

INFORMATION COLLECTION
SUPPORTING STATEMENT
OMB Number 0910-0409
Docket Number 02N-0070

Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and
Monitoring - 0910-0409

JUSTIFICATION

1. Circumstances of Information Collection

The Food and Drug Administration (FDA) is requesting OMB approval of the information collection requirements contained in 21 CFR 315.4, 315.5, and 315.6. These regulations require manufacturers of diagnostic radiopharmaceuticals to submit information that demonstrates the safety and effectiveness of a new diagnostic radiopharmaceutical or of a new indication for use of an approved diagnostic radiopharmaceutical.

In response to the requirements of section 122 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (P.L. 105-115), FDA, in the Federal Register of May 17, 1999 (64 FR 26657), published a final rule amending its regulations by adding provisions that clarify FDA's evaluation and approval of in vivo radiopharmaceuticals used in the diagnosis or monitoring of diseases. The regulation describes the kinds of indications of diagnostic radiopharmaceuticals and some of the criteria that the agency would use to evaluate the safety and effectiveness of a diagnostic radiopharmaceutical under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) (the act) and section 351 of the Public Health Service Act (42 U.S.C. 262) (the PHS Act). Information about the safety or effectiveness of a diagnostic radiopharmaceutical enables FDA to properly evaluate the safety and effectiveness profiles of a new diagnostic radiopharmaceutical or a new indication for use of an approved diagnostic radiopharmaceutical.

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The rule clarifies existing FDA requirements for approval and evaluation of drug and biological products already in place under the authorities of the act and the PHS act (the information collection requirements for biological products are no longer submitted for approval to OMB in this package but are included under OMB Control Number 0910-0124). The information, which is usually submitted as part of a new drug application (NDA) or biologics license application (BLA) or as a supplement to an approved application, typically includes, but is not limited to, nonclinical and clinical data on the pharmacology, toxicology, adverse events, radiation safety assessments, and chemistry, manufacturing, and controls. The content and format of an application for approval of a new drug are set forth in 21 CFR 314.50. Under 21 CFR part 315, information required under the act and needed by FDA to evaluate the safety and effectiveness of in vivo radiopharmaceuticals still needs to be reported.

2. Purpose and Use of the Information

Information about the safety or effectiveness of a diagnostic radiopharmaceutical would enable the agency to properly evaluate the safety and effectiveness profiles of a new diagnostic radiopharmaceutical or a new indication for use of an approved diagnostic radiopharmaceutical, as required under section 505 of the act and section 351 of the PHS Act.

3. Use of Improved Information Technology

One of FDA's continuing objectives is to improve the speed and quality of its review and approval programs. A summary of CDER's efforts in this regard follows:

- Electronic Regulatory Submissions for Archive. The Food and Drug Administration Modernization Act of 1997 (FDAMA), along with the Prescription Drug User Fee Act (PDUFA) II reauthorization, mandate that the Agency shall develop and update its information management infrastructure to allow, by fiscal year 2002, the paperless receipt and processing of INDs and human drug applications, as defined in

PDUFA, and related submissions. Moving an information-intensive activity, such as drug regulatory review, from a paper-based to an electronic environment will provide a number of benefits. This is true simply from the perspective of generating, handling, and storing the huge volumes of paper commonly associated with applications. In general, these paper applications (often containing 100s of volumes) are submitted with several copies, a process that can take several days longer than preparation of a corresponding electronic submission, which the Center can easily reproduce. Preparation of applications in electronic form results in direct cost savings related to materials, supplies, and paper handling logistics (i.e., labor, facilities). However, this is expected to be only a small portion of the potential savings. The most substantial burden reduction may not be in information recording, reporting, and record-keeping, but in the flexibility, efficiency, speed, and ease of filing required information that will result in cost savings to regulated industry, as well as FDA.

During FY 2001, CDER published various Guidance documents for Industry:

1. Providing Regulatory Submissions in Electronic Format - Prescription Drug Advertising and Promotional Labeling (draft issued 1/2001)
2. Promotional material and drug advertising guidance (draft issued 2/2001)
3. Providing Regulatory Submissions in Electronic Format - Post-marketing Expedited Safety Reports (draft issued 5/2001)

FY 2002, guidance documents and target dates for publishing additional documents are provided below:

- a. Abbreviated New Drug Application guidance (draft issued 11/2001)
- b. Post-marketing Safety Reports (issued 12/2001)

- c. Issue final guidance documents to CBER for electronic submission of Investigational New Drug (ND) Applications (issue date 3/2002).
- d. Issue final guidance on promotional material and drug advertising guidance (issue date 5/2002).
- e. CDER & CBER) Develop and publish guidance documents for the electronic submission of Drug Master Files (DMF) and Annual
- f. Reports (issue date 9/2002).
- g. Electronic submission of IND and DMF are pending work on the electronic common technical document at the International Conference on Harmonization (issue date FY 2002).

In FY 2001, CDER has continued to expand the Electronic Document Room to manage the receipt and handling of full electronic NDAs. Approximately 71% of original NDAs received by CDER in FY 2001 included sections that conform to the electronic submission guidance.

