4164-01-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 and title "Current Good Manufacturing Practice for Positron Emission Tomography Drugs." Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: FDA PRA Staff, Office of Operations, Food and Drug Administration, Three White Flint North 10A63, 11601 Landsdown St., North Bethesda, MD 20852, PRAStaff@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 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 positron emission tomography (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 of 1997 (the Modernization Act). 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 informal 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.

In the Federal Register of December 29, 2015 (80 FR 81332), FDA published a 60-day notice requesting public comment on the proposed collection of information and the estimated annual burden for recordkeeping and third party disclosure. In response to the notice, FDA received several comments. The comments raised a number of issues that are discussed as follows.

(Comment 1) The comment disagreed with FDA's estimate that 129 PET drug production facilities are required to comply with part 212. Based on its records, the comment said that approximately 150 facilities are subject to the PET CGMP requirements.

(Response) We have revised the burden estimates to account for 150 PET drug production facilities.

(Comment 2) The comment disagreed with FDA's statement in section I of the December 29, 2015, Federal Register notice, "Investigational and Research PET Drugs." The comment said that PET facilities devote resources to comply with USP 32 Chapter 823, and that FDA should estimate the recordkeeping burden under USP 32 Chapter 823.

(Response) FDA agrees with the comment that facilities incur a burden to comply with USP 32 Chapter 823. However, compliance with USP provisions is beyond the scope of this information collection, which only pertains to the requirements under part 212.

(Comment 3) The comment said FDA "averages" the burden across different categories of respondents and responses, and that this approach results in lower burden estimates. For example, the comment said that most recordkeeping will continue to be with a paper-based system and not an electronic system, and that the costs are different for each system. In addition, there are differences between the costs incurred by commercial and academic facilities.

(Response) All commercial PET drug facilities 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 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 academic PET drug sites limited in personnel and resources do 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. 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. Also, providing an average estimate is consistent with PRA requirements and, based on our calculations, the number of academic sites that apply for drug applications represents a small percentage.

(Comment 4) The comment questioned FDA's methodology for determining the burden estimates, especially in table 2 where the actual burden may be underestimated "by a factor of 10 to 100."

(Response) In estimating the time to comply with these information collection requirements, we relied on informal communications we have had with PET producers, visits by

our staff to PET facilities, our familiarity with both PET and general pharmaceutical manufacturing practices, and the different facilities listed in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) submitted to FDA for PET drugs. FDA is willing to consider any specific estimates to replace the data we used in the tables, just as we did for the 150 facilities submitted by the comment. However, other than the 150 facilities, the comment has submitted no other specific estimates upon which we could base alternative estimates.

(Comment 5) The comment said more time is needed to prepare its analysis of FDA's information collection burden for part 212. The comment also offered to work with FDA in the future to develop estimates that more fairly reflect the burden to comply with these regulations.

(Response) As required under the Paperwork Reduction Act (PRA), FDA provided 60 days for respondents to submit comment in response to the December 29, 2015, notice. Upon submission to OMB, respondents are afforded 30 additional days to submit comments. Finally, because FDA must seek OMB approval for any information collection at least every three years, respondents are invited to submit comments accordingly. FDA considers all comments it receives and continually seeks ways to improve its burden estimates as well as the efficiency of its information collection activities, including suggestions from PET drug producers and facilities in estimating the burden of the information collection in part 212. Any specific estimates submitted by PET drug producers and facilities subsequent to the comment period provided for under the PRA will be reviewed and considered by FDA for future renewals of this information collection.

We estimate the burden of this collection of information as follows:

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

Activity; 21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper	Total Hours[2]
Batch Production and Control Records--212.20(c); 212.20(e); 212.50(a); 212.50(b)	150	1.71	256.5	20	5,130
Batch Production and Control Records--212.20(d) and (e); 212.50(c); 212.80(c)	150	501	75,150	0.50 (30 mins.)	37,575
Equipment and Facilities Records--212.20(c); 212.30(b); 212.50(d); 212.60(f)	150	15	2,250	1	2,250
Equipment and Facilities Records--212.30(b); 212.50(d); 212.60(f)	150	3,758	563,700	0.08 (5 mins.)	45,096
Records of Components, Containers, and Closures--212.20(c); 212.40(a); 212.40(b)	150	2	300	1	300
Records of Components, Containers, and Closures--212.40(e)	150	36	5,400	0.17 (10 mins.)	918
Laboratory Testing Records--212.20(c); 212.60(a); 212.60(b); 212.61(a); 212.70(a); 212.70(b); 212.70(d)	150	25	3,750	1	3,750
Laboratory Testing Records--212.60(g); 212.61(b); 212.70(d)(2); 212.70(d)(3)	150	501	75,150	0.17 (10 mins.)	12,776
Conditional Final Releases--212.70(f)	150	1	150	1	150
Out-of-Specification Investigations--212.20(c); 212.71(a); 212.71(b)	150	36	5,400	1	5,400
Reprocessing Procedures--212.20(c); 212.71(d)	150	1	150	1	150
Distribution Records--212.20(c); 212.90(a); 212.90(b)	150	501	75,150	0.25 (15 mins.)	18,788
Complaints--212.20(c); 212.100(a)	150	1	150	1	150
Complaints--212.100(b); 212.100(c)	150	1	150	0.50 (30 mins.)	75
Total					132,508

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] Number rounded to the nearest whole number.

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

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Avg. Burden per Disclosure	Total Hours[2]
Sterility Test Failure Notices--212.70(e)	150	.25	37.5	1	38

[1] There are no capital costs or operating and maintenance costs associated with this information collection.
[2] Number rounded to the nearest whole number.

I. Investigational and Research PET Drugs

Section 212.5(b)(2) 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 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 the Modernization Act), and accordingly, we do not estimate any recordkeeping burden for this provision.

II. 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 256.5 PET drugs produced, with a total recordkeeping burden of approximately 5,130 hours. We estimate that it would take a PET production facility an average of 30 minutes to complete a batch record for each of approximately 501 batches. Our estimated burden for completing batch records is approximately 37,575 hours.

III. 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 2,250 hours. We estimate that recording maintenance and cleaning information would take approximately 5 minutes a day for each piece of equipment, for a total recordkeeping burden of approximately 45,096 hours.

IV. 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 300 hours. We estimate that each facility would receive approximately 36 shipments annually and would spend approximately 10 minutes per shipment entering records. The annual burden for maintaining these records would be approximately 918 hours.

V. 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.

VI. 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 3,750 hours, and the associated annual burden for recording laboratory test results is approximately 12,776 hours.

VII. 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 notices per year to receiving facilities. The notice would be provided using email or fax transmission and should take no more than 1 hour.

VIII. 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 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.

IX. 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 5,400 hours.

X. 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.

XI. 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 hours for all PET producers.

XII. 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 addressed.

Dated: July 5, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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