirements for the Preparation of Sterile Radiopharmaceuticals

From the author: The statements in the following article are the author's personal opinions about <797> and do not represent the position of the Committee on Pharmacopeia, the SNM, or the Mayo Clinic on this subject.

The recent release of a revised general chapter titled "Pharmaceutical Compounding—Sterile Preparations" (<797>) in the *United States Pharmacopeia 27* and *National Formulary 22 (USP 27-NF 22)* deals with new procedures and requirements for the preparation and labeling of compounded sterile preparations (CSPs) (*1*). The revised version of <797> was first published in the 2002 March/April issue of *Pharmacopeial Forum* (*PF*) (*2*), followed by a second revision published in the 2003 May/June issue of *PF* (*3*). During the public review and comment period (i.e., May–July 2002), the USP received approximately 150 comments from various parties concerning the *PF* proposal for <797>. Judging by the commentary published in *USP 27-NF 22*, none of the comments received by the USP are specifically related to radiopharmaceuticals (*4*).

It is the utmost responsibility of any health care practitioner involved in the preparation of CSPs to ensure that drug preparations are safe and effective, and I believe that the requirements and standards as described in <797> will serve to prevent harm to patients that could result from any mishaps (e.g., contamination, technical errors, incorrect ingredients, etc.) during the compounding process. However, some issues and requirements as stated in <797> are unclear and/or inappropriate with regard to the preparation of sterile radiopharmaceuticals. To ensure that <797> is rightly applicable to the compounding of radiopharmaceuticals, these issues should be properly addressed by the USP.

A Pharmacy Issue?

The target audience for the chapter is not only the pharmacy group but, according to the introduction section of <797>, also "health care institutions, pharmacies, physician practice facilities, and other facilities." (*1*). Thus, the procedures and requirements in <797> are not solely for the pharmacy but will affect other professional areas (e.g., physicians who prepare or supervise others who prepare sterile drug preparations).

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Enforceable Guidance

The "Commentary" section of *USP 27-NF 22* indicates that the reason the USP decided to renumber and rename <797> was to "provide better enforceable guidance to qualified health care professionals who compound sterile preparations" (*4*).

As such, <797> may be viewed by the FDA as practice standards, and thus the agency may exercise "enforcement discretion" with regard to any potential violation. In addition, the state boards of pharmacy and medicine may adopt the procedures and requirements as stipulated in <797>, promulgate their own standards similar to those in <797>, and then enforce them accordingly.

Pharmacy Compounding

In general, the term "compounding" does not include drug preparation that is performed in accordance with directions contained in approved labeling (e.g., package insert) provided by the manufacturer. Although <797> provides detailed procedures and requirements for CSPs, it fails to define the term "compounding."

One of the definitions in <797> of a drug product that should be designated as a CSP is poorly written and, as such, requires further clarification: a. Preparations prepared according to the ma[n]ufacturer's labeled instructions and other manipulations when manufacturing sterile

products that expose the original contents to potential contamination.

Given this definition, when a drug product is prepared in accordance with the manufacturer's label instructions and without any manipulation that deviates from the package insert, should such a product be considered a CSP? In addition, the term "potential" is so vague that no prepared drug product could possibly be exempt from potential classification as a CSP.

CSPs and the Associated Risk Levels

A system of 3 risk levels (low, medium, and high) is used in <797>, with each level assigned according to the corresponding likelihood of microbial, chemical, and/or physical contamination (*1*). With each assigned risk level for a CSP (especially for high-risk operations), <797> stipulates specific procedures and requirements (e.g., floor plan, air quality, personnel cleansing/gowning, quality assurance, etc.) (*1*).

Low-Risk Level CSPs. To meet the criteria for being classified as low risk, CSPs must be compounded entirely within an International Organization of Standardization (ISO) Class 5 (former Class 100 per U.S. Federal Standard No. 209E) or better air quality, using only sterile ingredients, products, and components (fewer than 3 manufactured products) that are kept in closed or sealed packaging systems, as well as using sterile needles, syringes, devices, and containers during single transfers (*1*). In addition, for low-risk preparation, in the absence of passing a sterility test, storage periods cannot exceed 48 hours at controlled room temperature, 14 days at a cold temperature, or 45 days in a solid frozen state at –20°C or colder (*1*).

Based on these conditions, it seems that only radiopharmaceuticals that are compounded for single unit-dose use are qualified to be considered as low-risk-level CSPs.

Medium-Risk Level CSPs. In addition to being compounded under low-risk conditions, one or more of the following conditions must exist for a drug preparation to be deemed at medium risk of contamination (*1*):

1. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to a single patient on multiple occasions. The CSPs are compounded with aseptic manipulations.

2. The compounding process includes complex aseptic manipulations other than the single-volume transfer.

3. For a low-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed 30 hours at controlled room temperature, 7 days at a cold temperature, or 45 days in solid frozen state at –20° or colder.

Condition 1 seems to apply to compounded multidose radiopharmaceutical preparations as well as to the majority of the compounded ^{99m}Tc kit preparations. Although the radiolabeling process of autologous leukocytes may fit well with condition 2 as specified, it is uncertain whether patient blood can be perceived as a "sterile" ingredient/component.

