Regulatory Requirements for PET Drug Production

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Learning Objectives: On successful completion of this activity, participants should be able to describe (1) regulatory requirements for production of NDA and ANDA PET drugs, including an overview of specific requirements for compliance; (2) regulatory requirements for the production of PET drugs for clinical research use; and (3) FDA preapproval inspections and postapproval reporting requirements.

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The Food and Drug Administration (FDA) issued the final rule for title 21 of *Code of Federal Regulations* part 212 regarding the regulations on current good manufacturing practice for PET drugs. The regulations are intended to ensure that PET drugs meet the safety and quality assurance requirements of the Federal Food, Drug, and Cosmetic Act. The new regulation became effective December 12, 2011, but the FDA used regulatory discretion to allow new drug applications and abbreviated new drug applications to be filed until June 12, 2012, without interruption of the existing PET drug production for human use. The production of PET drugs for both clinical use and clinical research use are outlined in this continuing education module, including an overview of specific requirements for compliance. Additionally, FDA preapproval inspections and postapproval reporting requirements are reviewed.

Key Words: FDA part 212; USP chapter <823>; NDA/ANDA; FDA inspections; annual reporting

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On December 10, 2009, the Food and Drug Administration (FDA) issued the final rule for title 21 of *Code of Federal Regulations* part 212 (21 CFR 212) regarding the regulations on current good manufacturing practice (CGMP) for PET drugs (*1*). The regulations are intended to ensure that PET drugs meet the safety and quality assurance requirements of the Federal Food, Drug, and Cosmetic Act. The new regulations became effective December 12, 2011, but the FDA used regulatory discretion to allow new drug applications (NDAs) and abbreviated NDAs (ANDAs) to be filed until June 12, 2012. The FDA did require all production facilities to be compliant with the new CGMP-for-PET rule by December 12, 2011. In addition to the FDA-approved radiopharmaceuticals ^{18}F-FDG, ^{13}N-ammonia, and ^{18}F-sodium fluoride that require manufacturing under an NDA or ANDA, all research PET radiopharmaceuticals (e.g., ^{18}F-fluorothymidine, ^{18}F-fluoromisonidazole, ^{18}F-fluorodopa, and ^{11}C-methionine) used in human studies are now required to have either investigational new drug (IND) or Radioactive Drug Research Committee approval.

CGMP is a minimum standard that ensures a drug meets the requirements for safety and has the appropriate identity, strength, quality, and purity. CGMP is demonstrated through written documentation of procedures and practices and through their implementation in the production facility. Many of the historic documents and practices being used in PET drug formulation at established cyclotron facilities had to be reevaluated to ensure that all regulatory requirements needed to achieve compliance with FDA CGMP for PET were met.

The impact of the regulation is obviously important for both commercial and academic PET radiopharmaceutical manufacturers. The purpose of this continuing education module is to review the history of the regulatory process for PET drugs and provide the PET imaging community with current information on the implementation of 21 CFR 212.

HISTORY OF THE REGULATION OF PET DRUGS

The path to FDA regulation of PET drugs was a long and controversial process. ^{18}F-FDG was originally developed in the early 1970s as a research tool in the academic setting. In the 1980s and 1990s ^{18}F-FDG began to be used more widely in clinical practice. In the early 1990s, the FDA became aware of the more widespread clinical use of ^{18}F-FDG and other PET drugs to assess a variety of diseases. ^{18}F-FDG and other tracers were prepared under the practice of pharmacy. The FDA considered how PET drugs used for clinical care should be regulated to ensure that they were safe and effective for their intended applications.

The formal process began in 1995 when an FDA *Federal Register* notice was published indicating the agency's intention to regulate PET facilities as traditional drug manufacturers and to subject the manufacturing of PET radiopharmaceuticals to CGMP for finished pharmaceuticals (*2*).

