Coalition for PET Drugs
http://coalitionforpetdrugapproval.org/
(703) 326-1190

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Leslie Kux
Assistant Commissioner for Policy
U.S. Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2013-N-0242
Agency Information Collection Activities: Proposed Collection; Comment Request; Current Good Manufacturing Practice for Positron Emission Tomography Drugs

Via Electronic Submission

Dear Ms. Kux:

The Coalition for PET Drug Approval (also known as the Coalition for PET Drugs, or just Coalition) was organized in November 2010 to help manufacturers of drugs for positron emission tomography (PET) understand requirements related to the implementation of 21 CFR part 212, and to communicate with the Food and Drug Administration (FDA) on behalf of this community. Since that time, the Coalition has played an instrumental role in numerous policy issues on the behalf of PET drug manufacturers. We appreciate the opportunity to provide comments on the collection of information related to the PET GMPs.

Background on Positron Emission Tomography (PET)

PET is an imaging technique that is used to assess the biochemical processes that define the physiology of living organisms. Since diseases first manifest themselves as changes in "normal" physiology, and then later by changes in "normal" anatomy, PET imaging provides earlier detection than traditional anatomical imaging techniques such as x-ray, CT, and MRI. PET imaging is also a very sensitive technique, which can often detect diseased tissue before it is apparent anatomically. For these reasons, PET imaging is frequently referred to as "molecular imaging," and offers the promise of individualized treatment based on the specific disease state of the individual patient. From a practical standpoint, PET imaging studies are performed in combination with CT scans to provide more precise information about various diseases in neurology, oncology, and cardiology. PET imaging is a relatively simple procedure that employs small doses of radioactive tracers (i.e., PET drugs). PET scans are commonly performed in hospitals and routine outpatient settings.

Background on PET Drug Manufacturers

PET drugs are necessary in order to perform a PET scan. Due to their unique physical properties, PET drugs are inherently a different class of drugs compared to traditional drug products. The inherent differences of PET drugs impact all aspects of the PET drug manufacturing environment. For example, instead of one or two production facilities that may be required for the nationwide supply of a traditional drug product, the Coalition estimates that approximately 150 manufacturing facilities are required to provide nationwide coverage of currently approved PET drugs. This is due to the short radioactive half-lives of PET products with a range from 10 - 110 minutes. Each PET drug facility is a very

small operation staffed by two to eight employees. Many PET drug manufacturing facilities are part of academic medical centers that produce PET drugs solely for internal use. In addition, some PET drug manufacturers are not-for-profit organizations associated with government agencies such as the National Institute of Health and state university hospitals.

The inherent differences of PET drugs were recognized by Congress through the passage of the 1997 FDA Modernization Act[1] and later by the FDA through the development of good manufacturing practice standards (GMPs) for PET drugs, 21 CFR Part 212.[2] The FDA has recognized these differences in other areas as well, most notably with regard to inspectional practices for PET drug manufacturers,[3] reductions in user fees.

Comments Related to Collection of Information

In the Federal Register notice, the FDA invited comments on four topics. The Coalition will address each topic below.

1. *Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility.*

   The Coalition supports the collection of this information as it believes it is necessary for the proper performance of FDA's functions. The Coalition believes that accurate assessments of the recordkeeping requirements are important for the FDA to fully understand the full impact recordkeeping has on PET drug manufacturers. Due to the small size of a PET drug manufacturer this impact is proportionately much greater than that experienced by a general pharmaceutical manufacturer. As explained further below the great preponderance of record keeping will continue to be a paper based system as the cost for an electronic system is far beyond the resources of most PET drug manufacturers. Within the Federal Register notice regarding IND and RDRC PET drugs the statement was made;

   > 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.

   Especially in regards to IND PET drugs, even if prepared per <823> this statement does not accurately represent the record-keeping burden. The requirements and record keeping requirements of <823> are very similar to those of 21 CFR 212. Many sites maintain the same records for their PET drugs regardless of whether they are produced under 212 or <823 >. It is well recognized that the data produced under these similar record-keeping conditions enhances its value when it is submitted to the FDA in an NDA application.

