Supporting Statement
Radioactive Drug Research Committee Report
On Research Use of Radioactive Drug;
Membership Summary and Study Summary - 21 CFR Part 361.1

[Docket No. 2004N-0269]
OMB Number 0910-0053
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Supporting Statement

A. Justification

1. **Circumstances Necessitating Information Collection**

The Food and Drug Administration (FDA) is requesting OMB approval of the information collection requirements contained in 21 CFR 361.1 These information collection requirements are:

21 CFR 361.1 (c)(2) – Requires recordkeeping by a Radioactive Drug Research Committee (RDRC). Each RDRC must meet at least once each quarter in which research activity has been authorized or conducted. Minutes of these meetings must be kept and must include the numerical results of votes on protocols involving use in human subjects.

21 CFR 361.1 (c)(3) – Requires reporting by an RDRC. Each RDRC must submit an annual report to the FDA that includes the names and qualifications of its members and of any consultants used by the RDRC (reported on Form FDA 2914 - Membership Summary), and a summary of each study conducted during the preceding year (reported on Form FDA 2915 – Study Summary). Additionally, this regulation requires that a RDRC submit a special summary of information at the time any study is approved that involves more than 30 research subjects or research subjects under 18 years of age (reported on Form FDA 2915 – Study Summary).

21 CFR 361.1 (c)(4) – Requires reporting by an RDRC. Each RDRC must report changes in membership and applications for new members to the FDA as soon as, or before, vacancies occur (reported on Form FDA 2914 – Membership

Summary).

21 CFR 361.1 (d)(5) – Requires recordkeeping by an RDRC. Each RDRC must obtain the consent of research subjects or their legal representatives in accordance with 21 CFR 50, and must obtain from each female subject of childbearing potential a statement in writing that she is not pregnant, or must confirm that she is not pregnant based on a pregnancy test, before she may participate in any study.

21 CFR 361.1 (d)(8) – Requires reporting by an RDRC. An RDRC must report to the FDA all adverse reactions probably attributable to the use of a radioactive drug in a research study.

These regulations implement provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (i)), which require the Secretary, DHHS, to promulgate regulations that permit drugs that have been generally recognized as safe and effective to be used solely for basic informational research use. Title 21, Code of Federal Regulations, Part 361.1, enacted on July 25, 1975, sets forth specific regulations regarding the establishment and composition of RDRCs and their role in approving and monitoring research studies utilizing radiopharmaceuticals. No study involving administration of a radioactive drug to research subjects under 21 CFR 361.1 is permitted without the authorization of a FDA approved RDRC (21 CFR 361.1 (d)(7)). The research that may be undertaken with a radiopharmaceutical drug under 21 CFR 361.1 must be intended to obtain basic information and not to carry out a clinical trial. The types of basic research permitted are specified in the regulation, and include studies of metabolism, human physiology, pathophysiology, or biochemistry.

21 CFR 361.1 designates certain research uses of radioactive drugs as generally recognized as safe and effective (GRAS/E). When a drug is designated as GRAS/E, it is <u>not a new drug</u> as defined by the Food, Drug, and Cosmetic Act. When a new drug is used in humans and the drug is <u>not yet approved for marketing</u>, a Notice of Claimed Investigational Exemption for a New Drug (IND) application is required. An IND is not needed to study a drug that is <u>not a new drug</u>. A RDRC can determine that a radioactive drug to be used in a research study is <u>not</u>

a new drug if the conditions of its use as specified in the investigator's protocol meet the requirements of 21 CFR 361.1. Approval of research studies by an RDRC eliminates the need for submission of an IND to the FDA.

Types of research studies not permitted under this regulation are also specified, and include those intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial). These studies require submission of an IND under 21 CFR 312.1 and the associated information collection are covered in OMB Approval 0910-0014.

2. **How, by Whom, and for What Purpose Information Used**

FDA's approval of a RDRC is based on assessment of the qualifications of committee members and assurance that all necessary fields of expertise are covered (reported on Form FDA 2914 – Membership Summary)). Following approval, FDA periodically reviews the composition of the RDRCs. Approval may be withdrawn at any time the requirements of 21 CFR 361.1 are not met.

