UNITED STATES FOOD AND DRUG ADMINISTRATION

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

OMB Control No. 0910-0667

SUPPORTING STATEMENT

Part A. Justification

1. Circumstances Making the Collection of Information Necessary

This information collection supports Food and Drug Administration (FDA, us or we) regulations pertaining to the Current Good Manufacturing Practice (CGMP) for Positron Emission Tomography (PET) drugs. PET is a medical imaging modality involving the use of a unique type of radiopharmaceutical drug product. Our CGMP regulations codified in part 212 (21 CFR part 212) are intended to ensure that PET drugs meet the requirements of the Federal, Food, Drug, and Cosmetic Act (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 (FDAMA) (Pub. L. 105-115). These CGMP requirements are designed according to the unique characteristics of PET drugs, including their short half-lives, and the fact that most PET drugs are produced at locations close to the patients to whom the drugs are to be administered. The CGMP regulations require the establishment of written procedures as well as recordkeeping related to ongoing manufacturing of individual PET drugs, testing, and product release activities, including any third-party disclosure requirements for producing PET drugs. To estimate the amount of time that respondents have spent complying with the requirements, we relied on informal communications with PET producers, FDA staff visits to PET facilities, our experience with PET drug applications, including amendment and supplemental submissions, our general knowledge of pharmaceutical manufacturing practices, and various CGMP compliance reports FDA received from 2019 through 2021.

We therefore request extension of OMB approval for the information collection provisions found in part 212 of our regulations (21 CFR 212) and discussed in this supporting statement.

2. Purpose and Use of the Information Collection

Respondents to the information collection are producers of PET drugs. We use the information to ensure compliance with CGMP regulatory requirements applicable to PET drugs, including: personnel and resources; quality assurance (QA); equipment and facilities; control of components; in-process materials and finished products; production and process controls; laboratory controls; and acceptance criteria.

3. Use of Improved Information Technology and Burden Reduction

While the regulations cover record availability, quality, and retention, they do not prescribe a specific means of recordkeeping other than that records be reasonably accessible to FDA upon inspection. Because electronic submissions are the standard means of submitting information to

FDA, however, we estimate the vast majority of respondents will use electronic means to fulfill the recordkeeping requirements. FDA accepts any recordkeeping method that complies with the applicable requirements.

We have issued guidance documents to assistant respondents to the information collection. All guidance documents are issued in accordance with GGP regulations under 21 CFR 10.115 and provide opportunity for comment at any time. All guidance documents including those regarding PET drugs are available from our website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection. Information collection is required in accordance with statutory provisions that are exclusively the responsibility of FDA pertaining to the manufacture and distribution of PET drugs, and pursuant to 21 CFR 212.

5. Impact on Small Businesses or Other Small Entities

Although the information collection applies to small and large businesses alike, we provide resources, including small business and industry assistance, to respondents to our website at https://www.fda.gov/industry/small-business-assistance and through staff within our Center for Drug Evaluation and Research (CDER). No undue burden is posed on small entities as a result of the information collection.

6. Consequences of Collecting the Information Less Frequently

The information collection schedule is consistent with statutory and regulatory requirements associated with CGMP regulations applicable to PET drugs.

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

There are no special circumstances for 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 April 7, 2022 (87 FR 20420), we published a 60-day notice requesting public comment on the proposed collection of information. Five comments were received and are summarized here.

The comments did not question the necessity of this proposed collection with two of the comments specifically stating that they support the collection of information as it is necessary for the performance of FDA's functions. However, the comments questioned the FDA's burden collection estimates.

FDA believes that this proposed collection is necessary in keeping with the Agency's mission of ensuring the safety and efficacy of human drugs. Regarding the estimates included, FDA has taken a generalized approach for these estimates, assuming that corporate firms will take on certain burdens for all facilities under their purview, rather than calculating all burdens per facility, and understanding that due to variation among facilities the number of batches and products being produced will vary. We have also only included estimates for tasks that are included within part 212 and note that three comments referenced tasks, such as Annual Product Review, that are

outside the scope. We also note that there are no new information collections or revisions to these existing information collections since 2019. We will continue to update the burden estimate as circumstances warrant.

9. Explanation of Any Payment or Gift to Respondents

There are no incentives, payments or gifts associated with this information collection.

