February 23, 2016

U.S. Pharmacopeial Convention
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Re: Comments on USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations

The Society of Nuclear Medicine and Molecular Imaging’s (SNMMI) more than 17,000 members set the standard for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals and meetings, and leading advocacy on key issues that affect molecular imaging and therapy research and practice. We appreciate the opportunity to provide comments to the USP in response to the revision of General Chapter <797> Pharmaceutical Compounding – Sterile Preparations.

The SNMMI appreciates the efforts of the USP’s Compounding Expert Committee (CEC) for their work on the revision of <797>. The SNMMI also recognizes that <797> affects many aspects of the complex healthcare delivery system associated with sterile drug products. Within this context, we believe that sterile radiopharmaceuticals are a separate class of products that require accommodation and consideration for the unique characteristics of radioactive components, including transportation and distribution requirements unique to radioactive drugs under the regulation of the Department of Transportation and the Nuclear Regulatory Commission. Accordingly, the SNMMI requests the USP to recognize radiopharmaceuticals as a unique class of products and to adopt the recommendations outlined in this letter.

The preparation of sterile radiopharmaceuticals often requires an assessment for a radioactive component metric that is commonly not addressed by the manufacturer’s labeling or directions. Under the provisions of the current draft of <797>, the standard preparation of sterile radiopharmaceuticals falls under the same strict requirements for the preparation of sterile drugs from non-sterile components. The SNMMI believes that this designation is restrictive and inappropriate for the simple dilution and reconstitution inherent in the standard preparation of sterile radiopharmaceuticals with U.S. Food and Drug Administration (FDA) approved products and adjuvants.

For the preparation of sterile radiopharmaceuticals from non-sterile or non-FDA approved components, we fully acknowledge and support categorization as compounded radiopharmaceuticals.

The SNMMI also believes that changes and adjustments in radioactive aspects during radiopharmaceutical preparation should not be included within the scope of compounding as these activities do not constitute any changes to approved drug product identity or chemical purity. This recognition should be codified in <797>.

The SNMMI proposes the following language for inclusion in the special practice section of <797>:

Preparation of sterile radiopharmaceuticals following the aseptic guidelines of this chapter is not considered compounding when:
a. A radiopharmaceutical product is prepared, diluted, or repackaged in a way that does not conflict with the approved labeling, except for the statements designating the amount of radioactive additions, the product as a single dose or single use product, and related language (e.g., discard remaining contents).

b. A radiopharmaceutical product is prepared, diluted, or repackaged with FDA approved containers, adjuvants and associated components.

c. A radiopharmaceutical assigned Beyond Use Date (BUD) is assigned according to approved labeling or up to 18 hours if microbial challenge studies performed on the formulation of the diluted, mixed, or repackaged sterile radiopharmaceutical product in the type of container in which it will be packaged demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD.

In support of this request, the SNMMI believes the CEC should recognize and establish the following. First, that the preparation of FDA-approved injections for a single patient for administration in the clinical environment within 60 minutes of completion of preparation is a recognized practice when the preparation follows FDA-approved product labeling and professional clinical practices for administering drugs and Centers for Disease Control and Prevention guidelines for infection control. Second, that the CEC retain language from previous versions of <797> that clearly identify and establish preparation of injections in non-classified, segregated areas with accompanying language to assure activities are in accordance with good aseptic technique.

With respect to this request, we ask the CEC to re-evaluate the proposed categorical compounding level requirements in order to include aseptic verification requirements that are appropriate to the patient-side clinical environment. In accordance with this request we also ask the CEC to reaffirm previous chapter risk assessments for compounded sterile radiopharmaceuticals in an ISO-5 environment and assign a specific Category 1 exclusion that specifies for an ISO-8 barrier exclusion for compounding of sterile multi-patient radiopharmaceuticals using sterile FDA-approved components and adjuvants.

The SNMMI agrees that sterile compounding of sterile radiopharmaceuticals in an ISO-5 environment using non-sterile and or non-FDA approved products should be classified under Category 2 with associated ISO-7 barrier controls.

Category 1 and Category 2 environmental monitoring and personnel controls should reflect the risks entailed thereof. As such, the SNMMI feels that the environmental and personnel monitoring in the proposed chapter is overly prescriptive and restrictive with respect to sterile radiopharmaceutical preparation. For Category 1, we respectfully ask that the viable and non-viable particulate monitoring requirement for Category 1 be maintained at 6-month intervals when alert levels for environmental surface or personnel monitoring are not exceeded more than 3 times in a quarter. We agree that monthly monitoring should be initiated upon evidence of an action level exceeded for any single personnel or environmental sample and maintained for a full quarter where no additional alert level has been exceeded. We also request that the Category 1 competency testing and media
fill requirement be limited to once a year under the above mentioned action and alert level scheme for alert levels and immediately required upon evidence of an action level.

The SNMMI agrees that the proposed scheme of re-evaluation, retraining, and requalification is appropriate according to the category assigned to the aseptic task. We ask that a Category 1 requalification period following pause in compounding be established at 6 months.

In short, the SNMMI proposes that the de minimis aseptic preparation verification requirement be limited to yearly media fills and garbing assessments appropriate to simple dilution and reconstitution of FDA-approved products. In this requirement we agree that media fill verification must duplicate the most technically-demanding aseptic practice performed at the designated preparation site according to the specific FDA-approved product labeling.

As the definitive chapter on sterile compounding, USP chapter <797> has established procedures and practices to protect the public and maintain a high standard of pharmaceutical quality. However, the USP has consistently struggled to adequately address the unique aspects of radiopharmaceuticals and the specialty of nuclear pharmacy with regard to <797>. Following the initial publication of <797>, and in anticipation of the first revision of the chapter, an ad hoc panel on radiopharmaceuticals proved to be invaluable in establishing workable and reasonable guidelines for the preparation of sterile radiopharmaceuticals. The SNMMI believes the CEC should repeat that exercise to reach out and utilize the expertise readily available in nuclear pharmacy and the nuclear medicine community to assist in creating the appropriate standards for radiopharmaceutical preparation and compounding. Therefore, the SNMMI recommends a two-pronged approach. First, the SNMMI recommends that the USP establish an expert panel with expertise in nuclear pharmacy and nuclear medicine to assist the CEC. The goal of the expert panel would be to make recommendations for sterile radiopharmaceutical preparations to the CEC. Second, the SNMMI recommends that the USP recognize radiopharmaceuticals as a unique class of products and develop a new general chapter entitled “Radiopharmaceutical Compounding – Sterile Preparations.” The SNMMI recognizes that these recommendations are labor intensive, but we strongly believe this approach will effectively serve the short- and long-terms needs of patients, pharmacists, and physicians involved in the preparation and handling of sterile radiopharmaceuticals.

SNMMI appreciates the opportunity to comment on this USP Chapter. As always, SNMMI is ready to discuss any of its comments or meet with USP on the above issues. In this regard, please contact Susan Bunning, Director, Health Policy and Regulatory Affairs, by email at sbunning@snmmi.org or by phone at 703-326-1182.

Sincerely,

Hossein Jadvar, MD, PhD, MBA, MPH, FACNM
SNMMI President