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4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-0242]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Current Good Manufacturing Practice for Positron Emission Tomography Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or emailed to oira_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-0667. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Ila S. Mizrachi, Office of Information Management, Food and Drug Administration, 1350 Piccard Dr., PI50-400B, Rockville, MD 20850, 301-796-7726, Ila.Mizrachi@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Current Good Manufacturing Practice for Positron Emission Tomography Drugs--(OMB Control Number 0910-0667)--Extension

Positron emission tomography (PET) is a medical imaging modality involving the use of a unique type of radiopharmaceutical drug product. FDA's current good manufacturing practice (CGMP) regulations at 21 CFR part 212 are intended to ensure that PET drug products meet the requirements of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) regarding safety, identity, strength, quality, and purity. The CGMP requirements for PET drugs are issued under the provisions of the Food and Drug Administration Modernization Act (FDAMA). These CGMP requirements are designed to take into account the unique characteristics of PET drugs, including their short half-lives and the fact that most PET drugs are produced at locations that are very close to the patients to whom the drugs are administered.

The CGMP regulations are intended to ensure that approved PET drugs meet the requirements of the FD&C Act as to safety, identity, strength, quality, and purity. The regulations address the following matters: Personnel and resources; quality assurance; facilities and equipment; control of components, in-process materials, and finished products; production and process controls; laboratory controls; acceptance criteria; labeling and packaging controls; distribution controls; complaint handling; and recordkeeping.

The CGMP regulations establish several recordkeeping requirements and a third-party disclosure requirement for the production of PET drugs. In making our estimates of the time spent in complying with these information collection requirements, we relied on communications we have had with PET producers, visits by our staff to PET facilities, and our

familiarity with both PET and general pharmaceutical manufacturing practices. The estimated annual recordkeeping and third-party disclosure burden is based on there being approximately 129 PET drug production facilities. Table 1 provides an estimate of the annual recordkeeping burdens. Table 2 provides an estimate of the annual third-party disclosure burdens associated with this collection.

A. Investigational and Research PET Drugs

Section 212.5(b) provides that for investigational PET drugs produced under an investigational new drug (IND) and research PET drugs produced with approval of a Radioactive Drug Research Committee (RDRC), the requirement under the FD&C Act to follow current good manufacturing practice is met by complying with the regulations in part 212 or with United States Pharmacopoeia (USP) 32 Chapter 823. We believe that PET production facilities producing drugs under INDs and RDRCs are currently substantially complying with the recordkeeping requirements of USP 32 Chapter 823 (see section 121(b) of FDAMA), and accordingly, we do not estimate any recordkeeping burden for this provision.

B. Batch Production and Control Records

Sections 212.20(c) through (e), 212.50(a) through (c), and 212.80(c) set forth requirements for batch and production records as well as written control records. We estimate that it would take approximately 20 hours annually for each PET production facility to prepare and maintain written production and control procedures and to create and maintain master batch records for each PET drug produced. We also estimate that there will be a total of approximately 221 PET drugs produced, with a total recordkeeping burden of approximately 4,420 hours. We estimate that it would take a PET production facility an average of 1 hour to complete a batch

record for each of approximately 501 batches. Our estimated burden for completing batch records is approximately 64,629 hours.

C. Equipment and Facilities Records

Sections 212.20(c), 212.30(b), 212.50(d), and 212.60(f) contain requirements for records dealing with equipment and physical facilities. We estimate that it would take approximately 1 hour to establish and maintain these records for each piece of equipment in each PET production facility. We estimate that the total burden for establishing procedures for these records would be approximately 1,935 hours. We estimate that recording maintenance and cleaning information would take approximately 5 minutes a day for each piece of equipment, with a total recordkeeping burden of approximately 40,237 hours.

D. Records of Components, Containers, and Closures

Sections 212.20(c) and 212.40(a), (b), and (e) contain requirements on records regarding receiving and testing of components, containers, and closures. We estimate that the annual burden for establishing these records would be approximately 259 hours. We estimate that each facility would receive approximately 36 shipments annually and would spend approximately 30 minutes per shipment entering records. The annual burden for maintaining these records would be approximately 2,322 hours.