The FDA monitors an RDRC's activities by reviewing its annual reports (reported on Forms FDA 2914 and 2915), by periodic review of meeting minutes and study protocols, and through on-site inspections. The purpose of this monitoring is to determine whether the research studies are being conducted in accordance with the regulation and to assure the safety of human subjects. Monitoring by the FDA also allows for the identification of studies that initially complied with the requirements of 21 CFR 361.1 but which have evolved into clinical trials or other research studies that are not permitted under 21 CFR 361.1. and that require the submission of an IND.

3. **Consideration of Information Technology**

RDRCs are required to submit all reports in paper format. The FDA is not able to accept reports in electronic format at this time. However, the FDA is amenable to, and is actively seeking the implementation of, the use of information technologies in the future, such as electronic submission of forms FDA 2914 and 2915. The existing procedures provide a consistent means

for the review of RDRC activities. There are no legal obstacles to reducing the burden.

4. **Identification of Duplication**

The FDA is the only federal agency responsible for regulating the activities required by 21 CFR 361.1.

5. **Small Businesses**

Collection of this information does not involve small businesses. Most Committees are affiliated with large institutions. However, the Document Management and Reporting Branch, Division of Management and Budget, Center for Drug Evaluation and Research (CDER), provides general assistance to the research community. The Division of Medical Imaging and Radiopharmaceutical Drug Products (CDER) can also provide assistance.

6. **Consequences of Less Frequent Information Collection**

The composition of the Committee membership is reported to the FDA on Form FDA 2914 (Membership Summary) yearly along with the annual report. Changes in membership may occur at any time during the year, and must be reported (also on Form FDA 2914) as soon as, or before, vacancies occur on the Committee. Less frequent reporting could allow unqualified members to serve on RDRCs for extended periods of time thereby placing the safety of human research subjects at risk as these RDRCs continue to evaluate and approve research protocols.

Approved study protocols are reported to the FDA on Form FDA 2915 (Study Summary) in the annual report. Less frequent reporting could result in safety risks to human subjects due to a delay in the detection of studies that are inappropriate under 21 CFR 361.1.

In an effort to reduce the reporting burden, RDRCs that are not currently conducting active research protocols or do not anticipate conducting any research protocols in the near future may request inactivation until such time as appropriate research projects are identified. To date, 116 Committees have requested inactivation, thus relieving themselves of the information collection requirements of 21 CFR 361.1. RDRCs may request reinstatement by submitting form FDA 2914 (Membership

Summary) with the Curriculum Vitae(s) of any new members, and will again be subject to the information collection requirements of 21 CFR 361.1 once approved by FDA.

7. **Inconsistencies with 21 CFR 1320.6**

This information collection is consistent with the requirements of 5 CFR 1320.6.

8. **Consultation Outside FDA**

In the Federal Register notice of July 23, 2004 (Volume 69, Number 141), the FDA requested comments on the proposed collection of information. No comments were received.

Recently, three Committee chairpersons, listed below, were contacted by phone and asked for their assessment of time expended, cost, and views on completing form FDA 2914 (Memebrship Summary) and form FDA 2915 (Study Summary). These individuals were selected from RDRCs of different geographic areas and of varying levels of activity. The estimates provided by the chairpersons for work hours per year and cost associated with the information collection activities required by 21 CFR 361.1 are reflected in part 12 of this supporting statement. The chairpersons indicated a general satisfaction with the form contents. Following are the major suggestions/comments made by one or more chairpersons:

1. Mechanism for electronic submission of forms should be provided.
2. Form FDA 2914 – Membership Summary: A curriculum vitae should be requested of all members of the committee, including “OTHER VOTING MEMBERS” and “COMMITTEE CONSULTANTS”, and instructions should reflect that “qualifications” includes a curriculum vitae.
3. Form FDA 2915 – Study Summary:
   a) The form should ask for additional information, such as the maximum number of doses of nonradioactive drug per subject per “single study”, the total absorbed dose per “single study”, and the reference/procedure used to estimate radiation absorbed dose from associated imaging equipment used as part of the study.
   b) The format of the “RADIATION ABSORBED DOSE” section should more readily permit the ability to address multiple radioactive drugs being administered to a