10. Assurance of Confidentiality Provided to Respondents

In preparing this Supporting Statement, we consulted our Privacy Office to ensure appropriate identification and handling of information collected.

This ICR collects personally identifiable information (PII). PII is collected in the context of the subject individuals' professional capacity and the FDA-related work they perform for their employer (e.g., point of contact at a regulated entity). The PII submitted for the field alert report (FAR) via Form FDA 3331a (New Drug Application/Abbreviated New Drug Application) is name, telephone number, and email address. FDA determined that although PII is collected it is not subject to the Privacy Act of 1974 and the particular notice and other requirements of the Act do not apply. Specifically, FDA does not use name or any other personal identifier to retrieve records from the information collected. Through appropriate form design, FDA limited submission fields and minimized the PII collected to protect the privacy of the individuals.

Under the Freedom of Information Act (FOIA) (5 U.S.C. 552), the public has broad access to government documents. However, FOIA provides certain exemptions from mandatory public disclosure of government records (5 U.S.C. 552(b)(1-9)). FDA will make the fullest possible disclosure of records to the public, consistent with the rights of individuals to privacy, the property rights of persons in trade and confidential commercial or financial information.

11. Justification for Sensitive Questions

The collection of information does not involve sensitive questions.

12. Estimates of Annualized Burden Hours and Cost

12a. Annualized Hour Burden Estimate

FDA estimates the burden of this collection of information as follow:

Table 1.--Estimated One-Time Recordkeeping Burden for Corporate Firms[1]

Information Collection Activity; 21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper	Total Hours[2]
Subparts C and F**;** §§ 212.20 to 212.50					
Master Batch Production and Quality Control Procedures (§§ 212.20(c) and (e) and 212.50(a) and (b))	4	10	40	8	320
Subparts C, D, F, and G**;** §§ 212.20 to 212.60					

Equipment and Facilities Records (SOP) (§§ 212.20(c), 212.30(b), 212.50(d), and 212.60(f))	4	13	52	5	260
Subparts C and E**;** §§ 212.20 to 212.40					
Records of Components, Containers, and Closures (SOP) (§§ 212.20(b) and 212.40(a) and (b))	4	1	4	8	32
Records of Components, Containers, and Closures (specification data sheets) (§§ 212.20(b) and (c) and 212.40(a) and (b))	4	25	100	2	200
Subpart H; § 212.71					
OOS Investigations (SOP) (§ 212.71(a) and (b))	4	1	4	8	32
Subpart J; § 212.90					
Distribution Records (SOP) (§ 212.90(a))	4	1	4	8	32
Subparts C and K; §§ 212.20 to 212.100					
Complaints and Returned Product (§§ 212.20(e) and 212.100(a), (b), and (c))	4	3	12	8	96
Total			216		972

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

Table 2.--Estimated One-Time Recordkeeping Burden for Academia, Small Firms, and High-Risk Component Manufacturers[1]

Information Collection Activity; 21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper[2]	Total Annual Records	Average Burden per Recordkeeper	Total Hours[2]
Subparts C and F; §§ 212.20 to 212.50					
Batch Production and Control Records (§§ 212.20(c) and 212.50(a) and (b))	63	8	504	8	4,032
Subparts C, D, F, and G; §§ 212.20 to 212.60					
Equipment and Facilities Records (SOP) (§§ 212.20(c), 212.30(b), 212.50(d), and 212.60(f))	63	12	756	8	6,048
Subparts C and E; §§ 212.20 to 212.40					
Records of Components, Containers, and Closures (SOP) (§§ 212.20(b) and 212.40(a) and (b))	63	2	126	8	1,008
Records of Components, Containers, and Closures (specification data sheets) (§§ 212.20(b) and (c) and 212.40(a) and (b))	63	21	1,323	0.5	662
Subparts C and H; §§ 212.20 to 212.71					
OOS Investigations (SOP) (§§ 212.20(c) and 212.71(a) and (b))	63	1	63	8	504
Subpart J; § 212.90					
Distribution Records (SOP) (§ 212.90(a))	63	1	63	8	504
Subparts C and K; §§ 212.20 to 212.100					
Complaints and Returned Product (§§ 212.20(e) and 212.100(a), (b), and (c))	63	3	189	8	1,512
Total			3,024		14,270

