USP and PET Radiopharmaceuticals

1997 FDAMA Puts Standard-Setting Body at Center of Regulatory Process

Over the last decade, the framework for the regulation of radiopharmaceuticals for use with PET has been marked by controversy, has reached the ranks of Congress, and remains unfinished to this day. While this regulatory process evolves at the Federal level, the United States Pharmacopeia (USP) has continued its role in drug standards development and informational activities relating to PET radiopharmaceuticals. These activities are aimed at providing guidance to the profession, thereby helping to ensure maintenance of high standards of public health.

Although the USP has been involved with PET radiopharmaceuticals since 1988, its role in the regulation of these pharmaceuticals took on added importance with the passage of the FDA Modernization Act of 1997 (1997 FDAMA), which declared that PET radiopharmaceuticals would be considered adulterated if not prepared in compliance with USP standards (i.e., in compliance with standards published in USP monographs and general chapters relating to this class of drug) (*1*). Because this ruling is relatively new, many in the PET community are only now becoming familiar with the central role the USP now plays in PET radiopharmaceuticals.

FDA's Draft CGMP Rule/Guidance and USP

The 1997 FDAMA also stipulates that the FDA must establish approval procedures and current good manufacturing practice (CGMP) requirements for PET radiopharmaceuticals (*1*). Although the FDA has not yet issued the final rule for the CGMP requirements, the draft versions of the rule and guidance for PET radiopharmaceuticals were released by the FDA in March 2002 (*2*,*3*). Both of these documents include many of the principles and concepts as stated in the general chapter "Radiopharmaceuticals for Positron Emission Tomography—Compounding" (USP⟨823⟩) (*4*). This is because the FDA believes that USP⟨823⟩ "largely reflects the consensus views of the PET community and FDA on how to properly produce PET drug products" (*2*,*3*). In addition, the draft CGMP guidance also incorporates many other general chapters and monographs from the USP to specifically address certain proposed requirements (*4*–*7*) (Tables 1 and 2). As a result, the USP has become an integral element of the regulatory framework for the preparation of PET radiopharmaceuticals, and the FDA will rely heavily on the USP in setting up the final CGMP rule and guidance.

The purpose of this article is to provide a general insight into the workings of the USP and, specifically, its role in the regulation of PET radiopharmaceuticals. In addition, it is our hope that this will serve as a stimulus to individuals within the PET community to become involved in the activities of the USP.

The United States Pharmacopeia, Inc.

The USP, Inc. is a private, nonprofit, scientific organization incorporated in the District of Columbia. Over the years since 1820, when it published a "recipe book" for 217 drugs and drug preparations, its mission has evolved into one of setting standards for drugs and providing drug information. USP standards are widely recognized as authoritative and are enforced by the FDA and state agencies. USP establishes these standards through an open participatory process with established integrity. Volunteers from all aspects of industry, education, medicine, and pharmacy carry out these activities.

The Council of Experts

Drug standards are established by the Council of Experts and by Expert Committees, USP's scientific decision-making bodies. Membership is drawn from the scientific and health care profession communities. The USP Nominating Committee selects qualified candidates to run for election to the Council of Experts. Those elected by delegates at the USP Convention then serve as chairs of the various Expert Committees. The Nominating Committee also selects nominees for membership on the Expert Committees. Members serve 5-year terms. The USP Web site (www.usp.org/volunteers/nominate/) provides information on how to become involved in this process.

Of the 62 Expert Committees, 2 deal directly with radiopharmaceuticals. The committee charged with setting standards for radiopharmaceuticals is the Expert Committee on Radiopharmaceutical and Medical Imaging Agents, in the Noncomplex Actives and Excipients Division. Drug information related to radiopharmaceuticals is the responsibility of the Expert Committee on Radiopharmaceuticals in the Information Division.

TABLE 1
2004 USP-NF General Chapters Related to the FDA CGMP Requirements for PET Radiopharmaceuticals (*5*)

USP general chapter		
No.	Title	Citation of draft CGMP rule or guidance
⟨71⟩	Sterility Tests	Draft CGMP guidance: X. Finished Drug Product Controls and Acceptance Criteria
⟨85⟩	Bacterial Endotoxins Test	Draft CGMP guidance: X. Finished Drug Product Controls and Acceptance Criteria
⟨621⟩	Chromatography	Draft CGMP guidance: V. Facilities and Equipment
⟨821⟩	Radioactivity	Draft CGMP guidance: V. Facilities and Equipment
⟨823⟩	Radiopharmaceuticals for PET-Compounding	Main principles and concepts for draft CGMP rule and guidance
⟨1015⟩	Automated Radio-chemical Synthesis Apparatus	Draft CGMP guidance: V. Facilities and Equipment
⟨1225⟩	Validation of Compendial Methods	Draft CGMP guidance: VIII. Laboratory Controls

Public Review and Comment Process for Standards Development

The USP establishes standards for drugs through a rigorous peer-review process conducted by the Council of Experts and Expert Committees, as well as through a review-and-comment process that is open to the general public. USP standards are under continuous revision. A request for revision can come from any interested entity or individual. A guideline (i.e., *USP Guideline for Submitting Requests for Revision to the USP-NF* [National Formulary]) on how to request revisions to the USP is available on the Web site (www.usp.org/standards/revisionguideline/index.html). This guideline also provides recommendations to sponsors on submitting information to support revisions to the United States Pharmacopeia and National Formulary (USP-NF).