There were 1185 electronic submissions, which represents a 134% increase in the number of electronically submitted NDAs in FY 2001 over FY 2000. At the end of FY 2001, the EDR housed electronic submissions for 460 NDAs, a 69% increase compared to the 271 NDAs at the end of FY 2000. The first quarter of FY 2002 continues to show increases in the number of electronic submissions. At the end of the first quarter FY 2002, the EDR has already received electronic submissions for an additional 100 NDAs making a total of 560 electronically submitted NDAs. By the fourth quarter of FY 2002, CDER expects to accommodate Periodic Safety reports, and Annual Reports.

In FY 2001, CDER developed and implemented an Adverse Event Reporting System (AERS) electronic submission module that is currently accepting the electronic submission of AERS 15-day reports without attachments. This effort involves the receipt and physical processing of electronic adverse event reports and development of software to electronically extract data from the

reports and insert it into the AERS database. In the near future, functionality will be provided to accept periodic reports without attachments. The electronic submission software is also being modified to accept submissions in the new XML Data Type Definition (DTD) format.

- Secure E-Mail. During a drug's development cycle, communications between CDER review divisions and the company developing the drug is sensitive and proprietary. Prior to using secure E-mail, CDER methods of "secure" communication included U.S. mail, courier, telephone, and facsimile. These methods, some of which are not entirely secure, can be inefficient or time consuming, and can significantly contribute to the overall length of time involved in the drug review process. The widespread use of E-mail across the Internet offers a more efficient and scaleable means of information exchange. However, security risks of communicating over the Internet are well known. In addition, with the increasing threat of terrorism, the internet is one of the easiest and most often used port of entries for Hackers and other intruders who wish to gain access to confidential information, disrupt and destroy our IT applications and infrastructure. The information technology industry is answering security concerns by developing new standards of cryptographic techniques, E-mail formats, authentication algorithms, and other related aspects of secure communications. After conducting a formal requirements study for secure E-mail which led to the selection of Worldtalk Corporation's WorldSecure Server as the base pilot platform. CDER completed a pilot, the final system design and implemented the production system in October of 1999. The system is currently installed on all CDER PCs and is used by our reviewers to communicate with over 15 companies and more than 150 individuals in those companies. The system also provides virus scanning and extensive E-mail filtering capabilities. The Secure Electronic Mail System, ensures that all e-mail sent by CDER employees to regulated industry, and all mail

received from regulated industry members who possess secure mail capabilities is encrypted. It is vital that we protect the security of our e-mail system to the fullest extent possible. Terrorists may attempt to intercept drug approval or other forms of sensitive information transmitted to and from industry. This information can then be used by potential terrorists groups to plan attacks on the American public or sabotage our nations drug supplies. The implementation of encryption software/hardware such as Secured Mail, ensures the safety and security of CDER's important IT resources and data.

ICH M2. FDA is involved in several standards-related projects that impact the format and content of regulatory submissions. FDA plays an active role in the development of standards and guidelines as issued by organizations such as the National Institute of Standards and Technology (NIST), the International Organization for Standardization (ISO), and the US Pharmacopeia.

A major standards development activity in which the Agency actively participates is the International Conference on Harmonization (ICH), a collaborative effort involving the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in those three regions. The purpose of ICH is to recommend ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements to curtail regulatory duplication by working towards a common worldwide drug and biologic registration package.

The activities within the ERSR program are influenced most by the ICH M2 Expert Working Group (EWG) which focuses on Electronic Standards for Transmission of Regulatory Information. The goal of M2 is to identify, evaluate, and recommend appropriate and relevant standards to facilitate the electronic transfer of regulatory information between industry authorities and among regulatory

agencies. The FDA representative from CDER serves as the Rapporteur for the M2 EWG and the FDA's representatives from CBER and OIRM are deputy topic leaders. The M2 EWG maintains a series of recommendations for facilitating electronic communications, including recommendations for physical media, networking, secure EDI transmission over the Internet, and electronic document format. FDA is also active in the ICH M4 EWG, which focuses on the Common Technical Document (CTD) for the technical content of sections of the NDA.

Throughout the remainder of the PDUFA II period, CBER , CDER and OIRM will continue to play active roles in the standards development activities of the ICH and other standards organizations and these standards will be implemented, where appropriate, within the ERSR Program.

4. Efforts to Identify Duplication

FDA is the only agency that requires the filing of an application for the marketing of diagnostic radiopharmaceuticals for human use. No other component of the agency or other government agencies require similar information or data to be filed. The information to be submitted under the regulations is not available from any other source.

5. Involvement of Small Entities

FDA requires the equal application of its regulations to all enterprises. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help to small businesses. CDER's Office of Communications, Training, and Manufacturers Assistance provides assistance to small businesses subject to FDA's regulatory requirements.