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

Table 3.--Estimated Annual Recordkeeping Burden for Corporate Firms[1]

Information Collection Activity; 21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper	Total Hours[2]
Subparts C and F; §§ 212.20 to 212.50					
Batch Production Records (create batch-related records per year) (§§ 212.20(c) and (e) and 212.50(a) and (b))	91	240	21,840	0.5	10,920
Creating Any New Batch Records and Quality Records for New or Existing Drugs (§§ 212.20(c) and (e) and 212.50(a) and (b))	4	9	36	8	288
Subparts D, F, and G; §§ 212.30 to 212.60					
Equipment and Facilities Records (calibration and cleaning records systems) (§§ 212.30(b), 212.50(d), and 212.60(f))	91	480	43,680	0.25	10,920
Subparts C and E; §§ 212.20 to 212.40					
Records of Components, Containers, and Closures for incoming inspection (§§ 212.20(b) and (c) and 212.40(a) and (b))	4	48	192	2	384
Subparts G and H; §§ 212.60 to 212.70					
Laboratory Testing Records (record laboratory test results) §§ 212.60(g), 212.61(b), and 212.70(d)(2) and (d)(3)	91	240	21,840	0.5	10,920
Subpart H; § 212.71					
Out-of-Specification Investigations (record events and investigations) (§ 212.71(b))	91	2	182	2	364
Subparts H and K; §§ 212.70 to 212.100					
Complaints (§ 212.100(b) and (c))	4	5	20	2	40
QA and Release of Batches (§ 212.70)	91	240	21,840	0.25	5,460
Subpart J; § 212.90					
Distribution Records (§ 212.90(b))	91	240	21,840	0.25	5,460
Total			131,470		44,756

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

Table 4.--Estimated Annual Recordkeeping Burden for Academia and Small Firms[1]

Information Collection Activity, 21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper	Total Hours[2]
Subparts C and F; §§ 212.20 to 212.50					
Batch Production Records (filling batch-related records per year) (§§ 212.20(c) and (e) and 212.50(a) and (b))	49	96	4,704	0.5	2,352
Creating Any New Batch Records and Procedures for New Drugs (§§ 212.20(c) and (e) and 212.50(a) and (b))	49	3	147	8	1,176
Subparts D, F, and G; §§ 212.30 to 212.60					
Equipment and Facilities Records (calibration and cleaning records) (§§ 212.30(b), 212.50(d), and 212.60(f))	49	480	23,520	0.5	11,760
Subparts C and E; §§ 212.20 to 212.40					
Records of Components, Containers, and Closures (incoming acceptance tests) (§§ 212.20(b) and (c) and 212.40(a) and (b))	49	12	588	0.5	294
Subparts G and H; §§ 212.60 to 212.70					
Laboratory Testing Records (QC test results) §§ 212.60(g), 212.61(b), and 212.70(d)(2) and (d)(3)	49	96	4,704	0.5	2,352
Subpart H; § 212.71					
Out-of-Specification Investigations (record events and investigations) (§ 212.71(b))	49	2	98	2	196
Subparts H and K; §§ 212.70 to 212.100					
Complaints (Record events and investigations) (§ 212.100(b) and (c))	49	2	98	2	196
QA and Release of Batches (§ 212.70)	49	96	4,704	0.25	1,176
Subpart J; § 212.90					
Distribution Records (§ 212.90(b))	49	96	4,704	0.25	1,176
Total			43,267		20,678

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

Table 5.--Estimated Annual Recordkeeping Burden for High-Risk Component Manufacturers[1]

Information Collection Activity; 21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper	Total Hours[2]
Subparts C and F; §§ 212.20 to 212.50					
Batch Production (creating manufacturing records and batch-related records per year) (§§ 212.20(c) and (e) and 212.50(a) and (b))	14	24	336	0.5	168
Subparts D, F, and G; §§ 212.30 to 212.60 and 212.90					
Equipment and Facilities Records (calibration and cleaning records systems) (§§ 212.30(b), 212.50(d), and 212.60(f))	14	130	1,820	0.5	910
Subparts C and E; §§ 212.20 to 212.40					
Records of Components, Containers, and Closures (incoming acceptance test) (§§ 212.20(c) and 212.40(a) and (b))	14	24	336	0.5	168
Subparts G and H; §§ 212.60 to 212.70					
Laboratory Testing Records (record QC test results) §§ 212.60(g), 212.61(b), and 212.70(d)(2) and (d)(3)	14	24	336	0.5	168
Subpart H; § 212.71					
OOS Investigations (record events and investigations) (§ 212.71(b))	14	1	14	1	14
QA and Release of Batches (§ 212.70)	14	24	336	0.25	84
Subpart J; §§ 212.90 to 212.50					
Distribution Records (§ 212.90(b))	14	24	336	0.25	84
Total			3,514		1,596

