USP Public Standards for Compounded Sterile Radiopharmaceuticals: Recommendations from SNMMI

Written by the SNMMI Committee on Radiopharmaceuticals (COR) and approved by the SNMMI Board of Directors (BOD)

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SUMMARY

For more than 60 years, the United States Pharmacopeia (USP) has been an innovator in the development of effective public standards that support the safe and effective use of radiopharmaceuticals in the U.S. and throughout the world. More than 70 individual drug monographs and several general chapters exist for radiopharmaceutical products. Through the creation and maintenance of these monographs and chapters, the USP has consistently exceeded their mandate to improve global health through public standards, even during times when substantial changes in regulations and the marketplace have created formidable obstacles for radiopharmaceuticals.

Since the 1970s, standards for sterile compounding have evolved through a series of recommendations from various organizations, including the National Association of Boards of Pharmacy, the American Society of Health-System Pharmacists, and the USP. Although well intentioned, these efforts did not produce a suitable standard until 2004 when the USP officially published general chapter <797> *Pharmaceutical Compounding—Sterile Preparations*, which described compounding standards for the entire spectrum of sterile preparations. In 2008, the first revision of <797> became official, which, for the first time, contained a section on radiopharmaceuticals as compounded sterile preparations (CSPs). However, this revision lacked a comprehensive delineation of common practices in nuclear pharmacy that constitute compounding. Given the pivotal role the USP has played in other public standards for radiopharmaceuticals and the predominant role played by pharmacy in the field of nuclear

medicine, it is surprising that a comprehensive delineation of compounding practices for sterile radiopharmaceuticals does not exist in the USP.

Sterile radiopharmaceuticals represent a unique class of drug products where compounding activities include the use of radionuclide generators, the preparation of commercially manufactured radiopharmaceutical kits, the dilution of FDA-approved multi-dose vials, the labeling of human blood products with radionuclides, the preparation of patient-specific doses, etc. These activities occur in an environment where individualized patient needs and the safe handling of radioactive materials demand a high level of professional care and clearly defined standards that support these activities.

The purpose of this article is to promote the development of clear and effective USP public standards that meet patient and practitioner needs for compounded sterile radiopharmaceuticals today and in the future. The article provides: (1) an introduction to the USP; (2) a description of USP standards for radiopharmaceuticals and compounding, including general chapters and monographs; (3) a delineation of some common compounding practices for radiopharmaceuticals; (4) an introduction to the Committee on Radiopharmaceuticals (COR) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI); and (5) recommendations from the COR to strengthen USP compounding standards for sterile radiopharmaceuticals.

INTRODUCTION TO THE USP

The USP is a non-governmental, non-profit organization whose mission is to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. The USP accomplishes this through the efforts of dedicated staff, committees of expert volunteers, and close coordination with the U.S. Food and Drug Administration (FDA). USP public standards are designed to assure the identity, strength, quality, and purity of drug substances and drug products. The USP achieves this mission through a transparent, collaborative, and iterative process that allows comments and inputs from the public, the FDA, and other stakeholders.

USP standards may be classified into two categories: general chapters and monographs. As their name implies, general chapters contain information that is broadly applicable across the USP. General chapters may describe tests and techniques used in individual monographs to determine quality characteristics of drug substances and/or drug products. General chapters may also describe aspects of pharmaceutical storage, handling, packaging, etc.

In addition to general chapters, the USP maintains a compendium of standards for individual drug substances and products. These standards take the form of USP monographs, which are typically developed after FDA approval of the drug product for commercial marketing. USP monographs are based on information and data supplied to the USP by a pharmaceutical company (sponsor) whose product has been approved by the FDA.

Although the USP does not enforce their standards, the FDA legally recognizes the USP as an official compendium and may enforce compliance with USP standards under the adulteration and misbranding provisions of the Federal Food, Drug, and Cosmetic Act (FDCA). These provisions extend broad authority to the FDA to prevent the marketing of drugs that do not meet USP standards.

USP public standards have served as recognized benchmarks for quality since the early 1800s. Such standards are vital to ensuring that all medications, including radiopharmaceuticals,

uniformly meet the needs of patients and health care practitioners. History has too often shown that the lack of a public standard can lead to unknown and dangerous consequences for patients and consumers.