Revision includes either creation of a new standard (i.e., monograph or general chapter) or revision of an existing standard. When received, the USP assigns the request for revision to a scientific liaison, who will work with the sponsor(s) to ensure that the request incorporates the appropriate information and background materials. When complete, the scientific liaison forwards the request to members of the responsible Expert Committee(s). These members evaluate the submission for technical accuracy, proper validation, and suitability. The Expert Committee(s) may approve or decline the request for revision or may request additional information. With the approval of the Expert Committee(s), the scientific liaison will prepare the request for revision for publication, submitting it for the USP's editorial and publication process for the *Pharmacopeial Forum* (*PF*). Most requests for revision appearing in the *PF* are open for public comment for a period of not less than 60 days. Interested parties are referred to the USP Web site (www.usp.org/standards) for more details.

TABLE 2
PET Radiopharmaceuticals Listed in 2004 USP-NF (*5*)

^{11}C-carbon monoxide
^{11}C-flumazenil
^{11}C-mespiperone
^{11}C-methionine
^{11}C-raclopride
^{11}C-sodium acetate
^{18}F-fluorodeoxyglucose
^{18}F-fluorodopa
^{18}F-sodium fluoride
^{13}N-ammonia*
^{15}O-water
^{82}Rb-rubidium chloride

* Proposed revision (*6*).

Pharmacopeial Forum

The USP publishes *PF* bimonthly as the working vehicle of its Council of Experts. The *PF* provides interested parties an opportunity to review and comment while the Council of Experts and its expert committees develop standards for the USP–NF. The USP welcomes comments and data on potential, proposed, or official standards. Comments and responses are published in the *PF*.

Because it is likely that the *PF* is not widely available within the nuclear medicine community, alternate avenues for dissemination of information on relevant activities of the USP should be developed. One such possibility would be to post *PF* information related to PET radiopharmaceuticals on the SNM Web site, provided that agreeable terms between the USP and SNM could be reached.

The PET community is fortunate to be a relatively small and close-knit group with multiple forums in which to exchange ideas and information. Activities of the USP should be brought into this dialogue through increased interaction with the Expert Committees via various professional nuclear medicine organizations, as well in the published literature. This article is intended as a beginning to this process.

In addition, individuals are urged to contact Expert Committee chairs or USP staff liaisons to bring issues to the attention of a specific committee.

USP Standards for PET Radiopharmaceuticals

USP activities with direct impact on the practice of nuclear medicine and PET include the development of individual product monographs and general chapters that address related topics. The USP first provided standards for PET radiopharmaceuticals in 1988 and currently includes several general chapters and official monographs related to PET radiopharmaceuticals (Tables 1 and 2). The 2004 USP-NF contains 73 monographs for radiopharmaceuticals, of which 12 are PET radiopharmaceuticals (Table 2).

Monographs provide drug standards and test methodologies to be used to determine compliance with each standard. Use of alternate analytical methodologies is allowed, although all such methods must be validated against the official method. Inclusion of a particular standard in a monograph does not necessarily address the frequency of testing for that standard. For example, a standard for radionuclidic purity does not necessarily imply that this is a release criterion for the product. It may be possible only to show compliance with this standard after complete decay of the primary radionuclide. Currently, for PET radiopharmaceuticals, frequency of testing is dictated by USP⟨823⟩, "Radiopharmaceuticals for Positron Emission Tomography–Compounding" (*4*), and ultimately will be dictated by CGMP regulations when finalized by the FDA.

Active Involvement in the Development and Revision Process for USP Standards

To ensure that the progress of PET technology will not be stifled by impractical or restrictive CGMP regulation, the PET community should be aware of current general USP chapters and monographs that are related to PET radiopharmaceuticals. In addition, it is critical for our colleagues who work in the PET field to familiarize themselves with the development and review process for USP standards. As stated previously, the FDA believes that USP⟨823⟩ "largely reflects the consensus views of the PET community and FDA. . . . " However, if USP standards are to truly reflect the views of the PET community, widespread involvement from that community in USP revision processes is necessary.

We have presented an overview and brief history of the central role the USP has played in the evolution of standards setting and regulation of PET radiopharmaceuticals. USP welcomes input from interested organizations. Members of the PET community are urged to become involved and to provide input into USP activities. Committee chairs and staff liaisons whose work is most relevant to standard setting and regulations of PET radiopharmaceuticals are:

- Expert Committee on Radiopharmaceuticals and Medical Imaging Agents
  Chair: Ronald J. Callahan, PhD
  (callahan@helix.mgh.harvard.edu)
  USP Staff Liaison: Andrzej Wilk, PhD, senior scientific associate
  (aw@usp.org).
- Expert Committee on Radiopharmaceuticals
  Chair: Barry A. Siegel, MD
  (siegelb@mir.wustl.edu)
  USP Staff Liaison: Denise S. Penn, RPh, senior drug information specialist
  (dsp@usp.org)

Colleagues from across the spectrum of nuclear medicine practice are urged to get involved in USP PET-related activities.

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5. United States Pharmacopeia. *The United States Pharmacopeia.* 27th ed., and *The National Formulary,* 22nd ed. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2004.
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