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After the FDA rule was published in 1995, the FDA held several stakeholder workshops to educate the PET community on how the rule would be regulated. As a result of discussions at these workshops, the PET stakeholders realized that the FDA regulatory scheme as proposed in 1995 would be challenging and unworkable because of the unique aspects of PET drug production compared with conventional pharmaceutical manufacturing. These included, among others, the short half-life of the final PET drug product, the distributed production requirements, and limited staffing at most facilities. As a result of opposition to the FDA's proposal to regulate PET production, Congress intervened in the regulation of PET drugs in 1997. Specific legislative language regarding PET regulation was added to the Food and Drug Modernization Act (FDAMA), which was signed by President Clinton in 1997 (*3*). Section 121 of the provision addressed the FDA approach to PET drugs. The FDA was directed to take into account the special characteristics of PET radiopharmaceuticals and the operations and processes required to produce them. By this Act, the FDA was required to provide procedures for the approval of PET drugs and CGMP standards for PET drugs.

To address the requirement to provide procedures for the approval of PET drugs, and since PET drugs had been used clinically for 10–20 y, the FDA decided to conduct its own review of the published literature to evaluate the safety and effectiveness of certain PET drugs and facilitate the process of submitting NDAs for these products. The FDA published a *Federal Register* notice on March 10, 2000, regarding the safety and effectiveness of ^{18}F-FDG, ^{18}F-sodium fluoride, and ^{13}N-ammonia (*4*). With the publication of this notice, the FDA created a mechanism for producers of these PET drugs to file an NDA 505(b)(2) by referencing the March 2000 *Federal Register* notice on safety and efficacy—rather than filing a full NDA 505(b)(1), which requires associated clinical data. 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 for NDA applications, manufacturing establishments, and drug products. The notice described circumstances under which some or all of these fees may be reduced or waived. ANDA applications are not subject to the PDUFA fees.

The FDA, after enactment of FDAMA, continued to develop workable CGMP standards for PET drugs, publishing several draft rules in 1999, 2002, and 2005. Regulatory action was finalized on December 10, 2009, when the FDA published the final CGMP rule and guidance (*1,5,6*). The period provided in FDAMA for final implementation of the final rule was 2 y from the date of final action by the FDA. Publication of this final rule triggered the 2-y period for PET producers to submit an NDA or an ANDA for clinical PET drugs, ^{18}F-FDG, ammonia, and sodium fluoride.

Before any FDA regulatory requirements, the first ^{18}F-FDG NDA was submitted in 1994 by Methodist Medical Center (and CTI, Inc.) in Peoria, Illinois, for 2 clinical indications: to assess myocardial glucose metabolism and to identify epileptic foci with altered glucose metabolism. In 2004 (*7*) and 2005 (*8*), 2 additional medical institutions submitted NDAs for ^{18}F-FDG and received approval. User fees were waived for these applications. Similarly, in 2007, an NDA was approved for ^{13}N-ammonia (*9*). In the spring of 2011, the National Cancer Institute received NDA approval for ^{18}F-sodium fluoride (*10*). These approvals paved the way for any producer of ^{18}F-FDG, ^{13}N-ammonia, and ^{18}F-sodium fluoride to submit an ANDA application for these PET drugs, since the listed NDAs serve as the required reference listed drug (RLD).

21 CFR 212 CGMP FOR PET DRUGS

The rule, 21 CFR 212, presents PET CGMP requirements that are the minimum standards for quality production of PET drugs at all PET drug production facilities, including not-for-profit academic institutions and commercial producers. 21 CFR 212 addresses the methods to be used in the facilities and controls used for the production, quality assurance, and holding or distribution of PET drugs intended for human use (*1*). It is a rule (or regulation) that contains binding requirements that manufacturers must follow and is enforceable in the courts. It is the standard that each manufacturer must implement to help ensure that a drug remains safe and effective during its labeled shelf-life. The details on how to comply are provided in the manufacturer's standard operating procedures. Topics covered under CGMP are personnel; quality assurance; facilities and equipment; components, containers, and closures; production and process controls; laboratory controls; stability testing; and record keeping. Part 212 helps to achieve a high level of assurance that the final PET drug products meet the requirements for safety, purity, and efficacy. The CGMP-for-PET regulations do differ from traditional drug CGMPs (21 CFR 211 (*11*)) because of the characteristics of PET drugs, as required by FDAMA.

PET drugs are a unique group of radiopharmaceuticals that incorporate radionuclides with short lives usually ranging from 2 to 110 min. These short lives place constraints on the production and quality control testing of the drug products, and the drug expiration times are typically less than 12 h. Additionally, the mass of the active ingredient usually ranges from nanogram to microgram quantities (significantly less than therapeutic drugs). Each batch of PET drug is required to have complete quality control testing (except sterility) completed before release for human use.