THE USP AND RADIOPHARMACEUTICALS

USP public standards played a critical role in the development and evolution of radiopharmaceuticals. Beginning with *USP 15* in 1955, the USP published the first monograph for a radioactive substance, "Sodium Radio-Iodide (I^{131}) Solution" [*sic*] (*1*). This was a pioneering step in the recognition of radiopharmaceuticals as drugs, which in turn helped catalyze and ultimately define the field of nuclear pharmacy in the U.S. (*2*). Thirty years later in *USP 22*, the USP published the first monograph for a positron-emitting radiopharmaceutical (fludeoxyglucose F 18 injection) (*3*).

In addition to individual monographs for radiopharmaceuticals, the USP also published general chapters that provided practice standards pertinent to nuclear medicine. Beginning again with *USP 15* in 1955, the USP published general information describing instrumentation and techniques for radioactivity measurements used for radiopharmaceuticals (*4*). In 1975 with *USP 19*, *<821> Radioactivity* appeared in its current form (*5*,*6*).

In *USP 22* in 1990, the USP took a very important step with the publication of general chapters related to the synthesis and compounding of positron-emitting radiopharmaceuticals (*7*,*8*). Together with monographs for fludeoxyglucose F 18 injection and other PET radiopharmaceuticals, these general chapters provided the U.S. Congress with the public standards necessary to permit the enactment of the FDA Modernization Act of 1997 (FDAMA). Section 121 of this act defined compounded positron emission tomography drugs as being not adulterated if these drugs were produced in conformity with standards and monographs of the USP. FDAMA also required the Secretary of Health and Human Services to develop FDA approval procedures and good manufacturing practice regulations for PET radiopharmaceuticals (*9*). Importantly, while the FDA worked to meet their obligations under FDAMA, nuclear pharmacists and physicians could legally compound PET radiopharmaceuticals for commercial use according to USP standards (*10*). The net effect is that USP public standards enabled the establishment of a nationwide supply of PET radiopharmaceuticals from 1997 until 2012 when the FDA completed their mandated obligations under FDAMA, which resulted in an effective and unique regulatory model for PET radiopharmaceuticals that only exists in the U.S. Without the USP's innovative leadership, the benefits of PET imaging procedures for millions of patients each year would not have materialized in the U.S.

As noted earlier, the development and maintenance of USP standards are accomplished by volunteer expert committees organized by the USP. Historically, the USP maintained dedicated committees in various forms consisting of members with expertise in radiopharmaceuticals. However, beginning in 2005, dedicated committees for radiopharmaceuticals were eliminated and expertise for radiopharmaceuticals was incorporated into other expert committees. In order to deal with particular issues that required specific expertise in radiopharmaceutical topics, the USP created ancillary *ad hoc* expert panels as needed. For the most part, this strategy has worked well. However, due to the focused charge and temporary existence of such panels, a sense of continuity is not possible over the long term. In addition, different temporary panels were formed by different expert committees, which hindered alignment of activities by different panels on large-scale issues affecting radiopharmaceuticals (e.g., compounding of sterile radiopharmaceuticals).

THE USP AND COMPOUNDING

Beginning with *USP 27* in 2004, the USP published general chapter <797> *Pharmaceutical Compounding—Sterile Preparations*, which described standards for the preparation of compounded sterile preparations (CSPs). This chapter evolved from a long history that started in the 1970s through a series of recommendations from various organizations, including the National Association of Boards of Pharmacy, the American Society of Health-System Pharmacists, and the USP. Although well intentioned, these efforts did not produce a suitable standard because previous efforts in this practice area were merely recommendations (*11,12*). The creation of <797> was an innovative step by the USP to fill the need for a public standard on sterile compounding that is enforceable by state Boards of Pharmacy, accreditation organizations, and even the FDA.

The first draft of <797> appeared in 2002 as a public comment proposal to replace USP general chapter <1206> *Sterile Drug Products for Home Use* (*13*). In this draft and in the final version that appeared in 2004, radiopharmaceuticals were mentioned only once in the introduction; moreover, the chapter did not contain specific standards for radiopharmaceuticals, including the delineation of various practices considered as compounding in nuclear pharmacy.

