FDA cGMP Requirements for PET Drugs

On December 9, 2009, the U.S. Food and Drug Administration (FDA) issued a regulation (21 *Code of Federal Regulations* [CFR] Part 212) establishing Current Good Manufacturing Practices (cGMP) for PET drugs. All PET drugs, such as ^{18}F-FDG, ^{18}F-NaF, and ^{13}N-ammonia, used in the clinical practice of nuclear medicine, regardless of whether they are obtained from a commercial vendor or an academic facility, must be manufactured in compliance with 21 CFR Part 212 by December 12, 2011. The rule requires the submission of a new drug application (NDA) or abbreviated new drug application (ANDA) for any PET drug product marketed for clinical use in the United States. In addition, all PET producers are also required to register with the FDA as a Drug Establishment by the December 12, 2011, deadline.

Production of research PET drugs under an Investigational New Drug (IND) application or under the authority of an institutional Radioactive Drug Research Committee (RDRC) may follow either the cGMP regulations in 21 CFR Part 212 or the current *United States Pharmacopeia* (USP; 32nd edition) General Chapter <823> titled "Radiopharmaceuticals for Positron Emission Tomography–Compounding."

Submitting an NDA or ANDA

The FDA prefers the use of the electronic Common Technical Document (eCTD) format and submission through the agency's electronic portal. The agency will also accept hybrid applications in pdf format submitted on CD/DVD; it is recommended that the documents be in CTD format with hyperlinks. Paper submissions will also be accepted; however, this is discouraged because of the complexity of handling paper documents. All applications must be validated and accepted for review by the December 12, 2011, deadline. The FDA will allow those facilities that have submitted an ANDA or NDA before this deadline to continue to market and sell their products during the review and approval of their applications. Failure of an existing facility to file an ANDA or NDA prior to December 12, 2011, means the facility must stop marketing and selling their PET products until the applications are approved by the FDA, which may take up to 3 y.

FDA guidance on "Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration & Drug Listing" is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339. An ANDA Checklist for CTD or eCTD format can be found at: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM151259.pdf

Facility Inspection

After the December 12, 2011, deadline for submission of the NDA or ANDA, FDA will gradually increase the number of inspections of all registered PET facilities to verify conformance with the new Part 212 rule. The agency has indicated special training will be provided to inspectors so they will be familiar with the unique characteristics of PET products and how to inspect Part 212. Facilities filing an ANDA or NDA must be ready for inspection at the time of ANDA or NDA submission. The FDA has committed to developing and making available an inspection guide and training manual for inspectors of PET drug production facilities.

PET Drugs from a Commercial Vendor

If a facility purchases PET radiopharmaceuticals from a vendor, the facility should verify that the vendor is in compliance with 21 CFR Part 212, cGMP for PET Drugs. A vendor should provide evidence, such as an approved application number or a letter of submission from the FDA, to indicate that either (1) the PET drugs are manufactured in accordance with an FDA-approved NDA or ANDA; or (2) the vendor has submitted an NDA or ANDA to the FDA by the December 12, 2011, deadline.

Additional information is available on the FDA Web site regarding submission of NDAs or ANDAs and about the 21 CFR Part 212 regulations. This information includes: "Positron Emission Tomography (PET): Questions and Answers about CGMP Regulations for PET Drugs," www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/usm193476.htm. The FDA has also published a guidance document "PET Drugs—Current Good Manufacturing Practice (CGMP)" to provide the agency's current thinking on how to comply with the new regulation (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070306.pdf).

The FDA recently held a public meeting to discuss preparing NDAs or ANDAs for ^{18}F-FDG, ^{13}N-ammonia, and ^{18}F-NaF injection in PET imaging. A webcast of the meeting is available at: www.fda.gov/Drugs/NewsEvents/ucm236825.htm.

The SNM is an active member of the Coalition for PET Drug Approval. The purpose of the coalition is to help the community understand requirements related to the implementation of 21 CFR Part 212 and the submission process for PET NDAs or ANDAs. The coalition wants to make a positive impact on the overall implementation process by interacting with the FDA for the PET community. Questions were submitted to the FDA on behalf of the coalition. The members are now preparing answers to these questions based on information obtained during the FDA public meeting held on March 2, 2011. The questions and answers will be posted on the coalition Web site at www.coalitionforpetdrugapproval.org.

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