single research subject.
c) The submission of forms for studies that did not enroll any subjects in the preceding calendar year places a time burden on Committees that could be reduced by removal of redundancies in the reporting.
d) In cases where the same radioactive drug is used in multiple research studies, the necessity of repeating the pharmacological dose, radionuclide, drug, contaminant, and (part of the) radiation absorbed dose information for each study individually is redundant. A mechanism for reporting this information only once would simplify reporting. The necessity of reporting the general information (RDRC Committee number, IRB name/address, etc.) for each study approved by the same RDRC is also redundant.
e) The instructions for Section B.1. repeat the instructions for Section A.1. and should be removed.
f) Instructions should provide clarification of the extent of the radiation dosimetry calculations that must be included in the report for those drugs for which no reference exists to estimate radiation absorbed dose; the acceptability of ORISE radiation dosimetry estimates should be addressed.
f) The full text of the regulation defining confidential information (21 CFR 20.61)should be provided in the instructions.

Other suggestions of the chairpersons not specifically listed include requests for: clarification or definition of certain terms and phrases; replacement/addition/deletion of specific words, terms, or units of measure for the sake of clarity or consistency or to reflect current practice; discontinuation of the use of abbreviations; changes in format of submitted information and the amount of space provided for responses.

These suggestions have been implemented or are under review by FDA for possible future implementation. Suggestions for changes that would require a rewrite of 21 CFR 361.1 were also provided, which are outside the scope of this information collection assessment.

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9. **Payment or Gift**

No payment or gift was provided to the chairpersons contacted.

10. **Confidentiality Provisions**

The contents of submitted Forms FDA 2914 (Membership Summary) and FDA 2915 (Study Summary) are available for public disclosure unless confidentiality is requested by the investigator and it is evident from the report(s) that the material contains trade secret or confidential commercial information as defined in 21 CFR 20.61. When confidentiality is requested and justified, the forms will be marked as not releasable and will be maintained in a manner similar to other confidential information. Data will be secured in a locked area with access limited to appropriate FDA personnel. Applicable confidentiality will be maintained as long as the data are maintained.

11. **Sensitive Questions**

No questions of a private or sensitive nature are asked.

12. **Total Hour Burden to Respondents**

The estimated annual burden for this information collection is 2,142 hours.

Table 1 -- Estimated Annual Reporting Burden

| 21 CFR Section | Form | No. Of Respondents | Annual Frequency per Response | Total Annual Responses | Hours per Response | Total Hours |
|---|---|---|---|---|---|---|
| 361.1(c)(3)<br>361.1(c)(4) | FDA 2914<br>FDA 2914 | 80 | 1.0 | 80 | 1 | 80 |
| 361.1 c)(3) | FDA 2915 | 50 | 6.8 | 340 | 3.5 | 1190 |
| 361.1(d)(8) | | 50 | 6.8 | 340 | 0.1 | 34 |
| Total | | | | | | 1304 |

\1\There are no capital costs or operating and maintenance costs associated with this collection

Table 2 -- Estimated Annual Recordkeeping Burden

| 21 CFR Section | Form | Number of Record Keepers | Annual Frequency per Record Keeping | Hours per Record Keeper | Total Hours |
|---|---|---|---|---|---|
| | | | 1 per quarter= | | |

| Table 2 -- Estimated Annual Recordkeeping Burden | | | | | |
|---|---|---|---|---|---|
| 361.1(c)(2) | | 80 | 4 per year | 10 | 800 |
| | | | 6.8 | | |
| 361.1(d)(5) | | 50 | | 0.75 | 38 |
| Total | | | | | 838 |

The information entered on Form FDA 2914 (Membership Summary) and Form FDA 2915 (Study Summary) is extracted from data maintained by the RDRCs for their operation and from reports to the institutions with which the RDRCs are affiliated.