High-Risk Level CSPs. These include CSPs compounded with the use of nonsterile ingredients or sterile ingredients, components, devices, and mixtures exposed to air quality inferior to ISO Class 5 (this includes storage in environments inferior to ISO Class 5 or opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives) (*1*). Also, for a high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed 24 hours at controlled room temperature, 3 days at a cold temperature, or 45 days in solid frozen state at –20°C or colder (*1*).

According to these criteria, eluate obtained from a ^{99m}Tc generator may be deemed as either a "contaminated" ingredient or an ingredient that is at "high risk" to become contaminated with infectious microorganisms in the event that a generator is not kept in an ISO Class 5 environment. It is neither practical nor required to store an ~300- to 400-pound item (i.e., total weight of the auxiliary shield and generator) in an ISO Class 5 hood. In accordance with the package insert directions for storage of a ^{99m}Tc generator, it is required only that the generator be stored at a controlled room temperature (*5*).

<797> vs. <823>

A separate general chapter in the *USP 27-NF 22*, "Radiopharmaceuticals for Positron Emission Tomography—Compounding" (<823>), deals specifically with compounding guidance for radiopharmaceuticals used in PET procedures (*6*). <823> has been recognized as the standard for compounding and preparing PET drugs per Section 121 of the FDA Modernization Act of 1997 (1997 FDAMA) (*7*) and the FDA draft rule and guidance of current good manufacturing practice for PET radiopharmaceuticals, respectively (*8*,*9*).

<797> does indicate its application with regard to certain compounded radiopharmaceuticals (including compounded PET radiopharmaceuticals). Because both <793> and <823> are classified as "enforceable guidance" under the USP numbering system, it is unclear to those involved in the compounding of radiopharmaceuticals whether or not standards included in <797> are intended to supercede those in <823>.

It may be convenient to remove the term *radiopharmaceuticals* from <797> so that <797> does not apply to the compounding of radiopharmaceuticals and then to expand <823> to include all radiopharmaceuticals (i.e., PET and non-PET radiopharmaceuticals). However, because of the specific connections of <823> to PET radiopharmaceutical regulations (*7*–*9*), it may not be prudent to take <823> beyond PET radiopharmaceuticals.

Nuclear Pharmacy Compounding Guidelines

The 1997 FDAMA established parameters under which the compounding of drug products is appropriate and lawful, but it was expressly stated that these criteria do not apply to radiopharmaceuticals (*10*). To proactively develop a set of professional compounding guidelines for nuclear pharmacy, the Section on Nuclear Pharmacy Practice, American Pharmacists Association (APhA; formerly the American Pharmaceutical Association), formed the Nuclear Pharmacy Compounding Practice Committee in early 1998. After a nearly 4-year effort by the committee, the *Nuclear Pharmacy Compounding Guidelines* were approved by the Board of Trustees of the APhA in September 2001 and published in November 2001 (*11*). This set of guidelines is the first nationally recognized document that provides realistic and practical compounding guidance for nuclear pharmacy practice.

In mid-August 2001, the Nuclear Pharmacy Compounding Practice Committee submitted the *Nuclear Pharmacy Compounding Guidelines* to the USP to be considered for possible inclusion in the General Chapter section of the USP-NF. Although much discussion about this proposal ensued, the USP recently decided that the *Nuclear Pharmacy Compounding Guidelines* cannot be included as a general chapter (*12*). The USP indicated that "while the document would serve as an excellent guideline for practitioners, some of the elements [e.g., "controversial" definition of the term "compounding," regulatory references to 1997 FDAMA, and the Federal Food, Drug, and Cosmetic Act] were deemed as not suitable for a general chapter" (*12*,*13*). Moreover, according to the USP, the recent publication of USP <797> changes the landscape, making it "redundant" to have a separate general chapter to address the compounding of radiopharmaceuticals (*12*).

Conclusion

There is no doubt that <797> has established a set of well-thought-out procedures and standards for compounding sterile preparations and will prevent harm to our patients. However, our community should carefully evaluate the suitability and applicability of the stipulated criteria and procedures in <797> with regard to our daily practice in preparing various sterile radiopharmaceuticals. In addition, I feel that the safety record of radiopharmaceuticals should be taken into consideration in reviewing and commenting on this general chapter.

Any issue related to <797> that could make compliance either difficult or impossible in the compounding of sterile radiopharmaceuticals should be brought to the attention of the USP Expert Committee on Parenteral Products—Compounding and Preparation, which is responsible for the revision of <797>, as well as the USP Expert Committee on Radiopharmaceuticals and the USP Expert Committee on Radiopharmaceuticals and Medical Imaging Agents (the latter groups are assigned to handle issues specifically related to radiopharmaceuticals).

To speak with a cohesive voice and ensure that there is no confusion on these issues, I believe that a task force should be established within the SNM so that comments and concerns about <797> from various practitioners within our nuclear medicine/nuclear pharmacy community can be brought forth and properly coordinated. Starting on July 1, 2004, the surveyors of the Joint Commission on Accreditation of Healthcare Organizations will address the requirements as stipulated in <797> during their surveys of institutions that compound sterile preparations (*14*). Thus, the SNM should form this task force as soon as possible to identify problematic areas in <797>, as well as to coordinate any comments and suggestions raised by the general membership of the Society.

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