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

Table 6.--Estimated One-Time and Annual Recordkeeping Burden for External Control Testing Laboratories[1]

Information Collection Activity; 21 CFR Citation	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeper	Total Hours[2]
Subpart G; § 212.60					
One-Time Recordkeeping Assay Validation (creating SOP and performing validation)	23	6	138	9	1,242
Subparts C, E, and F; §§ 212.20, 212.40, and 212.50					
Annual Recordkeeping Incoming Acceptance Tests Records (§§ 212.20(c), 212.40(a) and (b))	23	24	552	0.5	276
Annual Recordkeeping Batch Testing (creating testing records for sterility, periodic quality indicator test, or any test) (§§ 212.20(c) and (e) and 212.50(a) and (b))	23	8	184	0.5	92
Subparts D, F, and G; §§ 212.30, 212.50, and 212.60					
Annual Recordkeeping Equipment and Facilities Records (calibration, cleaning, and maintenance records) (§§ 212.30(b), 212.50(d), and 212.60(f))	23	98	2,254	0.25	564
Subpart H; § 212.71					
Annual OOS Investigations (recording events and investigations) (§ 212.71(b))	23	1	23	1	23
Annual QA and Release of Test Results	23	8	184	0.25	46
Total			3,335		2,243

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

[2]Totals have been rounded to the nearest whole number.

Table 7.--Estimated Annual Third-Party Disclosure Burden for PET Drug Producers[1]

Information Collection Activity; 21 CFR Section	No. of Sterility Failure Incidents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours[2]
Subpart H; § 212.70					
Sterility Test Failure Notices[3] (§ 212.70(e))	7	3	21	2.5	53

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.
[2]Totals have been rounded to the nearest whole number.
[3]Two reports are sent to FDA per incident, and 1 notification is sent to the receiving site.

Section 212.5(b) (21 CFR 212.5(b)) provides that for investigational PET drugs produced under an investigational new drug application (IND) and research PET drugs produced with approval of a Radioactive Drug Research Committee (RDRC), PET producers must meet the requirement (FD&C Act) to follow CGMP by complying with the regulations under part 212 or complying with United States Pharmacopeia (USP) 32 Chapter 823. We believe that PET production facilities producing drugs under INDs and RDRCs are already substantially complying with the recordkeeping requirements of USP 32 Chapter 823 (see section 121(b) of FDAMA). Some IND and RDRC PET facilities also produce PET drugs approved under abbreviated new drug applications (ANDAs) or new drug applications (NDAs), and our estimates include these facilities. The facilities described above are included under academia or small firms. The corporate sites that also produce IND PET drugs are included in the estimated 91 individual corporate sites.

A. One-Time Recordkeeping Burden for Corporate Firms

We estimate that corporate firms will have to employ one-time and annual recordkeeping. We estimate that, for some major PET manufacturing corporations, most of the quality, manufacturing, and testing procedures are developed at the corporate level and issued to the individual production and testing sites located in various States across the country. It is estimated that a total of 91 of these individual corporate sites are controlled among 4 major corporations. Thus, we have calculated the burden for 4 recordkeeping activities as a one-time effort for creating standard operating procedures (SOPs) and master batch records (MBRs) instead of 91 recordkeeping activities for individual corporate sites.

Each corporate firm is estimated to expend approximately 8 hours to create 1 MBR per PET drug. We estimate that 4 corporate firms will each create and maintain 10 MBRs associated with production and quality control (QC) testing procedures (a total of 40 records), which results in a total recordkeeping burden of approximately 320 hours.

