Current Good Manufacturing Practice for
Positron Emission Tomography (PET) Drugs

OMB Control No. 0910-0667

SUPPORTING STATEMENT Part A

A. Justification

1. Circumstances Making the Collection of Information Necessary

This information collection is intended to ensure that Positron Emission Tomography (PET) drug products meet the requirements of the Federal Food, Drug, and Cosmetic Act (the act) regarding safety, identity, strength, quality, and purity. Positron emission tomography is a medical imaging modality involving the use of a unique type of radiopharmaceutical drug product. The majority of PET drug products are injected intravenously into patients for diagnostic purposes. Most PET drugs are produced using cyclotrons and other production equipment at locations that are close to the patients to whom the drugs are administered (for example, in hospitals or academic institutions). Due to their short half-lives, PET drugs usually are administered to patients within a few minutes or hours of production.

Under section 501(a)(2)(B) of the act, a drug is adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with Current Good Manufacturing Practice (CGMP) regulations to ensure that such drug meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. FDA has the authority under section 701(a) of the act to issue regulations for the efficient enforcement of the act regarding CGMP procedures for manufacturing, processing, and holding drugs and drug products. Our CGMP requirements for non-PET drug products are set forth in 21 CFR parts 210 and 211. The CGMP regulations help ensure that drug products meet the statutory requirements for safety and have their purported or represented identity, strength, quality, and purity characteristics. The recordkeeping requirements in the CGMP regulations provide FDA with the necessary information to perform its duty to protect public health and safety. CGMP requirements establish accountability in the manufacturing and processing of drug products, provide for meaningful FDA inspections, and enable manufacturers to improve the quality of drug products over time. The CGMP recordkeeping requirements also serve preventive and remedial purposes and provide crucial information if it is necessary to recall a drug product.

2. Purpose and Use of the Information Collection

Respondents to the collection are manufacturers of PET drugs. The information collection is used to ensure compliance with CGMP regulatory requirements applicable to PET drugs including: Batch Production and Control Records; Equipment and Facilities Records; Records

of Components, Containers, and Closures; Process Verification; Laboratory Testing Records; Sterility Test Failure Notices; Conditional Final Releases; Out-of-Specification Investigations; Reprocessing Procedures; Distribution Records; and Complaints.

3. Use of Improved Information Technology and Burden Reduction

Generally, recordkeeping required by CGMP regulations are developed and maintained by the respondents. Because the CGMP regulations provide great latitude on how these requirements are to be implemented, manufacturers may establish their own methods of recordkeeping. FDA accepts any recordkeeping method which meets the objectives of 21 CFR parts 210, 211, and 212. For example, drug manufacturing establishments may use automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, to comply with these recordkeeping requirements.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of any other information collection which may be duplicative.

5. Impact on Small Businesses or Other Small Entities

While the information collection applies to small and large businesses alike, FDA provides small business and industry assistance to respondents on its website and through its Center for Drug Evaluation and Research (CDER).

6. Consequences of Collecting the Information Less Frequently

FDA believes that the information collection schedule is consistent with its statutory mandate to ensure compliance with CGMP regulations applicable to PET drugs.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

There are no special circumstances associated with this collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

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. Two comments were received in response to the notice, considered by the agency, and are discussed in the Federal Register of July 11, 2016 (81 FR 44876). In response to specific comment regarding the number of production facilities, the agency increased its estimated number of respondents from 129 to 150 as discussed more fully under Number 12a. below.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift is provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

Certain data and information collected during an inspection of a drug manufacturing establishment for the purpose of enforcing compliance with the CGMP regulations are considered confidential and not releasable to the public. Confidentiality is maintained for trade secret or confidential, commercial, or financial information under 21 CFR 20.61 and investigatory records under 21 CFR 20.64. In addition, certain sections of 21 CFR 314.430 provide confidentiality of information contained in NDAs and ANDAs.

11. Justification for Sensitive Questions

This information collection does not involve questions that are of a personally sensitive nature.

12. Estimates of Annualized Hour Burden and Costs

12a. Annualized Hour Burden Estimate

We estimate the annual 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	Avg. 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	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	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	918

Activity; 21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Avg. Burden per Recordkeeper	Total Hours[2]
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	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	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	75
TOTAL			807,106.5		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.

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 21 CFR 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.

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.

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.

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.

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.

Laboratory Testing Records

Sections 212.20(c), 212.60(a), (b), and (g), 212.61(a) through (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.

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 e-mail or facsimile transmission and should take no more than 1 hour.

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.

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.

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.

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.

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.

12b. Annualized Cost Burden Estimates

We estimate the annual cost of this information collection as follows:

Table 3 – Estimated Annual Recordkeeping Costs

	Number of Establishments	Labor (Months)	Wage (Year Salary)[1]	Cost[2]
RECORDS DAILY IMPLEMENTATION, AUDITS, UPDATES:				
Academic PET Producers	28	2.25	$164,300	$554,512.23
Commercial PET Producers	122	1.0	$164,300	$1,519,774.26
TRAINING:				
Academic PET Producers	28	.11	$164,300	$27,109.49
Commercial PET Producers	122	.11	$164,300	$167,175.17
TOTAL				$194,284.66

13. Estimates of Other Total Annual Cost Burden to Respondents and Recordkeepers

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

FDA costs for this information collection consists of periodic inspections of PET drug production facilities. We estimate that there are approximately 60 inspections annually at 40 hours per inspection, resulting in 5 FTEs X $145,000/FTE = $725,000 annual cost to FDA.

15. Explanation for Program Changes or Adjustments

While we have itemized individual burden by information collection provision in our Federal Register notices and will continue to do so in the future, we have revised the list that will publish on www.reginfo.gov. Specifically we have consolidated the 16 individual recordkeeping ICs into one IC, but we have retained the single 3rd Party Disclosure IC. We have also adjusted the number of respondents based on public comment from 129 to 150. This has resulted in an overall increase to the collection of **112,743** responses. At the same time, we have reduced the time burden per response for *Batch Production and Control Records* under 21 CFR Parts 212.20(d) and (e), 212.50(c), and 212.80(c) from one hour to one-half hour, which has resulted in an overall decrease in burden hours by **14,910**.

16. Plans for Tabulation and Publication and Project Time Schedule

Information collected under this requirement will not be tabulated or published.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

Display of OMB Expiration would be appropriate.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.