

Final PET CGMP Regulation

The path to U.S. Food and Drug Administration (FDA) regulation of PET radiopharmaceuticals has been long, contentious, and controversial. The formal process of identifying the future FDA regulatory scheme began in 1995 with the notice “Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop” (1) and was finalized on December 10, 2009, when the FDA published the final Current Good Manufacturing Practices (CGMP) regulation, 21CFR Part 212 (2), and “PET Drugs—CGMP Guidance” (3). With this new rule, the regulatory authority under which PET drugs are produced will change.

Because of the nature of PET drugs and the development of these agents in the academic arena, most PET radiopharmaceutical compounding historically has been regulated by the states that regulate the professions of pharmacy and medicine. Some commercial entities produce PET drugs under FDA manufacturing registration and (where required) state manufacturing licensure but without an approved drug application. Commercial distribution of patient doses of PET drugs usually occurs under the practice of pharmacy, and this practice is likely to continue. Other exceptions to the current regulatory mode apply to a few medical institutions that have gained approval for ¹⁸F-FDG and ¹³N-ammonia through approved New Drug Applications (NDAs), which are regulated by FDA.

After the rule making in 1995, FDA held several FDA/stakeholder workshops in an attempt to educate the PET community on how they would be regulated. As a result of those workshops and the realization by PET stakeholders that the FDA regulatory scheme was unworkable, legal action was taken against the agency. As a result, the courts overturned the 1995 FDA regulatory action. Congress became involved in the regulation of PET drugs in 1997 and enacted the FDA Modernization Act (FDAMA 1997) that year, including Section 121, “Positron Emission Tomography,” which addressed PET drugs (4). It stated:

That in order to take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs not later than 2 years after the date of enactment of this Act, the Secretary of Health and Human Services shall establish—

- Appropriate current good manufacturing practice requirements for such drugs
 - The Secretary, DHHS, shall not require the submission of NDAs or Abbreviated New Drug Applications (ANDAs) for compounded PET drugs—for a period of 2 years after the date on which the Secretary establishes these PET drug approval procedures and PET CGMP requirements.
- Appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); and



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After FDAMA was signed into law, several more FDA/stakeholder meetings were held in an attempt to develop a reasonable and achievable approach for a regulatory mechanism. FDA published a preliminary draft regulation in 1999, a preliminary draft proposed rule and draft guidance in 2002, and the proposed rule and draft guidance in 2005. Regulatory action culminated with the December 10, 2009, final CGMP rule and guidance. The period provided in FDAMA for final implementation of the final rule was 2 y from the date of the final action by FDA, so that new regulation will be effective on December 12, 2011.

To satisfy the requirement of Section 121 of FDAMA for “appropriate procedures for the approval of PET drugs,” FDA published a *Federal Register* notice on March 10, 2000, regarding the safety and effectiveness of ¹⁸F-FDG, ¹⁸F-sodium fluoride, and ¹³N-ammonia. This created a pathway for producers of these PET drugs to file human drug applications for those specific drug products. NDAs (505(b)(2)) could be filed for FDG, ammonia and sodium fluoride referencing the March *Federal Register* notice of safety and efficacy, thus eliminating the requirement to submit a full NDA (505(b)(1)), which would ordinarily contain results of complete clinical studies to demonstrate safety and effectiveness. Under the FDAMA, producers could still voluntarily submit drug applications.

The 2000 *Federal Register* notice also addressed user fees under the Prescription Drug User Fee Act (PDUFA). User fees are assessed against an NDA applicant, and fees are assessed for NDA applications, manufacturing establishments, and drug products. The notice described

circumstances in which some or all of these fees may be reduced or waived. ANDAs and applicants are not subject to the PDUFA fees.

In 2004 and 2005, 2 medical institutions received approval of NDAs for FDG that were voluntarily submitted (5,6). User fees were waived for these applications. Similarly, in 2007 an NDA was approved for ^{13}N -ammonia (7). These approvals have paved the way for any producer of ^{18}F -FDG and ^{13}N -ammonia to submit ANDA applications, which are not subject to user fees.

CGMPs are the minimum standards that each manufacturer must follow to produce the drug to help ensure that it remains safe and effective over its labeled shelflife. CGMP regulations cover nearly all areas of drug processing and handling, including the control of ingredients, methods of processing ingredients to make a finished drug, training, standard operating procedures, recordkeeping and review, testing of materials as well as finished products, and quality assurance and management control practices to be followed.

The CGMP for PET, 21 CFR Part 212, is the rule (or regulation) and contains binding requirements that manufacturers of PET drugs must follow. The rule is enforceable in the courts. The guidance document, on the other hand, describes FDA's current thinking on individual issues addressed by the rule but is not binding on FDA or the public. Guidance documents recommend approaches to complying with statutory requirements or regulations, but alternative approaches can be used if they meet the statutory and regulatory requirements.

Section 121 of FDAMA also provided a temporary safe harbor regulatory path for producers and FDA for the period of time until 2 y after publication of a final CGMP regulation. Specifically, FDAMA requires that under the Food, Drug, and Cosmetic Act (Section 501(a) (21 USC. 351(a)):

A compounded positron emission tomography drug and the methods used in, or the facilities and controls used for, its compounding, processing, packing, or holding must conform to or operated or administered in conformity with the positron emission tomography compounding standards (USP Chapter 823) and the official monographs of the United States Pharmacopoeia to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to possess.

The requirement, to follow United States Pharmacopoeia (USP) Chapter 823, "Radiopharmaceuticals for Positron Emission Tomography—Compounding," along with the entire

Section 121 of FDAMA, ends on December 11, 2011 (8). Prior to full implementation, U.S. facilities must continue to comply with USP Chapter <823>, which is the current legal standard for the production of PET drugs. The regulation requires that producers of PET drugs must be compliant with 21 CFR Part 212 by 2 y after the publication date.

After the effective date of the rule in 2011, PET drug producers will be required to submit either an NDA or ANDA for each of their PET drugs, whether or not these are produced for commercial distribution. PET drugs may no longer be produced under the practice of pharmacy and/or medicine after applications are approved. As a result of the regulation, producers of PET drugs will also be required to register their establishments and list their products according to 21CFR Part 207.

For the manufacture of investigational PET drugs for human use produced under an Investigational New Drug (IND) application (21 CFR Part 312.1–312.7) or produced with the approval of a Radioactive Drug Research Committee (21 CFR 361.1), the new rule (Section 212.5) allows the producer the option of complying with either USP Chapter <823> or Part 212. Because there is a choice to follow USP or Part 212, the PET Drug CGMP Guidance document can be used as a reference for approaches to satisfy regulatory requirements in the manufacture of investigational PET drugs.

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