U.S. PHARMACOPEIA (USP) 32 CHAPTER <823> VERSUS 21 CFR 212

Part 212 incorporates principles from the USP 32, as stated in chapter <823>, "Radiopharmaceuticals for PET—Compounding" (*12*). The USP chapter served as the rule for PET drug production from 1997 until part 212 was developed, as directed by FDAMA. According to the new part 212 rule, clinical drugs must be produced according to CGMP for PET, and research PET drugs must be produced under the approval of an institutional Radioactive Drug Research Committee (*13*) or under an FDA-approved IND (*14*) application. Research tracers may be produced either in accordance with part 212 or in accordance with 32 USP chapter <823>. USP chapter <823> defines most topics listed in the part 212 rule but is generally less specific.

A detailed description of each of the regulatory requirements along with a specific compliance narrative is given in *Guidance: PET Drugs—Current Good Manufacturing Practice (CGMP)* (*6*). The guidance document describes the FDA's current thinking on individual issues addressed by the CGMP-for-PET rule. It is not binding on the FDA or the public but recommends approaches to complying with statutory rules and regulatory requirements. The guidance document can also be used in combination with chapter <823> for the production of research PET drugs.

21 CFR 212 SPECIFIC REQUIREMENTS

The following sections describe the general requirements outlined in 21 CFR 212 and the companion guidance (*6*). The guidance for PET drugs helps to clarify some of the regulatory details.

Personnel

Part 212.10 stipulates that sufficient personnel with the education, background, training, and experience to perform their required functions be assigned to PET production and be provided with adequate resources to do their jobs. Their training should be documented and should include the aseptic process, medium fill testing, and all other procedures they will perform. Job responsibilities and assigned duties are clearly stated in written policies, such as job descriptions and standard operating procedures. Part 212.10 states that small PET drug production (producing 1–2 batches of a PET drug daily or weekly) may use 2 people for production and quality assurance. One highly qualified person can be designated to perform production and quality assurance. This is unlike 21 CFR 211 (traditional drug manufacturing requirements), which requires that a second person normally perform a check at various stages. Documented self-checks are allowed for small PET drug operations.

Quality Assurance

Part 212.20 is the umbrella of CGMP. It is the overall system of management review and process approval that builds quality into the system. It includes oversight of the program for receiving raw materials and approval or rejection of specifications, methods, processes, and proposed changes. It also requires review of production records and follow-up of any corrective action required.

Facilities and Equipment

Part 212.30 states that facilities must be adequate to ensure prevention of mix-ups and contamination and that equipment must be clean and suited to its intended purpose of preparation and testing of the PET drug product.

Components, Containers, and Closures

Part 212.40 requires that a system be defined for ordering and receiving raw materials. Specifications and written procedures are required for the components (materials used in the PET drug product preparation and testing) and the containers and closures (sterile vials) that will hold the final product.

Production and Process Controls

Part 212.50 requires written standard operating procedures and master production and control records that include identification of equipment and all components used in the preparation of the PET drug product.

Laboratory Controls

Part 212.60 describes the written quality control procedures and testing specifications. Equipment and analytic methods must be qualified. The materials used must be defined, and complete records must be maintained.

Stability Testing

Part 212.61 requires establishment of a written stability testing program—including annual stability testing—that can also be used to establish expiration times for PET drugs. The parameters evaluated for stability testing are detailed in the guidance document.

Finished Drug Product Controls and Acceptance Criteria

Part 212.70 requires written controls and acceptance criteria for finished drug products, in addition to the establishment of test procedures. For certain noncritical attributes, the guidance document allows a PET drug producer to conduct a periodic quality test. Examples include testing for radionuclidic purity, low-level nontoxic impurities, and class 3 residual solvents. Part 212.71 describes rejection of a PET drug batch as the action that must be taken if specifications are not met. It also allows and describes the procedure for reprocessing.