Sections 212.20(c), 212.30(b), 212.50(d), and 212.60(f) (21 CFR 212.20(c), 212.30(b), 212.50(d), and 212.60(f) contain written SOP provisions for equipment operation, maintenance, and cleaning, including maintenance of physical facilities. We estimate that 4 corporate firms will expend approximately 5 hours each to establish and maintain 13 procedures for equipment and facility maintenance (a total of 52 procedures), which results in a total recordkeeping burden of approximately 260 hours.

Sections 212.20(b) and 212.40(a) and (b) contain requirements on SOPs regarding receiving, testing, and accepting components. We estimate that 4 corporate firms will expend approximately

8 hours each to create 1 procedure for acceptance of raw materials and components (a total of 4 procedures), which results in a total recordkeeping burden of approximately 32 hours. We estimate that approximately 4 corporate firms will expend 2 hours each to create 25 specification data sheets for components (a total of 100 specification data sheets), which results in a total recordkeeping burden of approximately 200 hours.

Section 212.71(a) and (b) requires that PET drug firms establish procedures for rejecting PET drug batches that do not conform to established specifications and requires that PET drug firms establish procedures for investigating deviations and out-of-specifications (OOS) failures of products during manufacturing and testing. Section 212.50(a) also requires that firms establish written production and process control procedures to ensure and document that all key process parameters are controlled and that any deviations from the procedures are justified. We estimate that 4 corporate firms will expend approximately 8 hours each to establish 1 procedure (a total of 4 procedures), which results in a total recordkeeping burden of approximately 32 hours.

Section 212.90(a) requires the establishment and maintenance of written procedures for the distribution of PET drug products. We estimate that 4 corporate firms will each expend approximately 8 hours to establish and maintain 1 written procedure regarding the distribution of PET drugs (a total of 4 records), which results in a total recordkeeping burden of approximately 32 hours.

Sections 212.20(e) and 212.100(a), (b), and (c) require that PET drug firms establish and maintain written procedures for handling complaints and establish and maintain procedures for field alert reports (FARs). We estimate that 4 corporate firms will each establish 3 written procedures (a total of 12 procedures) and that each corporate firm will expend approximately 8 hours for each procedure. Establishing and maintaining written procedures results in a total recordkeeping burden of approximately 96 hours.

B. One-Time Recordkeeping Burden for Academia, Small Firms, and High-Risk Component Manufacturers

A total of 63 combined sites represent academia and small commercial firms, including some IND and RDRC sites manufacturing ANDA-approved and NDA-approved PET drugs, and high-risk component manufacturers. Of the 63 combined sites (herein and the other sections of this document referred to as "entities"), 14 producers of starting materials, precursors, generators, and sterile component material manufacturing for kits are also required to comply with selected regulations in part 212, according to the PET drug definition in section 121(a) of FDAMA and codified in section 201(ii)(1)(A) of the FD&C Act (21 U.S.C. 321(ii)(1)(A)). We refer to such producers as high-risk component manufacturers in tables 2 and 5.

The 63 entities will expend approximately 8 hours each to create MBRs and manufacturing and quality procedures. We estimate that the entities will each maintain 8 records (a total of approximately 504 records), which results in a total recordkeeping burden of 4,032 hours.

Each of the entities will expend approximately 8 hours to create equipment-related and facility-related procedures (consistent with corporate firms discussed in section II.A above). A total of 63 entities will each maintain an estimated 12 records (a total of 756 records), which results in a total recordkeeping burden of approximately 6,048 hours.

The estimated burden for the 63 entities to each create and maintain 12 procedures for acceptance of raw materials and components (a total of 126 procedures) is approximately 8 hours per procedure. The creation and maintenance of these procedures results in a total recordkeeping burden of approximately 1,008 hours.

We estimate that the 63 entities will each expend approximately 30 minutes to create and maintain 21 specification data sheets (a total of 1,323). The creation and maintenance of specification data sheets results in a total recordkeeping burden of approximately 662 hours.

We estimate that approximately 63 entities will each create 1 procedure relating to deviations and OOS investigations and 1 procedure relating to the distribution of finished products (2 procedures for a total of 126). Each of these entities will expend 8 hours per procedure, which results in a total recordkeeping burden of 1,008 hours--504 hours for each procedure.
We estimate that each of the 63 entities will create approximately 3 procedures relating to customer complaints, returned products, and FAR (a total of 189 records). Each of these entities will expend 8 hours per record, which results in a total recordkeeping burden of 1,512 hours.

