

Docket Number 00N-1224

OMB Control Number: 0910-0445

SUPPORTING STATEMENT

Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Holds

A. Justification

1. Circumstances of Information Collection

This information collection approval request is for a Food and Drug Administration (FDA) guidance for industry entitled "Submitting and Reviewing Complete Responses to Clinical Holds."

The guidance describes how to submit a complete response if an investigational new drug (IND) application is placed on clinical hold by FDA.

Section 117 of the Food and Drug Administration Modernization Act (Pub. L. 105-115), signed into law by the President on November 21, 1997, provides that a written request to FDA from the applicant of an investigation that a clinical hold be removed shall receive a decision in writing, specifying the reasons for that decision, within 30 days after receipt of such request. A clinical hold is an order issued by FDA to the applicant to delay a proposed clinical investigation or to suspend an ongoing investigation. An applicant may respond to a clinical hold.

Under section 505(i)(3)(C) of the Federal Food, Drug, and Cosmetic Act, any written request to FDA from the sponsor of an investigation that a clinical hold be removed must receive a decision, in writing and specifying the reasons, within 30 days after receipt of the request. The request must include sufficient information to support the removal of the clinical hold.

In the Federal Register of May 14, 1998 (63 FR 26809), FDA

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published a notice of availability of a guidance that described how applicants should submit responses to clinical holds so that they may be identified as complete responses and the agency can track the time to respond. FDA is now issuing a revised guidance.

The revised guidance states that FDA will respond in writing within 30-calendar days of receipt of a sponsor's request to release a clinical hold and a complete response to the issue(s) that led to the clinical hold. An applicant's complete response to an IND clinical hold is a response in which all clinical hold issues identified in the clinical hold letter have been addressed.

The guidance requests that applicants type in large, bold letters at the top of the cover letter of the complete response "Clinical Hold Complete Response" to expedite review of the response. The guidance also requests that applicants submit the complete response letter in triplicate to the IND, and that they fax a copy of the cover letter to the FDA contact listed in the clinical hold letter who is responsible for the IND. The guidance requests more than an original and 2 copies of the cover letter in order to ensure that the submission is received and handled in a timely manner.

2. Purpose and Use of Information

The guidance describes how to submit a complete response if an IND is placed on clinical hold by FDA. The revised guidance states that FDA will respond in writing within 30-calendar days of receipt of a sponsor's request to release a clinical hold and a complete response to the issue(s) that led to the clinical hold. An applicant's complete response to an IND clinical hold is a response in which all clinical hold issues identified in the clinical hold letter have been addressed.

3. Use of Improved Information Technology

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.

In September 1997, FDA published the Guidance for Industry on "Archiving Submissions in Electronic Format -- NDAs." This guidance provided for the receipt and archive of electronic Case Report Forms (CRF) and Case Report Tabulations (CRT) without an accompanying paper copy. In FY 1998, the agency established an Electronic Document Room (EDR) to manage the receipt and handling of all electronic submissions. In January 1999, FDA published the Guidance for Industry on "Providing Regulatory Submissions in Electronic Format - NDAs." This guidance document covers the full NDA and is not limited to CRTs and CRFs. Approximately 40% of original NDAs now include guidance-compliant electronic submissions (i.e., submissions for archive). Out of 86 original NDAs received since January 1999, 36 included electronic components and 9 were full electronic NDAs. The agency also received 43 electronic NDA supplements. Out of 6,978 NDA amendments, supplements, and amendments to supplements, 100 were electronic.

Secure E-Mail - During a drug's development cycle, communications between FDA's 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. 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. In 1998, CDER conducted 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 began testing WorldSecure Server in late 1998. A pilot system was put into place in January 1999. After the pilot's run, the production system's requirements were developed from the pilot's requirements and new information gathered from the pilot results. The design for a production system was based on these requirements. CDER recently installed a production system and additional firms are being given secure E-mail accounts.

ICH M2 - The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use was formed to minimize waste in the discovery, development, regulation, manufacture, marketing, and use of human therapeutic products worldwide. The regulatory authorities of Europe, Japan, and the United States joined with their respective pharmaceutical trade associations in an agreement to take action on harmonization by participating in the ICH.