Sterility testing for PET drug products must be initiated within 24 h according to chapter <823> or within 30 h after the end of synthesis according to part 212.70(e). Additionally, the guidance document allows a longer hold time if it can be demonstrated that the sample and test results will not be affected. Sterility can be verified using a single USP indicator organism, such as *Escherichia coli*. If a PET drug product does not conform to specifications, chapter <823> requires rejection of the nonconforming product, investigation of the unacceptable quality control test results, and documentation of the outcome of the investigation, all of which are similar to part 212. Both chapter <823> and part 212 (212.80 (*6*)) require labeling the final PET drug container before the start of synthesis, and full labeling of the final container or dispensing-administration assembly with all appropriate information at completion of synthesis.

NDA AND ANDA DIFFERENCES

An NDA is the approval pathway for new drugs that are to be marketed and sold in the United States. An NDA contains data from animal studies and IND trials that show the safety and efficacy of the drug and whether the benefits outweigh the risks. In addition, the NDA contains all the information concerning the manufacture and quality control of the drug product. FDA-approved new drugs are also known as RLDs.

An ANDA is the approval pathway for generic drugs that are to be marketed and sold in the United States. The *abbreviated* in *abbreviated NDA* refers to the fact that these applications generally do not require animal studies or clinical data to show safety and efficacy. A generic drug must be comparable to an RLD in characteristics, dosage form, formulation, intended use, quality, route of administration, and strength. The application must show bioequivalence to the RLD that is being used as the comparison.

NDAS, ANDAS, AND PET DRUGS

The decision on whether to file an NDA or ANDA for PET drugs depends on the drug product being made and its formulation. An NDA must be filed for a new molecular entity or to add an indication that is not already FDA-approved (*15*). For example, ^{18}F-FDG is currently not FDA-approved for the evaluation of dementia or infection imaging. When the drug product is already on the market, the ability to file an ANDA rests on whether the formulation is comparable to an RLD. Current RLDs can be found in the FDA Orange Book (*16*). Another example requiring an NDA is the final product formulation. 21 CFR 314.94(a)(9)(iii) states that for ANDA applications there must be equivalence of inactive ingredients with the RLD. The only exceptions to this requirement are for preservatives, buffers, and antioxidants. There can be different final product formulations of the same PET drug product due to various differences in the automatic synthesis modules, their reagents, and processes such as the presence of sodium chloride, which may affect the ability to achieve inactive ingredient equivalence. A suitability petition (i.e., waiver request) may be filed if there is a difference in strength from the RLD, but it must be approved before the ANDA is submitted and current review times can be between 60 and 120 d.

When an RLD is chosen for an ANDA application, care must be taken to ensure that the drug meets the RLD formulation. If not, an NDA will need to be filed even though it is not for a new molecular entity.

DRUG MASTER FILES

A drug master file (DMF) is a composite of proprietary information about materials used in the preparation of a drug product. It may be a substance, chemical, material component, container/closure, or piece of equipment used in the drug preparation process, and it is submitted by a holder (e.g., manufacturer) of certain subcomponents of the final drug production (e.g., a synthesis module cassette, precursor, or sterile vial). The holder of this material may not wish to provide to an individual all the information required to complete an NDA or ANDA but may allow the DMF to be referenced by an applicant. The applicant receives a letter of access from the holder, who also places a letter of access in the DMF. The letter of access will then be submitted to the FDA as part of the ANDA or NDA and triggers the review of the DMF by the FDA. A DMF may be referenced in multiple NDAs or ANDAs. It is advantageous to use DMFs whenever possible, as it reduces the burden of information to be provided as part of an NDA or ANDA. For example, there may be a DMF for the sterile final product vial that is used in the production of the drug product, which could include information for tests performed on the glass, the stopper, and other components of the vial.

There are several DMF subtypes. Type I DMF contains plant information; type II DMFs refer to drug substances, intermediates, drug products, or supplies used in the preparation of the drug product. Packaging materials are filed as type III DMFs. Additives, including excipients, colorants, flavors, essences, or components or intermediates used in the additive production, fall under type IV DMFs. Type V DMFs are reference information. For example, a type V DMF related to the PET field might include detailed information about a proprietary automated radiotracer synthesis unit.