C. Annual Recordkeeping Burden for Corporate Firms

As discussed in section II.A, we estimate that there are a total of 91 individual corporate sites controlled under 4 major corporations. The information collection discussed in this section relates to individual PET drugs manufactured at each of the sites located across the country.
We estimate that the 91 corporate sites will each expend approximately 30 minutes to fill 240 batches (approximately 20 batches each month and a total of 21,840 batches for all 91 sites), which results in a total recordkeeping burden of 10,920 hours. We further estimate that, annually, corporate firms may have to create some new batch records or quality records for newly introduced or existing drugs.

We estimate that the 4 major corporations will each expend approximately 8 hours to create 9 new quality procedure and MBRs (a total of 36 records), which results in a total recordkeeping burden of 288 hours.

We estimate that approximately 91 individual corporate sites will each expend approximately 15 minutes to create 480 records for equipment maintenance, cleaning, calibration, and facilities maintenance (a total of 43,680 records), which results in a total recordkeeping burden of 10,920 hours.

Sections 212.20(b) and (c) and 212.40(a) and (b) set forth requirements for acceptance of raw materials and component shipments received at the centrally controlled, corporate quality assurance (QA) facilities annually. We estimate that the 4 corporate QA sites, internally located within corporate administrative sites, will create 48 records for incoming raw material acceptance (a total of 192 records) for approximately 4 bulk shipments per month (12 x 4) on behalf of the individual corporate sites. Corporate QA sites will expend approximately 2 hours to create records, which results in a total recordkeeping burden of 384 hours.

Sections 212.60(g), 212.61(b), and 212.70(d)(2) and (d)(3) set forth requirements for documenting laboratory testing results obtained from each PET drug manufactured and referred to in laboratory testing, including final release testing. Each of the 91 individual corporate firms must maintain records of different tests for each of their products. We estimate that approximately 91 individual corporate sites will each expend 30 minutes to document 240 records of cumulative QC test results

(1 record that includes 5 to 6 tests and a total of 21,840 records), which results in a total recordkeeping burden of approximately 10,920 hours.

We estimate approximately 2 hours for each of the 91 individual corporate sites to record OOS events and perform investigations for each incident. We also estimate that the individual corporate sites will each conduct an average of 2 OOS investigations per site (a total of 182 records for OOS investigations), which results in a total recordkeeping burden of 364 hours. This estimate includes reprocessing or conditional release events, which are very rare.

Section 212.100(b) and (c) requires that PET drug firms document how they handle each complaint that they receive. We estimate that each of the 4 corporate QA sites will expend approximately 2 hours to document and investigate 1 complaint. Because complaints are usually investigated at the corporate firm level, we estimate that each corporate QA site will receive and handle 5 complaints annually (a total of 20 complaints for documentation), which results in a total recordkeeping burden of 40 hours.

Our estimate for PET drug firms-performing QA and release of manufactured PET drugs from the 91 individual corporate sites is approximately 5,460 hours from 21,840 released batches (15 minutes per batch for each of the 240 released batches).

Section 212.90(b) requires that corporate firms maintain distribution records. We estimate that each of the 91 corporate firms will expend approximately 5,460 hours to release 21,840 batches (15 minutes per batch for each of the 240 released batches).

D. Annual Recordkeeping Burden for Academia and Small Firms

We assume that each academia and small firm will expend the same amount of time to perform the same information collection activities as corporate firms (discussed in section II.A above). Approximately 49 academia and small firms will each expend approximately 30 minutes to fill 96 batch and production records (a total of 4,704 records), which results in a total recordkeeping burden of 2,352 hours.

For the 49 academia and small firms to create new MBRs or quality records, we estimate they will expend 8 hours per record (147 total records (3 per site)), which results in a total recordkeeping burden of 1,176 hours.

We estimate that approximately 49 academia and small firms will maintain 23,520 calibration and cleaning records (480 records per site), such as logbooks for each piece of equipment and documentation of calibration records in each PET production firm. The calibration efforts for academia and small firms is twice per year per equipment (10 pieces of equipment per site). In addition, we estimate that academic and small firms will each expend 30 minutes to maintain records, which results in a total recordkeeping burden of 11,760 hours.

