

Current Good Manufacturing Practices for PET Drug Products in the United States

The U.S. Food and Drug Administration (FDA) mandates minimum manufacturing standards for drugs for human administration to ensure that the products meet requirements of safety and have the identity, strength, quality, and purity they should possess. The FDA's current good manufacturing practice (CGMP) regulations (21 Code of Federal Regulations [CFR] Parts 210 and 211) outline these standards and have the force of law. However, radiopharmaceuticals used for PET imaging pose special manufacturing challenges because of their short radioactive half-lives and requirement for extensive radiation shielding, with resulting requirements for the establishment of special manufacturing facilities (PET facilities) at or near the hospitals and academic centers where they are administered. Because of the special nature of these agents, both the FDA and PET facility operators have agreed that certain provisions of the CGMPs applicable to traditional drugs, including traditional radiopharmaceuticals, are not appropriate at this time for the manufacture of PET radiopharmaceuticals. This review describes the history of the development of CGMPs specific to PET radiopharmaceuticals, reviews the current status of these manufacturing standards, and outlines some of the related controversies and unresolved issues.

Background

The earliest PET radiopharmaceuticals were primarily manufactured at production facilities located in universities and other academic-based institutions (1). These facilities produced small amounts of a limited number of PET radiopharmaceuticals for onsite clinical or research use. As the potential of PET imaging became more apparent, the number and use of PET radiopharmaceuticals expanded, as did the number of facilities involved in the manufacture of these agents. The availability of PET/CT technology, the advent of automated commercial synthesizers, and federal reimbursement for PET scans using ^{18}F -FDG in oncology have contributed to the rapid rise in PET radiopharmaceutical production over the past decade.

Although some academic-based PET facilities continue to manufacture PET radiopharmaceuticals for onsite clinical and research use, the more prominent trend has been toward establishment of centralized, for-profit facilities that distribute PET radiopharmaceuticals to multiple local or regional hospitals or clinics. This trend heightened the perceived need for increased regulatory oversight, resulting in a 1995 FDA *Federal Register* notice indicating the agency's intention to regulate PET facilities as

traditional drug manufacturers and to subject the manufacturing of PET radiopharmaceuticals to the CGMP standards applicable to traditional drugs (2).

Subsequent congressional action led to Section 121, Positron Emission Tomography, of the FDA Modernization Act (FDAMA) of 1997, which required the FDA to develop CGMP standards specific and applicable to this technology. In addition to directing the FDA to take into account while developing these standards the special characteristics of PET radiopharmaceuticals and the operations and processes required to produce them, the FDAMA required the FDA to address any relevant differences between not-for-profit institutions that compound PET radiopharmaceuticals for their patients or research subjects and centralized, commercial manufacturers of PET radiopharmaceuticals. The FDAMA specified that in the period preceding the finalization of these PET-specific CGMP standards that the manufacture of PET radiopharmaceuticals should comply with *U.S. Pharmacopeia* (USP) Chapter <823>, Radiopharmaceuticals for Positron Emission Tomography—Compounding, and USP PET radiopharmaceutical monographs, where applicable.

The FDA has not yet issued the final PET-specific CGMP. Under the FDAMA, the interim provisions will expire 2 y after the date on which FDA issues its final standards, at which time compliance with these regulations will be required. FDA has been working with the PET community since the issuance of the FDAMA to develop appropriate CGMP manufacturing requirements. These requirements would cover all manufacturing operations to the point of final release of a finished bulk product. The distribution of PET radiopharmaceuticals as individual patient unit dosages is considered part of the practice of pharmacy as regulated by state and local authorities and is therefore not addressed in PET-specific CGMP standards.

The manufacture of PET radiopharmaceuticals, then, remains subject to compliance with USP Chapter <823> and pertinent USP PET radiopharmaceutical monographs. USP Chapter <797>, Pharmaceutical Compounding—Sterile Preparations, addresses requirements for the dispensing of drugs, including unit dosages of PET radiopharmaceuticals.

FDA Development of PET-Specific CGMP Regulations

On February 19, 1999, the FDA held a public meeting to discuss its tentative approach to the development of PET-

specific CGMP standards, to be coded as 21 CFR Part 212. A preliminary draft of 21 CFR Part 212 and a related guidance document were issued later that year, followed by a public meeting to discuss the regulatory requirements (3). Based on comments received at and after this meeting, the FDA issued in April 2002 a preliminary draft proposed rule entitled Current Good Manufacturing Practice for PET Drugs—21 CFR Part 212, along with related guidance (4,5). These documents were again opened for public comment, resulting in the agency's publication in September 2005 of a proposed rule and draft guidance addressing the PET-specific CGMPs (6).

Differences in size, scope, and complexity of operations among PET facilities as well as differences between not-for-profit and for-profit status have been addressed in this latest draft of the proposed 21 CFR Part 212 standards. Although the FDAMA of 1997 proposed that PET-specific CGMPs take into account any relevant differences between not-for-profit institutions and commercial manufacturers, the FDA itself proceeded with the idea that CGMP requirements should not distinguish between these 2 types of entities. Instead, the FDA designed its draft regulations to be flexible enough for all types of PET centers, while at the same time ensuring product quality and safety. The proposed 21 CFR Part 212 standards and associated guidance document address resources, procedures, and documentation for all PET drug production facilities, both academic and commercial. These standards and associated guidance, however, allow for certain flexibility in the manufacture of PET radiopharmaceuticals for use or evaluation under research studies.