In 2006, the USP undertook the first revision of <797> (*14*). This revision, which became official in 2008, was based on a series of workshops held by the USP and more than 1500 comments received between 2000 and 2005. For the first time, this revision of <797> contained a section entitled “Radiopharmaceuticals as CSPs.” Importantly, this section clarified the role of <797> relative to chapter <823>, which had been poorly defined since neither chapter acknowledged the other when <797> initially became official in 2004. This section also addressed risk levels for some radiopharmaceutical CSPs, requirements for generator elution, requirements for storage and transportation of shielded vials, and handling of radiopharmaceutical CSPs according to ALARA principles. The expert committee that prepared this revision relied on expertise from a limited number of members from the nuclear pharmacy community, but the chapter did not delineate various practices considered as compounding in nuclear pharmacy.

In 2010, the USP published a proposal for the revision of <797> and solicited public comments (*15*). This proposal never became official; however, it was used as a basis for a new revision proposal that appeared for public comment in 2015 (*16*). The comments generated by this proposal are currently under evaluation by the USP expert committee responsible for compounding (*17*). The currently proposed revision contains a significant revision of the section entitled “Radiopharmaceuticals as CSPs.” In addition, the proposed revision has eliminated the reference to chapter <823> *Positron emission tomography drugs for compounding, investigational, and research uses*. As before, the expert committee that prepared this proposed revision relied on expertise from a limited number of members from the nuclear pharmacy community, but the proposed revision does not delineate various practices considered as compounding in nuclear pharmacy.

The currently official version of <797> contains standards for compounding across the entire spectrum of sterile preparations and is intended to apply to all persons who prepare CSPs and all settings where CSPs are prepared. This has led to a very complex chapter containing a large amount of information that does not apply to the compounding of sterile radiopharmaceuticals. From a practical standpoint, this has created a public standard that is difficult to understand, both on the part of pharmacy practitioners and state Boards of

Pharmacy. This is especially problematic in a specialty that is frequently misunderstood due to its distinctness and the technical nature of radiopharmaceuticals. In its current form, <797> does not provide a clear and effective public standard for compounding practices in nuclear pharmacy.

It should be noted that hazardous drugs also constitute a special category of drugs with unique properties and risks. The current revision of <797> contains a section entitled "Hazardous Drugs as CSPs," which describes special standards related to these unique characteristics. However, in order to provide detailed clear and effective practice and quality standards for the handling of hazardous drugs, a separate general chapter was created and published for public comment in 2013 (*18*). As a result, general chapter <800> *Hazardous Drugs – Handling in Healthcare Settings* appeared in 2016 (*19*) with a delayed implementation date of July 1, 2018. It can be argued that the creation of a separate general chapter for hazardous drugs may serve as a precedent for the creation of a separate chapter for radiopharmaceuticals based on their unique properties and risks.

THE FDA AND COMPOUNDING

The FDA regulation of compounding has been a complex issue since the enactment of the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938. Historically, the FDA has recognized that pharmacy compounding serves an important public health function, but the legal framework for the FDA's responsibilities and authority related to compounding has oftentimes been unclear or poorly defined. The net result is that the FDA has historically taken a limited role in this arena and the oversight of pharmacy compounding activities has largely been left to state Boards of Pharmacy. Recent public health tragedies that resulted from inadequate and/or inappropriate pharmacy compounding practices prompted Congressional action, which led to the enactment of the Drug Quality and Security Act of 2013 (DQSA). The DQSA reinstated section 503(a) of the FDCA, which was originally created in section 127 of FDAMA to define compounding, but was rescinded because its advertising restriction was ruled unconstitutional by the U.S. Court of Appeals for the Ninth Circuit. The DQSA also created "outsourcing facilities" under section 503(b) of the FDCA. Such facilities may distribute compounded drugs according to certain conditions including facility registration, adverse event reporting, FDA inspections, and compliance with good manufacturing practice regulations. The FDA recently issued guidance documents to clarify the agency's expectations for compounding under sections 503(a) and 503(b) of the FDCA (*20,21*). Thus, the responsibilities and authority of the FDA for compounding of non-radioactive drugs seem to be well defined at the present time.