Under §§ 212.20(b) and (c) and 212.40(a) and (b), academia and firms will maintain a total of approximately 588 raw material and component acceptance records (12 shipments per year). We estimate that they will expend 30 minutes to create records, which results in a total recordkeeping burden of 294 hours.

We estimate that approximately 49 academia and small firms will each expend 30 minutes to document a total of 4,704 laboratory QC test records (96 records per site), which results in a total recordkeeping burden of approximately 2,352 hours.

We estimate that approximately 49 academic and small firms will each maintain records of OOS and customer-complaint events and perform investigations and that they will expend approximately 2 hours annually for these activities. We also estimate an average of 2 OOS events and 2 customer complaints and investigations per firm, with a total of 392 hours for each category (196 for each site). This estimate includes any reprocessing or special batch release events, which have been rarely observed.

We estimate that approximately 49 academia and small firms will each perform QA and release of manufactured PET drugs and that they will expend 15 minutes per batch (96 batches per site), which results in a total recordkeeping burden of 1,176 hours for 4,704 batches.
Section 212.90(b) requires that academia and small firms maintain distribution records. We estimate that it will take approximately 15 minutes per batch (96 batches per site) to create a distribution record for each batch of PET drug product, with a total recordkeeping burden of approximately 1,176 hours for 4,704 batches per site.

E. Annual Recordkeeping Burden for High-Risk Component Manufacturers (Producers of Starting Materials, Precursors, Generators, and Sterile Raw Materials)

According to section 121(a) of FDAMA, the PET drug definition includes any non-radioactive or radioactive reagents, kits, nuclidic generators, target materials, synthesizers, or other apparatus or computer program to be used in preparation of PET drug. FDA performs risk assessments of each manufacturer and inspects such manufacturers. Producers of sterile kit components, precursors, and generators are included in this category, including producers of sterile raw materials. We have estimated that 14 such facilities be included in this category based on inspections and have included them in this section. These manufacturers must comply with selected sections of part 212 since they are not producing the final PET drug products to be administered to patients. As stated in section II.B, we refer to such producers as high-risk component manufacturers in tables 2 and 5.

We estimate that approximately 14 high-risk component manufacturers will expend 30 minutes to complete each manufacturing batch record (24 batches per site) and that there will be a total of 336 records, which results in a total recordkeeping burden of approximately 168 hours.
We also estimate that the 14 high-risk component manufacturers will each expend approximately 30 minutes to create and file equipment calibration and cleaning and facility maintenance-related records (130 records each and a total of 1,820), which results in a total recordkeeping burden of 910 hours.

We estimate that the 14 such manufacturers will each expend 30 minutes to document 24 records for components, containers, and closures for incoming acceptance tests (a total of 336 batches), which results in a total recordkeeping burden of approximately 168 hours from all sites.
We estimate that the 14 such manufacturers will expend 30 minutes to document 24 laboratory testing records for 336 batches, which results in a total burden of approximately 168 hours. These manufacturers will also document OOS investigations for any laboratory test failures (1 record for each site), which results in a total recordkeeping burden of 14 hours.

We also estimate that such manufacturers will perform QA and release manufactured PET drugs for a total of 336 batches (24 each) released annually. In addition, we estimate that such manufacturers will expend approximately 15 minutes per batch, which results in a total recordkeeping burden of 84 hours.

We estimate that such manufacturers will each expend approximately 15 minutes to create and maintain distribution records that will result in 336 records (24 each). The total recordkeeping burden hours will result in 84 hours.

F. One-Time and Annual Recordkeeping for External Control Testing Laboratories

We have included a new category of facilities--external control testing laboratories--in this information collection. These testing laboratories perform chemical, microbiological, or sterility testing functions to support manufacturing and release of final PET drug products. Assignment and inspection of control testing laboratories may be determined through risk-based assessments. We have estimated that 23 such facilities be included in this category, based on inspections and NDA and ANDA applications that FDA has received. These testing laboratories must comply with selected sections of part 212 (and compliance with 21 CFR part 211 is acceptable) since they are not producing the final PET drugs to be administered to patients. In this section, we refer to these testing laboratories as external testing facilities in general; however, in table 6, we refer to them as external control testing laboratories.