E. Process Verification

Section 212.50(f)(2) requires that any process verification activities and results be recorded. Because process verification is only required when results of the production of an entire batch are not fully verified through finished-product testing, we believe that process verification will be a very rare occurrence, and we do not estimate any recordkeeping burden for documenting process verification.

F. Laboratory Testing Records

Sections 212.20(c), 212.60(a), (b), and (g), 212.61(a) and (b), and 212.70(a), (b), and (d) set out requirements for documenting laboratory testing and specifications referred to in laboratory testing, including final release testing and stability testing. Each PET drug production facility will need to establish procedures and create forms for the different tests for each product they produce. We estimate that it will take each facility an average of 1 hour to establish procedures and create forms for one test. The estimated annual burden for establishing procedures and creating forms for these records is approximately 3,225 hours, and the annual burden for recording laboratory test results is approximately 10,728 hours.

G. Sterility Test Failure Notices

Section 212.70(e) requires PET drug producers to notify all receiving facilities if a batch fails sterility tests. We believe that sterility test failures might occur in only 0.05 percent of the batches of PET drugs produced each year. Therefore, we have estimated in Table 2 that each PET drug producer will need to provide approximately 0.25 sterility test failure notice per year to receiving facilities. The notice would be provided using email or facsimile transmission and should take no more than 1 hour.

H. Conditional Final Releases

Section 212.70(f) requires PET drug producers to document any conditional final releases of a product. We believe that conditional final releases will be fairly uncommon, but for purposes of the Paperwork Reduction Act (PRA), we estimated that each PET production facility would have one conditional final release a year and would spend approximately 1 hour documenting the release and notifying receiving facilities. The estimate of one conditional final

release per year per facility is an appropriate average number because many facilities may have no conditional final releases while others might have only a few.

I. Out-of-Specification Investigations

Sections 212.20(c) and 212.71(a) and (b) require PET drug producers to establish procedures for investigating products that do not conform to specifications and conduct these investigations as needed. We estimate that it will take approximately 1 hour annually to record and update these procedures for each PET production facility. We also estimate, for purposes of the PRA, that 36 out-of-specification investigations would be conducted at each facility each year and that it would take approximately 1 hour to document the investigation, which results in an annual burden of 4,644 hours.

J. Reprocessing Procedures

Sections 212.20(c) and 212.71(d) require PET drug producers to establish and document procedures for reprocessing PET drugs. We estimate that it will take approximately 1 hour a year to document these procedures for each PET production facility. We do not estimate a separate burden for recording the actual reprocessing, both because we believe it would be an uncommon event and because the recordkeeping burden has been included in our estimate for batch production and control records.

K. Distribution Records

Sections 212.20(c) and 212.90(a) require that written procedures regarding distribution of PET drug products be established and maintained. We estimate that it will take approximately 1 hour annually to establish and maintain records of these procedures for each PET production facility. Section 212.90(b) requires that distribution records be maintained. We estimate that it

will take approximately 15 minutes to create an actual distribution record for each batch of PET drug products, with a total burden of approximately 16,157 hours for all PET producers.

L. Complaints

Sections 212.20(c) and 212.100 require that PET drug producers establish written procedures for dealing with complaints, as well as document how each complaint is handled. We estimate that establishing and maintaining written procedures for complaints will take approximately 1 hour annually for each PET production facility and that each facility will receive approximately one complaint a year and will spend approximately 30 minutes recording how the complaint was dealt with.

In the Federal Register of March 20, 2013 (78 FR 17215), FDA published a 60 day notice requesting public comment on the proposed collection of information. We received 2 comments, each raising several issues.

(Comment 1) One comment said that the two tables in the Federal Register notice were unclear because only the part 212 section was cited and not the records pertaining to that section.

(Response) FDA appreciates the comment and we have revised the tables accordingly.