The ICH Multi-disciplinary Group 2 (M2) Expert Working Group (EWG) was established to determine electronic standards and provide solutions to facilitate international electronic communication in the three ICH regions. The first effort of the M2 EWG was to establish a series of recommendations that would form the basis for standardized electronic communication in each of the three regions. These recommendations included physical media formats, secure communications, and structured data formats. Building on these standards, the EWG then began work on a detailed specification for the secure, electronic transmission of individual case safety reports (adverse event reports). The

specification is intended to support transmission between industry partners, industry and regulatory authorities and between regulatory authorities in all three regions. The production of a specification for an electronic common technical document (CTD) was the next major effort assigned to the M2 EWG. The ICH steering committee agreed in March 1999 that this effort should be undertaken by the M2 EWG in cooperation with the subject matter expert working groups for each section of the CTD. The CTD working groups are charged with harmonizing the format and content of the application documents for new product applications. The resulting ICH guidances, when implemented, will change the content and format of NDA submissions to the FDA. The M2 specification will define the nature of an electronic submission for CTD submissions and could have a major impact on the way electronic submissions are received, archived, and reviewed.

4. Efforts to Identify Duplication

The information collection requested under the guidance does not duplicate any other information collection.

5. Involvement of Small Entities

Although new drug development is typically an activity completed by large multinational drug firms, the information collection requested under the guidance applies to small as well as large companies. Under the Regulatory Flexibility Act, FDA regularly analyzes regulatory options that would minimize any significant impact on small entities. FDA also assists small businesses in complying with regulatory requirements.

6. Consequences If Information Collected Less Frequently

As explained above, a clinical hold is an order issued by

FDA to the applicant to delay a proposed clinical investigation or to suspend an ongoing investigation. An applicant may respond to a clinical hold. The guidance describes how to submit a complete response if an IND is placed on clinical hold by FDA.

7. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

There is no inconsistency with the guidelines.

8. Consultation Outside the Agency

In the Federal Register of May 14, 1998 (63 FR 26809), FDA published a notice of availability of a guidance that described how applicants should submit responses to clinical holds so that they may be identified as complete responses and the agency can track the time to respond. After considering the comment received on that guidance, FDA is issuing a revised guidance.

9. Remuneration of Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under this guidance.

10. Assurance of Confidentiality

Confidentiality of the information submitted under this guidance is protected under 21 CFR 314.430 and under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the Act.

11. Questions of a Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden

Based on data concerning the number of complete responses to

clinical holds received by the Center for Drug Evaluation and Research (CDER) from July 1, 1998, to June 30, 1999, CDER estimates that approximately 48 responses are submitted annually from approximately 43 applicants, and that it takes approximately 284 hours to prepare and submit to CDER each response.

Based on data concerning the number of complete responses to clinical holds received by the Center for Biologics Evaluation and Research (CBER) in fiscal year 1999, CBER estimates that approximately 134 responses are submitted annually from approximately 110 applicants, and that it takes approximately 284 hours to prepare and submit to CBER each response.

Estimated Annual Reporting Burden

Complete Responses to Clinical Holds	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
CDER	43	approx. 1	48	284	13,632
CBER	110	approx. 1	134	284	38,056
TOTAL					51,688

There are no capital costs or operating and maintenance costs associated with this collection of information

13. Estimates of Annualized Cost Burden to Respondents

FDA's Economics Staff estimates an average industry wage rate of \$50.00 per hour for preparing and submitting the information requested under the guidance. This figure is an average of the following wage rates (based on the percentage of time required for each type of employee): Upper management at \$70.00 per hour; middle management at \$35.00 per hour; and clerical assistance at \$23.00 per hour. Using the averaged wage rate of \$50.00 per hour, and multiplied times the total hour burden estimated above, the total cost burden to respondents is \$2,584,400.

14. Estimates of Annualized Cost Burden to the Government

FDA estimates that there will be no additional costs associated with the receipt/review by FDA of the information submitted under the guidance. The guidance reflects current requirements in 21 CFR 312.42(e) which was amended in the Federal Register of December 14, 1998 (63 FR 68676), to include this 30-day response requirement.

15. Changes In Burden

This is a new approval request.

16. Time Schedule, Publication, and Analysis Plans

There are no publications.

17. Displaying of OMB Expiration Date

The agency is not seeking to display the expiration date for OMB approval of the information collection.

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement identified in Item 19, "Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.

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