   Beyond the FDA this data is helpful to the Coalition to recognize the true impact of recordkeeping and to provide impetus for the standardization of record contents amongst the

[1] Public Law 105-115, Title I, Subtitle B, Section 121, Positron emission tomography (1997).
[2] Federal Register, vol. 74, no. 236 p. 65409. See: Docket no. FDA–2004–N–0449 (formerly 2004N–0439).
[3] See: Positron Emission Tomography (PET) CGMP Drug Process and Pre-Approval Inspections/Investigations, Compliance Program Guide, 7356.002 and 7346.832.

PET drug manufacturers. This standardization will provide benefits not just to the PET drug manufacturers but also the FDA.

2. *The accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used.*

In general it is difficult to fully assess the FDA's methodology as there are numerous details missing. Did the FDA take into account the economies of scale that the large commercial companies enjoy vs. the individual academic sites? As it is imperative that the FDA not craft regulations that place one type of PET drug manufacturer at a disadvantage. Even between the two general categories of commercial vs. academic PET drug manufacturers there exists a large diversity within each of these two categories. This diversity will complicate the FDA's attempt to use "averages" to accurately address the impact for all PET drug manufacturers.

Legally the FDA has met the intent of the regulations by requesting this information via the Federal Register. However due to the diversity and in some cases small size of PET drug manufacturers numerous sites may not be aware of this request. The small sites only have 2-3 full time employees and will not have a dedicated regulatory affair specialist. Their regulatory affairs specialist will most likely also be involved in production, maintenance, quality control testing, etc. So while they will have first-hand experience to the record keeping burdens they may not see this request in a timely manner in the Federal Register. Given the uniqueness and diversity of PET drug manufacturers the FDA should in future requests; email the Federal Register notice to ensure prompt notification.

The Coalition respectfully questions the accuracy of the estimates in Table 1 as explained in the comments to our attachment below. In regards to a single PET drug production site (aka "record-keeper") there are wide variations in how the FDA staff interpreted these estimates vs. how we would interpret these estimates for a single site. Our estimates are not close this is just for the first section of table 1. Due to a lack of volunteered staff/time we were not able to complete our analysis for the full table. Many of us have performed the tasks listed in table 1 and believe our estimates are far more accurate than those proposed by the FDA. The Coalition would request a more comprehensive explanation of what is to be measured in each section of the table. This request would also need to be accompanied with an extension of time to comment so all can respond more accurately.

The Coalition respectfully questions the accuracy of the estimate in Table 2. This table estimates the total hours for the annual third party disclosure burden. This burden is associated with the sterility test failure notices described in 212.70(e). The table notes the annual total burden for all PET drug manufacturers (i.e., 129 respondents) is 32 hours. The Coalition questions the validity and the methodology used for this estimate in several ways.

First, this burden is associated with *sterility test failures*. In actual practice, the Coalition believes that, through FDA inspectional practices, letters to physicians are actually required for all *sterility test out-of-specification* results, even if the out-of-specification result is not due to a true sterility test failure (note that an out-of-specification result could be caused by a laboratory error and not a product failure). As such, the Coalition believes the frequency of disclosure is more the 0.25 as included in Table 2.

Second, the Coalition believes that the average number of hours per disclosure in Table 2, which lists this value as 1 hour, significantly underestimates the actual effort. For example, a single batch of a PET drug may be dispensed under prescription orders from numerous physicians and a notification is required for each prescribing physician. In addition to e-mail and FAX, the notification may require telephone calls to explain the details of the notification and answer questions.

Based on these points, the Coalition believes the estimated total in Table 2 could underestimate the actual total by a factor of 10 to 100. This brings into question other estimates in Table 1. There is insufficient time for the Coalition to conduct the necessary surveys and interviews in the community of PET drug manufacturers that would provide accurate information. This topic is discussed further in the next point.

3. *Ways to enhance the quality, utility, and clarity of the information to be collected.*

The Coalition believes that the quality of the information can be significantly enhanced by improving the accuracy of the estimated recordkeeping burden for each section of 21 CFR 212. This could be achieved by directly involving individual PET drug manufacturers in the establishment of these estimates. The existing estimates were originally developed when the Final Rule for the PET GMP regulations was published.[4] At the time, there was inadequate experience with PET drug manufacturing to develop accurate estimates. Now, with the benefit of almost 4 years of FDA regulation, PET drug manufacturers are in a position to make accurate assessments. The Coalition is willing to assist the FDA as an interface to the PET community in order to collect the data for these estimates.