(Comment 2) One comment said that the collection of information will not have any practical utility unless the reason for the proposed collection is to provide better FDA understanding of the PET drug production industry, to facilitate upcoming inspections, and to work with PET facilities in meeting areas of compliance under part 212. Another comment said that FDA has not adequately explained the purpose of these regulations.

(Response) FDA's CGMP regulations in part 212 are useful and necessary because they help ensure that PET drug products meet the requirements of the FD&C Act regarding safety,

identity, strength, quality, and purity. The requirements are specifically designed to take into account the unique characteristics of PET FDA drugs, including their short half-lives and the fact that most PET drugs are produced at locations that are very close to the patients to whom the drugs are administered. As mentioned by the comment, the collection of information also provides FDA with a better understanding of the PET production industry.

(Comment 3) One comment said that the number of PET drug production facilities estimated by FDA is not reflective of the current number of registered PET production facilities operating in the United States, and that the burden estimates are based on 129 PET drug production facilities surveyed. The comment said that the actual number of PET producers is over 150. The comment said that FDA did not divide the PET drug production facilities into commercial sites and academic sites, and questioned whether the data are a fair representation of both. The comment also said that commercial facilities are able to hire a team of personnel dedicated to regulatory compliance, whereas the individual sites, like the academic labs, must perform the same functions with a much smaller staff. The comment said that FDA's burden estimates for academic labs are too low and unrealistic.

(Response) The 129 PET drug production facilities are based on facilities listed in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) submitted to FDA. These 129 sites are producing PET drugs and are seeking approval from FDA for commercial distribution for clinical use (not for investigational or research use). It is unclear from the comment if the 150 sites include sites producing PET drugs for investigational use. FDA requests that the commenter provide any updated data on the number of PET drug sites. In addition, FDA believes it is fair to make a general estimate across academic and commercial

sites because the number of academic sites that apply for drug applications is a relatively small percentage.

(Comment 4) One comment said that the burden hour estimates are not accurate because each facility will compile their records differently and will use either a paper-based method or an electronic method. The comment said that FDA did not specify how many PET drug facilities are using paper-based records compared with electronic-based records, and that the burden hours for those using paper-based records would be higher than those using electronic recordkeeping. The comment said that the burden hour estimate is not a fair representation of the time needed for all PET facilities to comply with the recordkeeping requirements.

(Response) All commercial PET drug manufacturers are currently utilizing electronic records for recordkeeping as well as paper-based records. Commercial PET drug manufacturers comprise approximately 90 percent of the manufacturing sites. Many academic PET facilities still choose to use paper-based records. However, academic PET sites produce fewer batches for clinical use compared to commercial sites, and have fewer records. Sufficient resources and personnel are needed to perform the PET drug production activities, and we do not agree that academic PET drug sites limited in personnel and resources bear more of the regulatory burden. After a firm's recordkeeping process is established, the burdens are generally the same for entering records into an electronic system or a paper-based system. In addition, we question whether it is worthwhile to prepare separate estimates for commercial versus academic sites because academic sites are a small percentage of the total.

(Comment 5) One comment said that the estimate of 30 minutes per batch production and control record should be increased to 90 minutes because of the following responsibilities: Recording the identification number, tracking number, and lot number of each equipment item,

component, or reagent utilized in the production of the PET drug; reviewing and recording daily sterility data for 14 days after release and inoculation; and quality assurance review of all batch record entries.

(Response) FDA agrees that some of the responsibilities may take additional time, and we have increased the burden estimate to 1 hour.

(Comment 6) One comment said that the recordkeeping estimate of 10 minutes for components, containers, and closures should be increased to 60 minutes because of the following responsibilities: To document the receipt, quarantine, and release of each component at separate and distinctly timed intervals; to recover certificates of analysis; contacting vendors; requesting documents; receiving and printing documents and maintaining files for documents; and acceptance, which requires performing and recording lab results. For media, this includes completing packaging and shipping documents for offsite testing as well as specifying testing parameters to the contract lab.