However, this is not the case for the compounding of sterile radiopharmaceuticals. For example, section 503(a) of the DQSA explicitly does not apply to the compounding of PET drugs and radiopharmaceuticals, continuing the non-applicability for PET drugs and radiopharmaceuticals as previously outlined in FDAMA section 127. This exclusion may possibly be a product of the complex pathway that began in 1960s when the FDA first assumed regulatory authority of radiopharmaceuticals from the Atomic Energy Commission (now the Nuclear Regulatory Commission) (*22*). In the mid-1970s, the FDA exerted authority for radiopharmaceuticals as part of the FDCA, thus mandating that radiopharmaceuticals be considered as new drugs and be manufactured according to approved new drug applications (*23*). At this time, the FDA also committed to develop standards for nuclear pharmacy practice, which could have potentially defined compounding practices for nuclear pharmacy (*24*). The FDA fulfilled this commitment in 1984 with the issuance of a guideline that contained criteria for when a nuclear pharmacy should register as a drug manufacturing establishment (*25*). This

guideline notes some common practices in nuclear pharmacy, but it does not delineate various common practices considered as compounding in nuclear pharmacy.

Recently, as part of their implementation of the requirements defined in DQSA, the FDA has been in discussions with the nuclear pharmacy community regarding common practices associated with deviations from manufacturer's package inserts for radiopharmaceutical kits. The agency intends to offer guidance to clarify the regulatory landscape on this matter, but it is not known if this guidance will include a comprehensive delineation of various practices considered as compounding in nuclear pharmacy.

In summary, a timeline of key events on the part of the USP and the FDA for radiopharmaceuticals and nuclear pharmacy appears in Figure 1.

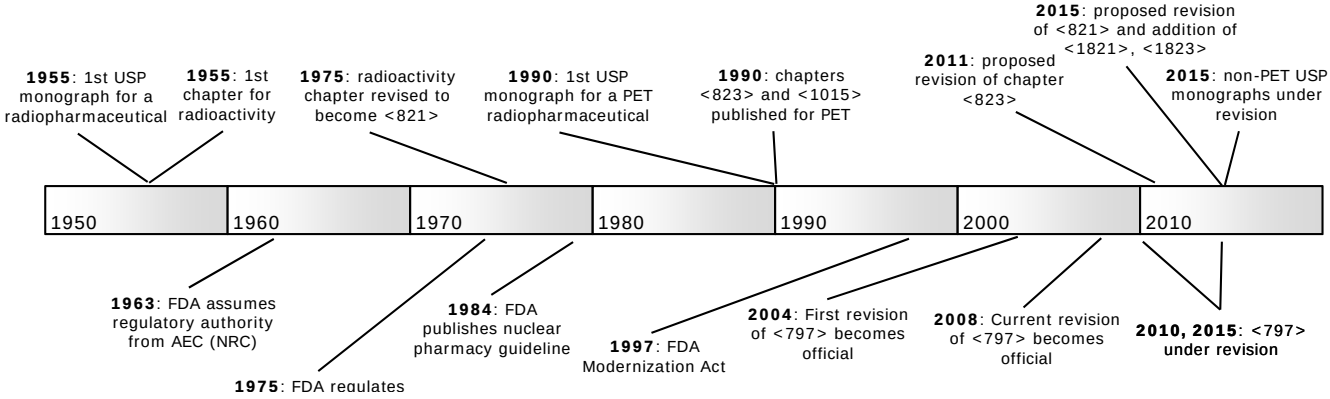

Figure 1. Timeline of key events in USP standards and FDA regulations for radiopharmaceuticals and nuclear pharmacy.

DELINEATION OF COMMON PRACTICES FOR STERILE RADIOPHARMACEUTICALS

Since neither the USP nor the FDA has defined standards that delineate various practices considered as compounding in nuclear pharmacy, there is confusion among practitioners and regulators. Much of this confusion results from the multiple, distinctly different definitions for the term "compounding" as used by the FDA, the USP, state Boards of Pharmacy, accreditation agencies, professional organizations, and others. These various definitions of compounding likely arose because of the different objectives of these groups, such as state regulation of professional practice vs. FDA regulation of compounding, and assurance of patient safety. Hence, activities termed compounding can range from simple manipulations such as aseptic transfer between containers to complex practices such as chemical synthesis and formulation from raw materials followed by sterilization.