6. Consequences if Information Collected Less Frequently

Manufacturers submit applications for approval of a diagnostic radiopharmaceutical to obtain permission to market the product in

interstate commerce. Less frequent collection of information or other methods of reducing the frequency of information would not provide the information needed by FDA to properly evaluate the safety and effectiveness of a diagnostic radiopharmaceutical or a new indication for use of an approved diagnostic radiopharmaceutical.

7. Consistency with the Guidelines in 5 CFR 1320.5

An applicant may be required to submit to FDA proprietary trade secrets or other confidential information when submitting a license application or supplement. FDA has instituted security measures to protect confidential information received from manufacturers and will, to the extent permitted by law, protect this information.

8. Consultation Outside the Agency

In the Federal Register of May 22, 1998, FDA published the proposed rule that preceded the promulgation of 21 CFR 315.4, 315.5, 315.6 and provided a comment period for the public on the information collection provisions. None of the manufacturers of diagnostic radiopharmaceuticals who submitted comments on the proposed rule questioned the need for submission of information to demonstrate the safety and effectiveness of a product to obtain marketing approval. Rather, their comments primarily sought clarification or proposed minor modification of the proposed regulations. These comments were addressed in the preamble of the final rule. In the Federal Register of March 14, 2002 (67 FR 11512), FDA published a notice requesting comment on this information collection. No comments were received.

9. Remuneration of Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality

The confidentiality of the information received by FDA under the final rule would be consistent with the Freedom of Information Act and the agency's regulations under 21 CFR Part 20. Manufacturers seeking to market a diagnostic radiopharmaceutical or a new indication for use

for an approved diagnostic radiopharmaceutical might be required to reveal proprietary information or trade secrets to gain FDA approval of the product or new indication. However, such information is deleted from the application before it is released under the Freedom of Information Act and FDA regulations.

11. Questions of a Sensitive Nature

Questions of a sensitive nature are not applicable to this information collection.

12. Estimates of Annualized Hour Burden to Respondents

Based on the number of submissions (that is, human drug applications and/or new indication supplements for diagnostic radiopharmaceuticals) that FDA received during FY 2000 and 2001, FDA estimates that it will receive approximately 2 submissions annually from 2 applicants. The hours per response refers to the estimated number of hours that an applicant would spend preparing the information required by the regulations. Based on FDA's experience, the agency estimates the time needed to prepare a complete application for a diagnostic radiopharmaceutical is approximately 10,000 hours, roughly one-fifth of which, or 2,000 hours, is estimated to be spent preparing the portions of the application that would be affected by these regulations. The regulation does not impose any additional reporting burden for safety and effectiveness information on diagnostic radiopharmaceuticals beyond the estimated burden of 2,000 hours because safety and effectiveness information is already required by 314.50 (collection of information approved by OMB until March 31, 2005, under OMB Control Number 0910-0001). In fact, clarification in these regulations of FDA's standards for evaluation of diagnostic radiopharmaceuticals is intended to streamline overall information collection burdens, particularly for diagnostic radiopharmaceuticals that may have well-established, low-risk safety profiles, by enabling manufacturers to tailor information submissions and avoid unnecessary clinical studies. The table below contains estimates of the annual

reporting burden for the preparation of the safety and effectiveness sections of an application that are imposed by existing regulations. The burden totals do not include an increase in burden. This estimate does not include the actual time needed to conduct studies and trials or other research from which the reported information is obtained.

Estimated Annual Reporting Burden

21 CFR Section	Number of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
315.4, 315.5, and 315.6	2	1	2	2,000	4,000
TOTAL					4,000

13. Estimates of Annualized Cost Burden to Respondents

The estimated annual cost to respondents is \$498,400.00.

Activity	Hours	Cost per hour	Total Cost
Reporting	4,000	\$31.15	\$124,600

FDA estimates that it should require an average of 2,000 hours of staff time per applicant to organize and submit the required safety and effectiveness information portions of a new application or supplement to an approved application. The estimate is based on a regulatory affairs specialist, at a pay rate of \$31.15/hour, who is responsible for preparing the safety and effectiveness portions of an application or supplement. The salary estimates include benefits but no overhead costs.

14. Estimates of Annualized Cost Burden to the Government

An estimate of the total cost to the Federal government associated with the review of NDAs and supplemental applications is provided in the table below. The estimate is based on full-time equivalents (FTEs) associated with the review of applications and supplements to applications and the average annual salaries for CDER reviewers. The amount of time and expense incurred by the government is due to the review of all material submitted with an application. This information is essential to determine the safety and effectiveness of products as required by FDA's mission to protect the public health. This information may include clinical data, safety updates, samples submitted for evaluation by the agency, case report tabulations, case report forms, and patient information.

Applications ¹	Number of FTEs	Average Annual Reviewer Salary	Total Cost
NDA	14	\$70,834.00	\$991,676.00

1 Includes original applications and supplements to approved applications.

15. Changes in Burden

Change in burden is a result of fewer submissions.

16. Time Schedule, Publication, and Analysis Plans

There are no tabulated results to publish for this information collection.

17. Exemption for Display of Expiration Date

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Certifications

There are no exceptions to Item 19 of OMB Form 83-I.