Thank you again for the opportunity to comment on this important matter. Please contact Caitlin Kubler, Manager of Regulatory Affairs, if you need additional information. Caitlin can be reached at (703) 326-1190 or ckubler@snmmi.org.

Sincerely,

Henry VanBrocklin, Ph.D.
Co-Chair
Coalition for PET Drugs

Sally Schwarz, RPh.
Co-Chair
Coalition for PET Drugs

[4] Federal Register, vol. 74, no. 236 p. 65430. See: Docket no. FDA–2004–N–0449 (formerly 2004N–0439).

Table 1.

21 CFR Section	No. of record-keepers	No. of records per record keeper	Total annual records	Average burden per recordkeeping	Total hours
Batch Production and Control Records 212.20(c) --*Specifications and processes.* You must approve or reject, before implementation, any initial specifications, methods, processes, or procedures, and any proposed changes to existing specifications, methods, processes, or procedures, to ensure that they maintain the identity, strength, quality, and purity of a PET drug. You must demonstrate that any change does not adversely affect the identity, strength, quality, or purity of any PET drug. 212.20(e) -- You must establish and follow written quality assurance procedures. 212.50(a) -- *Written control procedures.* You must have 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. 212.50(b) -- *Master production and control records.* You must have master production and control records that document all steps in the PET drug production process. The master production and control records must include the following information: (1) The name and strength of the PET drug; (2) If applicable, the name and radioactivity or other measurement of each active pharmaceutical ingredient and each inactive ingredient per batch or per unit of radioactivity or other measurement of the drug product, and a statement of the total radioactivity or other measurement of any dosage unit; (3) A complete list of components designated by names and codes sufficiently specific to indicate any special quality characteristic; (4) Identification of all major pieces of equipment used in production; (5) An accurate statement of the weight or measurement of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations are permitted in the amount of component necessary if they are specified in the master production and control records; (6) A statement of action limits on radiochemical yield, i.e., the minimum percentage of yield beyond which investigation and corrective action are required; (7) Complete production and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed; and (8) A description of the PET drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling.	129	1.71	221	20	4,420

Comments:

1. As we understand this section this is the time spent creating, revising, documenting the revisions, educating staff on changes to SOP's for (a) general SOP's, (b) manufacturing SOP's, (c) quality control SOP's and (d) specification sheets.
2. The number of record-keepers at 129 equals the number of PET facilities that you have listed earlier in the notice, this number is an approximation of the actual number but is not accurate, the amount of time spent per facility could be accurate but the total time spent for the whole industry will not be accurate.
3. For this section the number of records per record-keeper of 1.71 appears to be unsupportable as there are easily 16 or more SOP's for general procedures by themselves, let alone the manufacturing SOP's (~10), quality control SOP's (~40) and specification sheets (~30) for one PET drug. We're not sure of how nearly 100 separate SOP's for one PET drug could be estimated as 1.71 records, this needs further explanation.
4. Since the "total number of records per record-keeper" is suspect and that it is multiplied by an inaccurate number of "record-keepers" the "total annual records" may be of limited to no value.
5. The "Average burden per recordkeeping" estimate can be dramatically skewed by the creating task of this total as it represents the single largest and most difficult task, but is only done once. The other two tasks alone such as revising and documenting the revisions could more accurately be estimated as 50 hours for all of the 100 SOP's. We believe that the time spent training of staff of revised SOP's should be included in this section as this appears to be the best fit within the table, however we're not certain if the FDA has included it in its estimates. Educating staff of revised SOP's adds an additional 100 hours per facility. Our estimated total of 150 hours does not include the time spent creating all of these SOP's. The time needed to create all of these SOP's could be measured in months, however it's not certain how to average this time spent into an annual estimate.
6. The "total hours" like the "total annual records" may also be of limited to no value.