Investigational and Research PET Radiopharmaceuticals

In the United States, human research with non-FDA-approved radioactive drugs or biologic products must be conducted under an investigational new drug (IND) application or under the direct oversight of a radioactive drug research committee (RDRC) that operates in accordance with FDA regulations at 21 CFR Section 361.1 (7,8). To include the use of a radioactive drug in human research subjects under RDRC authority, the investigation must constitute a "basic research study" of the pharmacokinetics of the PET drug or must evaluate a physiologic or pathophysiologic process. Additional stipulations require that the physical quantity of the PET drug to be administered must be known (i.e., based on prior, valid human studies) not to cause any physiologic effects and that radiation absorbed doses must fall below certain regulatory limits (i.e., the PET drug must be generally recognized as safe and effective). The FDA has documented its contention that it is appropriate to have less-detailed CGMP requirements for investigational and research PET drugs to allow "more flexibility during the development of these radiopharmaceuticals," because many of these may have no commercial potential. Investigational and research PET

radiopharmaceuticals are defined as those "investigational PET radiopharmaceuticals for human use produced under an IND application in accordance with (21 CFR) part 312" and "research PET radiopharmaceuticals that are produced with the approval of a Radioactive Drug Research Committee in accordance with 21 CFR 361.1." The current draft version of CFR Part 212 states that, for early-phase clinical investigational and research PET radiopharmaceuticals, the requirement to follow CGMP is met by producing radiopharmaceuticals in accordance with the current USP Chapter <823>.

The USP, Inc., is a private, nonprofit scientific organization of experts who set standards for drugs and drug processes in the United States. USP standards are widely recognized as being of high scientific integrity, and compliance with the USP general information chapters (i.e., USP chapters with numbers lower than <1000>) and monographs may be enforced at the discretion of the FDA. The USP has been involved with PET radiopharmaceuticals since 1988 and assumed even greater regulatory importance in 1997 with the passage of the FDAMA (9). As previously noted, the FDAMA specifies that a compounded PET drug is "adulterated unless it is produced in compliance with USP compounding standards and official monographs for PET radiopharmaceuticals." The current version of USP Chapter <823> incorporates the views of both the FDA and the PET community on ways to properly produce PET drug products. Many of these principles have been incorporated into the latest draft of the PET CGMP standards, although active discussion and feedback on various issues continues in the PET community.

USP Chapter <823> sets forth requirements for PET drug production to include: control of components, materials, and supplies; verification of procedures; stability testing and expiration dating; quality control; and sterilization and sterility assurance. Although the draft 21 CFR Part 212 standards address a set of CGMP requirements for all PET radiopharmaceuticals marketed under a new drug application (NDA) or abbreviated NDA, they propose to retain USP Chapter <823> provisions governing the manufacture of PET radiopharmaceuticals for use in early-phase (i.e., phases 1 and 2) clinical investigations. In this regard, it is generally recognized that the provisions in USP Chapter <823> are somewhat less specific and explicit than the requirements in draft 21 CFR Part 212. However, at this time, FDA believes that they are "adequate to ensure that investigational and research PET drugs are produced safely under appropriate conditions." FDA still retains the authority to inspect facilities in which investigational and research PET radiopharmaceuticals are produced to verify compliance with USP Chapter <823>. However, it is proposed that these inspections would take place only on a for-cause basis (i.e., when the agency is made aware of a potential safety concern related to the production of an investigational or research drug).

Status of 21 CFR Part 212 and Unresolved Issues

In the absence of the FDA's issuance of final 21 CFR Part 212 standards, the manufacture of PET radiopharmaceuticals remains subject to compliance with USP Chapter <823>, as declared in Section 121 of FDAMA 1997. When these PET-specific CGMP standards and accompanying guidance are established as legislation, full compliance will be required within 2 y after the regulations become final. The exact nature of the final PET-specific CGMPs and the timing of these new regulations are uncertain. Many organizations have contributed to the draft CGMPs, including the USP, professional societies, and pharmaceutical companies. Even with these best efforts, 4 y have passed since the latest version of the draft 21 CFR Part 212 standards was published, and no timetable for issuance of the final regulations has been announced.

In this interval, various issues and concerns remain unresolved, and the manufacturing procedures outlined in USP Chapter <823> and proposed 21 CFR 212 are being applied inconsistently by both PET facilities and FDA auditors. Questions remain about which set of standards will apply to the development of PET radiopharmaceuticals under an IND. Certain aspects of manufacturing under USP Chapter <823> (e.g., air quality) need additional clarification to meet the expectations of auditors and inspectors. Other questions have surfaced about manufacturing issues (e.g., precursor quality at different stages of development) that are unclear in both USP Chapter <823> and the proposed 21 CFR 212 standards (10–12).

Regulations governing the manufacture of PET radiopharmaceuticals should be scientifically justified, protect the safety of patients, and be sufficiently flexible to accommodate the unique features of this technology. It is equally important to ensure consistent interpretation of CGMP guidelines by both manufacturers and regulators. In addition, given the potential of PET imaging, it is important to avoid policies that would unnecessarily limit new discoveries and the development of research tools that could improve human conditions. It is critically important to resolve these outstanding issues surrounding the manufacture of PET radiopharmaceuticals with finalization and implementation of the PET-specific CGMPs at 21 CFR Part 212.

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