Information on study subjects required on Form FDA 2915 (Study Summary) is extracted from written orders (prescriptions) or the subject's medical records. These records are normally maintained in the practice of medicine (i.e., patient identification, diagnostic and therapeutic orders, evidence of informed consent, tests and test results, etc.). Time burden estimates are based on a measurement of clerical, administrative, and professional resources required for the collection and compilation of the data. It is estimated to take 1 hour per respondent annually to complete form FDA 2914 (Membership Summary). There are 80 respondents totaling 80 burden hours. It is estimated to take 3.5 hours per report to complete form FDA 2915 (Study Summary). Approximately 340 reports are submitted annually totaling 1190 burden hours.

The minutes of the meetings, which must be kept in compliance with 21 CFR 361.1 (c)(2), are normal records of RDRC proceedings and are accepted by the FDA for inspection without any further compilation. The time to prepare these minutes varies, depending upon the number of protocols a RDRC has to review/discuss and vote on, and depending upon how an RDRC is structured. However, an average time to prepare minutes (writing/dictating, typing, proofreading) specifically related to studies conducted under this regulation can be estimated to take about 10 hours annually per record keeper. Records must be kept for 80 RDRCs totaling 800 burden hours.

13. **Total Annual Cost to Respondent**

The total estimated cost to the respondents is $85,680. This cost was estimated by telephone survey of contacted chairpersons. The figures vary, depending upon the geographic location, type of personnel utilized in preparing reports,

size of the RDRC membership and the number of protocols reviewed by the RDRC. An average salary of $40 per hour, (clerical and professional salaries combined) was used.

| | Time (hrs) | Cost (Per hr.) | Total Cost |
|---|---|---|---|
| Record keeping | 838 | $40.00 | $33,520 |
| Reporting | 1304 | 40.00 | 52,160 |
| | Total Cost to Respondents | | **$85,680** |

14. **Annualized Cost to FDA**

The estimate of the cost to the government is $72,850 per year. This figure is based on past experience, a current re-evaluation, and the cost of the following activities:

(1) Preparing letters to RDRCs;
(2) Printing Forms FDA 2914 and 2915;
(3) Clerical time for processing and mailing documents at $12.00 per hour; and
(4) Administrative and professional review time at $53 per hour

Table 3 - Estimated Cost to the Federal Government

| Item | Printing | Clerical Time (hrs) | Clerical Cost | Prof. Time (hrs) | Prof. Cost | Total Cost |
|---|---|---|---|---|---|---|
| Letter | $0 | 20 | $240 | 320 | $16,960 | $17,200 |
| 2914<br>2915 | $20<br>$100 | | | 250<br>800 | $13,250<br>$42,400 | $13,250<br>$42,400 |
| Total | 410.00 | 20 hrs | $240 | 1370 hrs | $72,610 | $72,850 |

15. **Explanation for Program Changes or Adjustments**

There are currently 201 approved Committees (of which approximately 116 are inactivated). The total annual burden for reporting and record keeping decreased slightly since the last supporting statement. Although the number of respondents decreased, the average number of study summaries (FDA 2915) submitted per RDRC increased from 5.0 to 6.8, and a burden for the reporting of adverse reactions to the Committees by investigators was included, which accounted for an increase in

the total annual reporting burden. The total record keeping burden includes an estimate of the time necessary to maintain informed consent records and written statements from female subjects that they are not pregnant. This burden was included as part of the reporting burden in the last supporting statement rather than in the record keeping burden. However, a reduction in the number of record keepers for meeting minutes resulted in an overall reduction in total record keeping burden.

Form FDA 2914 (Membership Summary) and Form FDA 2915 (Study Summary) have been revised by FDA with the intent of increasing the accuracy and completeness of the information reported. Major changes made include the addition of instructions for completing the forms, and the inclusion of specific areas to report radiation exposure to research subjects from other associated procedures that are part of the study protocol. Several of the suggestions identified by chairpersons in item 8 have been implemented, as well as comments submitted to the docket in response to the FR notice of July 23, 2004 (Volume 69, Number 141), also identified in item 8.

16. **Publication of Information Collection Results**

FDA does not intend to publish results of the information collection.

17. **Display of OMB Approval Date**

FDA is not seeking an exemption from display of the OMB control number and date.

18. **Exceptions to "Certification for Paperwork Reduction Act Submissions."**

There are no exceptions to the certification statement found in Item 19 (Certification for Paperwork Reduction Act Submissions) of OMB Form 83-I.