When used broadly, compounding can refer to activities including: (1) preparation (e.g., reconstitution of a kit with a radionuclide to yield a finished radiopharmaceutical product); (2) compounding of a physician-prescribed preparation that is not commercially available (e.g., by altering a radiopharmaceutical product, mixing of two or more products, or extemporaneous formulation of a preparation); and (3) dispensing (e.g., transfer of a product from its original vial into a patient dose container such as a syringe). Regardless of the terminology, the radiopharmaceutical must maintain its identity, strength, quality, and purity. Therefore, it is imperative to develop clear and effective standards that provide an understanding of these various practices.

As described above, there is much confusion and lack of agreement among practitioners and regulators regarding definitions of compounding and the categorization of specific practice activities. Importantly, the distinction between compounding vs. preparation and dispensing may have significant ramifications especially related to regulatory compliance. As a starting point for discussion and in an effort to begin the process of delineating common practices that constitute compounding, some examples are described in this section. These examples are based on the experience of the COR, but even within the COR are not uniformly agreed upon. Moreover, these examples do not comprise a complete list of common nuclear pharmacy practices. Instead, the examples are only intended to illustrate the unique aspects of radiopharmaceuticals that must be addressed in the recommendations going forward (see recommendations section at the end of this article).

It is important to note that all practices in this section must be performed with suitable controls for sterility assurance, regardless of whether or not the practice is considered compounding.

Examples of common practices in nuclear pharmacy that *are not* considered compounding by the COR (i.e., they are considered to be preparation [elution, reconstitution, dilution] or dispensing):

- Transfer of a sterile radiopharmaceutical solution from a manufactured product container (e.g., single- or multiple-dose vials) into a second container (e.g., syringe).
- Dilution of a sterile radiopharmaceutical solution after transfer into a second container (e.g., syringe).
- Elution of a manufactured sterile radiopharmaceutical generator in compliance with the manufacturer's package insert.
- Reconstitution of a manufactured, non-radioactive kit with sterile generator eluate,
- Preparation of a radiopharmaceutical from a manufactured, non-radioactive kit in compliance with the manufacturer's package insert.
- Preparation of a radiopharmaceutical from a manufactured, non-radioactive kit with minor deviations from the manufacturer's package insert. Minor deviations are defined as the addition of different quantities of radioactivity, addition of a different volume, changes in technology, and other situations not contemplated by the manufacturer at the time of approval. Such deviations are necessary since many package inserts for radiopharmaceuticals are outdated, vague, inconsistent, overly restrictive, or otherwise deficient (*26*). Minor deviations must result in a preparation that maintains compliance with USP monograph specifications.
- Reconciliation of the beyond use date (BUD) for a radiopharmaceutical prepared from a manufactured, non-radioactive kit when the BUD in the manufacturer's package insert is not clear, when BUD of a prepared kit differs from the generator eluate, or when extended BUD is supported by valid testing.
- Preparation of certain radiopharmaceuticals for urgent or immediate use (e.g., ^{99m}Tc-labeled red blood cells, etc.).

Examples of common practices in nuclear pharmacy that *are* considered compounding by the COR:

- Preparation of a radiopharmaceutical from a manufactured, non-radioactive kit with major deviations from the manufacturer's package insert. Major deviations are defined as manipulations not included in the manufacturer's package insert (e.g., filtration,

etc.), or the addition of other ingredients not included in the manufacturer's package insert (e.g., antioxidants, etc.).
- Sub-division of a multiple-dose vial of a radiopharmaceutical into aliquots for storage and later use.
- Preparation of non-FDA approved radiopharmaceuticals. This includes radiopharmaceuticals no longer marketed for reasons not related to safety, radiopharmaceuticals during a shortage, and other situations involving extemporaneous compounding.

SNMMI COMMITTEE ON RADIOPHARMACEUTICALS

The Committee on Radiopharmaceuticals (COR) is a committee of the Society of Nuclear Medicine and Molecular Imaging (SNMMI). The SNMMI is the world's leading nonprofit scientific and professional organization promoting the science, technology, and practical application of nuclear medicine and molecular imaging. With 18,000 members worldwide, the SNMMI is the largest organization devoted to nuclear medicine and molecular imaging. The COR is established under the authority of the SNMMI Board of Directors. The primary function of the COR is to coordinate the professional, scientific, research, education, and practice issues associated with radiopharmaceuticals. The COR consists of leading experts from academic institutions and commercial manufacturers.