(Response) To log in each incoming component may take 10 minutes, but the time needed to perform all procedures as described by the commenter, including verifying that the component meets the firm's internal specifications, will take longer. Therefore, we have we have increased the burden estimate to 30 minutes.

(Comment 7) One comment said that the estimate of 36 out-of-specification investigations per year should be increased to 120 investigations because FDA requires an investigation of not only those that are most serious but also every incident involving an unexpected result.

(Response) FDA disagrees that 36 out-of-specification investigations per year are too low based on the information from our field alert reporting system. Out-of-specification

investigations pertain to those products not meeting one or more of its release specifications. On the other hand, certain deviations in manufacturing also warrant investigations in order to prevent future recurrence. It is unlikely that a firm could have 120 total investigations per facility.

(Comment 8) One comment said that the use of automated collection techniques and other forms of information technology increase costs to producers: Software solutions with necessary validation costs could cost $100,000; support and maintenance could cost $20,000 per year; and applications training and implementing the electronic methods require several months of effort.

(Response) There will be initial costs to establish an electronic recordkeeping system, but once the system is set up, the annual costs will be minimal. FDA requires electronic records (i.e., batch records and analytical test records) to comply with the basic electronic records requirements at 21 CFR part 11, namely, record security and an audit trail. Those sites that are under corporate management can apply their electronic recordkeeping system to all sites within the same corporation.

(Comment 9) One comment asked to see the list of questions from the survey that was used to determine the time spent to comply with the recordkeeping requirements.

(Response) In making our estimates of the time spent in complying with these information collection requirements, we relied on communications we have had with PET producers, visits by our staff to PET facilities, and our familiarity with both PET and general pharmaceutical manufacturing practices. There was no formal survey to industry.

(Comment 10) One comment suggested that FDA establish an "on-line database" requiring a username and password for access to minimize the burden of the collection of information on respondents.

(Response) FDA believes the information collection burden is reasonable at this time, and we have no plans to implement an online database.

Table 1.--Estimated Annual Recordkeeping Burden[1]

21 CFR Section	Number of Recordkeepers	Number of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper	Total Hours
Batch Production and Control Records 212.20(c) and (e); 212.50(a) and (b)	129	1.71	221	20	4,420
Batch Production and Control Records 212.20(d) and (e); 212.50(c); 212.80(c)	129	501	64,629	1	64,629
Equipment and Facilities Records 212.20(c); 212.30(b); 212.50(d); 212.60(f)	129	15	1,935	1	1,935
Equipment and Facilities Records 212.30(b); 212.50(d); 212.60(f)	129	3,758	484,782	.08 (5 minutes)	40,237
Records of Components, Containers, and Closures 212.20(c); 212.40(a) and (b)	129	2	258	1	258
Records of Components, Containers, and Closures 212.40(e)	129	36	4,644	.5 (30 minutes)	2,322
Laboratory Testing Records 212.20(c); 212.60(a) and (b); 212.61(a); 212.70(a), (b), and (d)	129	25	3,225	1	3,225
Laboratory Testing Records 212.60(g); 212.61(b); 212.70(d)(2) and (d)(3)	129	501	64,629	.16 (10 min.)	10,728
Conditional Final Releases 212.70(f)	129	1	129	1	129
Out-of-Specification Investigations 212.20(c); 212.71(a)	129	36	4,644	1	4,644
Out-of-Specification Investigations 212.71(b)	129	1	129	1	129
Reprocessing Procedures 212.20(c); 212.71(d)	129	1	129	1	129
Distribution Records 212.20(c); 212.90(a)	129	1	129	1	129
Distribution Records 212.90(b)	129	501	64,629	.25 (15 min.)	16,157
Complaints 212.20(c); 212.100(a)	129	1	129	1	129
Complaints 212.100(b) and (c)	129	1	129	.5 (30 min.)	65
Total					149,266

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Third-Party Disclosure Burden[1]

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
Sterility Test Failure Notices 212.70(e)	129	.25	32	1	32

[1] There are no capital costs or operating and maintenance costs associated with this information collection.

Dated: July 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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