From the SNM Committee on Pharmacopeia

Exemption of Radiopharmaceuticals from <797>

A telephone conference was held on June 3 between the members of the U.S. Pharmacopeia (USP) Expert Committee on Radiopharmaceuticals and Medical Imaging Agents (RMI) and one of the primary authors of <797>. This primary author indicated that the USP committee responsible for <797> (i.e., the Expert Committee on Parenteral Products—Compounding and Preparation [PPC]) recognizes that it will need to exempt from the provisions of <797> the preparation of drugs that will be used within a certain limited time frame after preparation (for example, to address the reconstitution of drugs on the clinical floor by nursing staff). The specific time frame limit has yet to be defined by the PPC. This same exemption was also mentioned during a USP meeting titled "Practical Application on USP to Pharmaceutical Compounding, Packaging, and Dispensing," which was held on May 14 and 15 in Rockville, MD. Subsequent to the June 3 telephone conference, the RMI (which included representatives from the FDA) recommended to the PPC that the time frame for such an exemption be set at 6 hours. This 6-hour limit, which was supported by data from the FDA microbiologics section, initially led to the specification of a 6-hour expiration period for ^{99m}Tc-labeled radiopharmaceuticals lacking a bacteriostatic agent.

However, the aforementioned "6-hour rule" is not consistent with the shelf life of 12 hours as stipulated in package inserts for ^{99m}Tc-sodium pertechnetate and ^{99m}Tc-tetrofosmin (*1*,*2*). In addition, the Joint Commission on Accreditation of Healthcare Organizations Standard MM.4.20 (*3*) seems to support a shelf life of 24 hours for any drug product that is not prepared in a Class 100 environment. After numerous debates among the members of our committee, we feel that a 12-hour time frame for a reconstituted radiopharmaceutical may be the most reasonable compromise between safety and practicality. A 12-hour expiration for all reconstituted radiopharmaceuticals would be in line with the shelf life for ^{99m}Tc eluate, the key ingredient for ^{99m}Tc-labeled radiopharmaceutical products. In addition, the 6-hour limit is not practical for centralized nuclear pharmacies serving remote hospitals. Although the recommended shelf life of ^{99m}Tc-mebrofenin is 18 hours (*4*), we believe that it would be more accurate (*5*) and practical to adopt a single 12-hour expiration time for all reconstituted radiopharmaceutical products, despite the bacteriostatic agent (propylparaben) used in ^{99m}Tc-mebrofenin preparation.

If reconstituted radiopharmaceutical products having a shelf life less than 12 hours are exempted from <797>, the results will be that many nuclear pharmacies may opt not to acquire the proper equipment/facilities necessary to compound radiopharmaceutical products in accordance with <797>. As such, in the event of compassionate usage or product shortage, the aforementioned nuclear pharmacy facilities would not be able to prepare a radiopharmaceutical product that may be required for emergent need in providing patient care. As long as the 12-hour limit is observed, we believe that an exemption from <797> should be allowed for radiopharmaceutical products prepared under the previously described circumstances.

Revision of Section Titled "Aseptic Technique, PROCESSING"

It seems that some of the requirements as stipulated in <797> may be in conflict with the ALARA (as low as reasonably achievable) principle. The most noticeable of these stipulations include the use of a positive-pressure barrier isolator to minimize the entry of particles from outside ("Clean Room and Barrier Isolators," p. 3126) (*6*) when negative pressure is a must in areas in which radioactive gases or volatile radioisotopes are handled; the requirement for visual inspection of compounded sterile preparations (CSPs) in order to detect particulate matter and leakage ("Responsibility of Compounding Personnel," p. 3122; "Low-Risk Level CSPs," p. 3123) (*6*), which is not suitable for use with many radiopharmaceutical preparations containing high levels of radioactivity; and maintenance of a Class 100 environmental condition ("CSP Microbial Contamination Risk Levels," p. 3123–3124) (*6*) that is not practical for storage and elution of a heavily shielded radionuclide generator (*7*).

<797> does include statements ("CSP Microbial Contamination Risk Levels," p. 3123,) (*6*) that appear to provide the necessary flexibility to address the special issues associated with the preparation of radiopharmaceuticals:

> The characteristics described below for low-risk, medium-risk, and high-risk CSPs are intended as a guide to the breadth and depth of care necessary in compounding, but they are neither exhaustive nor prescriptive. The licensed

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> health care professionals who supervise compounding are responsible for determining the procedural and environmental quality practices and attributes that are necessary for the risk level they assign to specific CSPs.

Although we believe that the PPC intends to allow flexibility in compliance with <797> requirements, it is unclear as to whether the regulatory agencies (e.g., FDA and state boards of pharmacy) would have the same intention when they adopt the <797> standards. As such, we believe that rather than attempting to identify and justify every potential deviation from <797> that may be required in the preparation of radiopharmaceuticals, we should instead focus on ensuring that <797> incorporates statements that allow one to exercise professional judgment with regard to application of the various provisions of <797> to the preparation of radiopharmaceuticals.

<823>

<823> has been recognized as the standard for compounding and preparing PET radiopharmaceuticals as per Section 121 of FDAMA (*8*) and the FDA draft rule and guidance of current good manufacturing practice for PET radiopharmaceuticals (*9,10*). <797> does indicate its application with regard to certain compounded radiopharmaceuticals (including compounded PET radiopharmaceuticals) ("Introduction," p. 3122) (*6*). Upon consideration of the fact that at least one state board of pharmacy was prepared to require a pharmacy that manufactured PET radiopharmaceuticals to follow <797> rather than <823>, as well as the specific connections of <823> to PET radiopharmaceutical regulations (*8–10*), we believe that it is necessary that a statement be included in <797> to indicate that <823> is the proper USP general chapter for the requirements related to the compounding of PET radiopharmaceuticals.

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