FACILITY REGISTRATION

To determine whether 21 CFR 212 CGMP applies to PET drug preparation in your facility, you must determine whether FDA-approved PET drugs are being manufactured for use in clinical diagnosis in the same facility's PET imaging suites or if the PET drugs are being offered for sale to another facility for clinical imaging purposes. If either of these conditions exists, the production facility must be registered as a PET drug manufacturer with the FDA. If the facility is producing radiotracers for use in clinical research only under an IND or Radioactive Drug Research Committee application, then the facility does not need to be registered (*17*). Registered facilities must fully comply with part 212 and submit NDAs or ANDAs to cover the approved PET drugs that are manufactured for clinical use.

Registration and listing is required for all drug manufacturing establishments, with subsequent renewal annually (*18,19*). Since June 2009, all registrations for drug establishment and listing have been electronic. Instructions and guidance documentation for the electronic registration and listing system are available on the FDA website (*20,21*). The electronic registration and drug listings are established through the FDA electronic submissions gateway (*22*). Because establishing an electronic gateway may be time-consuming, it is recommended that this process be started as soon as possible. There are commercial companies that will assist with gateway establishment.

POSTDEADLINE NDA OR ANDA FILING

If an NDA or an ANDA was filed before the June 12, 2012, deadline, the FDA accepted the application and, without approving it, allowed the filing organization to continue to prepare, distribute, and market its PET drug products. For organizations that submitted an application after June 12, 2012, the application had to be fully reviewed and a preapproval facility inspection conducted and passed before the PET drug could be used clinically. Applicants may not produce and market that drug for clinical use until the FDA approves the application. Once the application is received, the FDA initiates the review process, which includes both a documentation review and a site inspection. Applicants are presented with a form 483, listing deficiencies, and are given the opportunity to address those issues. Once the process is complete, the applicant receives an establishment inspection report. The final response is a letter from the FDA informing the applicant whether the application has been approved.

USER FEES

Congress has authorized the FDA to collect application, establishment, and product user fees under the PDUFA (*23*). These fees, collected on NDA applications and products, provide the FDA with additional revenue to ensure timely review of NDAs and to conduct preauthorization inspections. Collection of these fees has helped reduce the NDA review time to 6–10 mo. Application fees are paid one time only with the NDA submission. Establishment and product fees are required annually.

In response to the growing FDA queue of unapproved ANDAs for pharmaceuticals, the Generic Pharmaceutical Association lobbied Congress to pass the Generic Drug User Fee Amendments in 2012 (*24*). This legislation amended the Food, Drug, and Cosmetic Act to authorize application, establishment, and product fees for generic drug manufacturers similar to PDUFA for new drug manufacturers. This legislation was working its way through Congress just as the ANDAs were being submitted by the PET manufacturing community. Facilities that are registered solely as PET drug manufacturers (i.e., no non-PET generic drug production) are exempt from the fees authorized in this act.

It is expected that most PET drug applications for ^{18}F-FDG, sodium fluoride, and ammonia will be manufactured under ANDAs that currently do not incur any fees. Submission of an NDA will initiate the collection of user fees. Under PDUFA, fees are adjusted annually and published in the *Federal Register* around August each year. The 2014 application fees are $2,169,100 for an NDA with clinical data and $1,084,550 for supplements with clinical data or applications not requiring clinical data (*24*). The product and establishment fees are $104,060 and $554,600, respectively (*24*). The establishment fee for PET drug producers is one sixth the full fee, or $92,433 (*24*). There is some fee relief for PET drug manufacturers, and fee waivers may be requested in writing. A detailed question-and-answer section is available on the FDA website. (*21*) If the PET drug manufacturer is a one-site nonprofit medical center whose outside distribution does not exceed 5% of the total doses for the given tracer, then the establishment fee is waived. Product fees must still be paid, with no one-site reduction or institutional-use waiver conditions. These fees may be substantial for PET drug products that are not as widely distributed as ^{18}F-FDG.