We estimate that approximately 23 external testing facilities will each expend 9 hours to complete testing SOP and validation of test methods and assays (6 records each and a total of 138), which results in a total recordkeeping burden of approximately 1,242 hours.

We estimate that 23 external testing facilities will expend approximately 30 minutes each to perform incoming acceptance test for testing materials and to create test result records, which results in a total recordkeeping burden of 368 hours. For incoming acceptance tests, sites will expend 276 hours (24 records for a total of 552), and for testing records, sites will expend 92 hours (8 records for a total of 184).

We estimate that 23 external testing facilities will each document 2,254 equipment cleaning and calibration records, 184 QA release records, and 23 OOS investigation records, which results in a total recordkeeping burden of approximately 564, 23, and 46 hours, respectively (see table 6).

Process Verification

Section 212.50(f)(2) requires the recordkeeping of any process verification activities and results. PET drug producers usually perform process verification as a one-time activity before a product is approved or if any major manufacturing process or equipment changes are made. We have estimated that PET drug producers will conduct process verification under one-time batch creation for existing products; annual new creation of MBRs; and manufacturing and quality procedures for ongoing activities, including media fills (see tables 1 and 2).

Conditional Final Releases

Section 212.70(f) requires that PET drug producers document any conditional final releases of a product. We believe that conditional final releases will be uncommon, and we have included them in the burden estimates under annual OOS investigations and final QA release efforts for each manufactured batch in tables 3 and 4.

Reprocessing Procedures

Sections 212.20(c) and 212.71(d) require that PET drug producers establish and document procedures for reprocessing PET drugs. We have rarely received reprocessing options for application of such drugs and, if reprocessing occurs, we have included such rare events in the burden estimates under annual QA release efforts in tables 3 and 4.

Third-Party Disclosure Burden for Sterility Test Failure Notices

Section 212.70(e) requires that PET drug producers notify all receiving facilities if a batch fails sterility tests. FDA receives FARs based on confirmed sterility failures of released PET drugs. Based on the last 3 years' sterility failure reports, we estimate that all 140 sites (91 individual corporate sites and 49 academia and small firms) will send notifications to the affected clinical or receiving facilities of approximately 7 failures. Therefore, we estimate that 7 PET drug producers will submit 2 reports to FDA and send 1 notification (a total of 3 reports) to FDA and the affected clinical or receiving site per year. PET drug producers would submit the notice to the receiving site by email or Fax and submit the FAR notice to FDA electronically and would expend 2.5 hours per incident, which results in a total burden of 53 hours.

12b. Annualized Cost Burden Estimate

	Number of Establishments	Labor (Months)	Wage (Annual Salary)	Cost
RECORDS DAILY IMPLEMENTATION, AUDITS, UPDATES				
Academia and Small Firms (Academia and Small PET Producers)	63	1.0	$266,762	$1,400,500.50
Corporate Firms (Commercial PET Producers)	91	2.25	$266,762	$4,551,626.63
TOTAL				$5,952,127.13
TRAINING				
Academia and Small Firms (Academia and Small PET Producers)	63	.11	$266,762	$154,055.06
Corporate Firms (Commercial PET Producers)	91	.11	$266,762	$222,523.97
TOTAL				$376,579.03

13. Estimates of Other Total Annual Costs to Respondents/Recordkeepers or Capital Costs

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

14. Annualized Cost to the Federal Government

Costs for the information collection include periodic inspections of PET drug production facilities. Two full-time employees are needed to conduct these inspections annually and we calculate $533,524 in total costs to the Federal Government.

15. Explanation for Program Changes or Adjustments

The information collection reflects adjustments. Our estimated burden for the information collection reflects an overall increase of 25,463 hours and corresponding increase of 84,709 records. We attribute this increase to the inclusion of external control testing laboratories that perform only specialized chemical, microbiological, or sterility testing functions to support manufacturing and release of final PET drugs. We have removed costs in ROCIS that were erroneously entered in our previous submission.

16. Plans for Tabulation and Publication and Project Time Schedule

No tabulated results, or production or project schedules are associated with the information collection.

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

The OMB expiration date will be displayed as required by 5 CFR 1320.5.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.