RECOMMENDATIONS

The development of and the adherence to clear and effective standards for the compounding of sterile radiopharmaceuticals are paramount for the protection of public health and for the supply of effective diagnostic and therapeutic radiopharmaceuticals. In this spirit, and considering the long-standing relationship between the nuclear pharmacy community and the USP, the SNMMI COR makes the following recommendations to the USP.

Recommendation 1

Delineate Common Practices that are Defined as Sterile Compounding within the Practice of Nuclear Pharmacy

The current lack of a universally accepted public standard that clearly and effectively delineates common practices within the practice of nuclear pharmacy must be addressed as soon as possible. The COR recommends that the USP immediately establish a panel with expertise in sterile compounding practices for radiopharmaceuticals. This panel may have to simultaneously report to the USP's existing expert committees on sterile compounding and on radiopharmaceutical monographs and general chapters. The COR recommends that the panel first conduct a survey of existing standards and information on compounding practices associated with sterile radiopharmaceuticals. Next, the panel should delineate common nuclear pharmacy practices, including those that are, and those that are not considered compounding. The delineated list should include, but not be limited to the practices described previously in this article. The resulting list should be evaluated and revised as necessary by both existing expert committees. Finally, the COR recommends that the panel publish the resulting list as a stimuli article in the *Pharmacopeial Forum* or other appropriate publications.

Recommendation 2

Create a Public Standard for the Preparation, Compounding, and Dispensing of Sterile Radiopharmaceuticals with the Practice of Nuclear Pharmacy

After completing the first recommendation, the COR recommends that the panel draft a new general chapter entitled "Radiopharmaceutical Preparation, Compounding and Dispensing – Sterile Preparations" and submit it for approval by both of the above-mentioned expert committees. The COR recommends that the USP publicize the draft of new general chapter in the *Pharmacopeial Forum* and through other standard forms of communication by the USP.

Recommendation 3

Reinstate an Expert Committee Dedicated to all Standards for Radiopharmaceuticals

The USP has successfully managed many changes in public standards for radiopharmaceuticals since the transition away from a dedicated expert committee for radiopharmaceuticals in 2010. The USP has accomplished this through numerous innovative approaches that have greatly improved public standards for today's generation of radiopharmaceuticals. The COR recognizes and commends the USP for these efforts. In the spirit of continuous improvement, the COR recommends that the USP reinstate an expert committee that is dedicated to all standards for radiopharmaceuticals, including those recommended in this article and those already in existence. Membership on the committee should include experts in all aspects of radiopharmaceuticals, including manufacturing, sterile and non-sterile compounding, SPECT diagnostics, PET diagnostics, and therapeutics.

The COR believes that radioactivity is the defining characteristic driving the unique nature of nuclear medicine and therefore should also define the responsibilities of this expert committee. Consequently, the COR believes the expert committee should not include responsibilities for non-radioactive products used as imaging agents (e.g., contrast agents, etc.).

The COR further believes that the consolidation of all expertise under the umbrella of a single expert committee will simultaneously strengthen USP standards and create efficiencies for the USP. This is important as new diagnostic radiopharmaceuticals are developed, approved, manufactured, and compounded in the unique environment of nuclear medicine. It is especially important as new therapeutic radiopharmaceuticals, theranostics, and other technologies advance the field of nuclear medicine toward personalized healthcare. The reinstatement of this committee will enable the USP to play a catalytic role in these developments and to continue its innovative leadership in public standards for radiopharmaceuticals that meet the needs of patients in the U.S. and around the world.

CONCLUSION

The COR and the SNMMI Board of Directors believe the recommendations in this article will strengthen USP standards associated with all aspects of radiopharmaceuticals, including the compounding of sterile radiopharmaceuticals. The implementation of these recommendations will be labor intensive, but they will build on the history of innovative leadership that the USP has provided the nuclear medicine community for decades. As a result, the USP will continue its worldwide leadership in this area for decades to come.

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