FDA AUDITS AND INSPECTIONS

PET drug manufacturers are subject to audits by the FDA. These audits fall into 1 of 3 categories: preapproval inspection, routine CGMP (surveillance) inspection, or for-cause (compliance) inspection. The preapproval inspection occurs when there is a new site, new molecular entity, or new sponsor identified within an NDA or ANDA. The objective of a preapproval inspection is to verify and ensure that a facility and its personnel are ready for production of the drug product identified in the NDA or ANDA and that there is adherence to CGMPs. The inspection focuses on conformance with commitments made in the application and the authenticity and accuracy of the data in the application. One should expect that the inspection will include observation of actual productions and practices, qualification of equipment and processes, and review of procedures and records. Receiving a routine CGMP inspection within 2 y of filing an NDA or ANDA may result in the waiving of a preapproval inspection if the routine CGMP inspection goes well. Routine CGMP inspections are performed on a 2-y cycle at sites selected by the Center for Drug Evaluation and Research and the district office. The objective of this type of audit is to verify CGMP compliance. For-cause inspections occur either as a follow-up for deficiencies in previous inspections or when an external complaint is brought to the FDA. In these targeted audits, past deficiencies or complaints are thoroughly examined to determine whether further corrective action is needed or whether the facility is back in compliance with CGMP.

FDA inspections follow a set protocol. They begin with the FDA consumer safety officers displaying their FDA credentials and issuing a written notice of inspection (form FDA 482). The officers then explain the purpose of the inspection and provide a general overview of how it will proceed. They then perform the inspection, during which they may choose to walk the facility; observe operations; review standard operating procedures, batch records, aseptic processing programs, or personnel training files; or interview personnel. The officers may comment on possible deficiencies as they are observed or may choose to present all at the conclusion of the day or at the conclusion of the inspection. The inspection closes with the officers notifying the facility of whether there were any inspectional observations and, if so, listing them on form FDA 483. It is in the best interest of a facility that receives this form to promptly send a letter to the FDA addressing all the observations, describing how they have been or will be corrected, or explaining why the facility disagrees with an observation. If the FDA deems the observations of minor significance or the facility's response positive, it is likely that no further action will occur. If the observations are of major significance, there are many potential ramifications, including a warning letter, recommendation that the application be denied, seizure, injunction, withdrawal of application, or legal prosecution.

ANNUAL REPORTING

For PET, the FDA allowed continued clinical distribution and use once a PET drug NDA or ANDA had been accepted for review, as long as the acceptance was before June 12, 2012. If there are any significant changes to an application, such as replacement of a synthesis module with a different type of synthesis module or the addition of a new facility, the pending application must be amended. In the absence of such changes, an annual report is not required until the application has been approved.

Once a PET drug NDA or ANDA is approved, there are several requirements for postmarketing reports. There is a new FDA publication, *Guidance for Industry: CMC Postapproval Manufacturing Changes to Be Documented in Annual Reports* (*25*). These postapproval manufacturing changes fall into the category of safety and annual changes (chemistry, manufacturing, and controls [CMC], animal safety, clinical). A serious and unexpected adverse event must be reported within 15 d of the firm's becoming aware of the incident. A 3-d field alert report is required for sterility and labeling defects. Quarterly safety update reports are required for 3 y after approval and annually thereafter. The safety reports are described in 21 CFR 314.80, "Postmarketing Reporting of Adverse Drug Experiences" (*26*). The more general annual reports for CMC and clinical information are described in 21 CFR 314.81, "Other Postmarketing Reports" (*27*).

The annual report requirements are limited when there are no significant adverse events and no major CMC changes.

SUMMARY

This brief overview was not intended to detail all the requirements for the preparation of an ANDA, NDA, or IND. The goal was to provide a basic understanding of both the CGMP-for-PET regulations and USP 32 chapter <823> and of what is required to be compliant in clinical practice and research. In conclusion, the regulations have taken effect and they affect all individuals involved in PET imaging. The PET production facility must be registered as a manufacturer with the FDA if the intention is to produce and distribute ^{18}F-FDG, ammonia, or sodium fluoride for use in clinical patient care. When purchasing ^{18}F-FDG, ammonia, or sodium fluoride from a supplier, ensure that the supplier is registered, has submitted an ANDA or NDA, and is in compliance with 21 CFR 212.

Research PET drugs can no longer be prepared under the practice of medicine and pharmacy. USP has removed the monographs for PET drugs that are not FDA-approved, as is consistent with the USP mission. Either an IND or a Radioactive Drug Research Committee application for each research PET drug must now be submitted and approved before these drugs can be used in research applications.

REFERENCES

1. Current good manufacturing practice for positron emission tomography drugs. *Fed Regist.* 2009;74:65409. To be codified at 21 CFR §210, 211, and 212.
2. Current good manufacturing practice for positron emission tomography drugs: preliminary draft proposed rule. *Fed Regist.* 1995;60:10594.
3. Food and Drug Modernization Act of 1997. U.S. Food and Drug Administration website. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm. Updated October 22, 2009. Accessed May 8, 2014.
4. Positron emission tomography drug products; safety and effectiveness of certain PET drugs for specific indications. *Fed Regist.* 2000;65:12999–13010.
5. Guidance on current good manufacturing practice for positron emission tomography drugs; availability. *Fed Regist.* 2009;74:65538.
6. *Guidance: PET Drugs—Current Good Manufacturing Practice (CGMP).* Silver Spring, MD: Food and Drug Administration; 2009.
7. NDA 21-768: FDG F 18 injection. U.S. Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21768lbl.pdf. Accessed May 8, 2014.
8. NDA 21-870: FDG F 18 injection. U.S. Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021870lbl.pdf. Accessed May 8, 2014.

9. Drug approval package: Ammonia N 13 injection. U.S. Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/22119s000TOC.cfm. Published October 2, 2007. Accessed May 8, 2014.
10. Cancer tracer synthesis resources. National Cancer Institute website. http://imaging.cancer.gov/programsandresources/Cancer-Tracer-Synthesis-Resources. Accessed May 8, 2014.
11. Positron emission tomography (PET): questions and answers about CGMP regulations for PET drugs. U.S. Food and Drug Administration website. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm193476.htm#PETDRUGSANDUSERFEES. Published December 9, 2009. Updated February 18, 2011. Accessed May 8, 2014.
12. *2011 USP 34 NF 29.* Rockville, MD: U.S. Pharmacopeial Convention; 2011.
13. Radioactive Drug Research Committee (RDRC) program. U.S. Food and Drug Administration website. http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Oncology/ucm093322.htm. Updated on August 29, 2013. Accessed May 8, 2014.
14. Investigational new drug (IND) application. U.S. Food and Drug Administration website. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm. Updated on October 18, 2013. Accessed May 8, 2014.
15. *Guidance: PET Drug Applications—Content and Format for NDAs and ANDAs.* Silver Spring, MD: Food and Drug Administration; 2011.
16. Orange book: approved drug products with therapeutic equivalence evaluations. U.S. Food and Drug Administration website. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Updated May 17, 2013. Accessed May 8, 2014.
17. Positron emission tomography (PET): additional questions and answers based on December 9, 2009 stakeholder call [response to question 7]. U.S. Food and Drug Administration website. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm207021.htm. April 8, 2010. Accessed May 8, 2014.
18. 21 CFR 207: registration of producers of drugs and listing of drugs in commercial distribution. 207.21(a); 21 CFR 207.3(a)(8). Food and Drug Administration website. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=207. Accessed June 4, 2014.
19. Drug registration and listing system (DRLS & eDRLS). U.S. Food and Drug Administration website. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm. Updated December 2, 2013. Accessed May 8, 2014.
20. Electronic drug registration and listing instructions. U.S. Food and Drug Administration website. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm. Updated March 17, 2014. Accessed May 8, 2014.
21. *Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing*. Rockville, MD: Food and Drug Administration; 2009.
22. Electronic submissions gateway. U.S. Food and Drug Administration website. http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Updated April 25, 2014. Accessed May 9, 2014.
23. Prescription Drug User Fee Act (PDUFA). U.S. Food and Drug Administration website. http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/default.htm. Updated May 6, 2014. Accessed May 9, 2014.
24. Generic drug user fee amendments of 2012. U.S. Food and Drug Administration website. http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm. Updated May 9, 2014. Accessed May 9, 2014.
25. *Guidance for Industry: CMC Postapproval Manufacturing Changes to Be Documented in Annual Reports.* Silver Spring, MD: Food and Drug Administration; 2014.
26. 21 CFR 314.80: postmarketing reporting of adverse drug experiences. Food and Drug Administration website. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.80. Updated June 1, 2013. Accessed May 9, 2014.
27. 21 CFR 314.81: other postmarketing reports. Food and Drug Administration website. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.81. Updated June 1, 2013. Accessed May 9, 2014.