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 for a drug or biologic. 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 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 issued a revised guidance in October 2000 which 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 AClinical Hold Complete Response@ in large, bold letters at the top of the cover letter of the 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 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

As mentioned, the guidance requests that applicants type in large, bold letters at the top of the cover letter of the complete response AClinical 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.

The following guidances for industry are among those that have been developed to improve the use of information technology in the submission of INDs and NDAs for human drugs and related reports:

- "Providing Regulatory Submissions in Electronic Format--NDAs" (January 28, 1999). This guidance provides information on how to submit a complete archival copy of an NDA in electronic format and applies to the submission of original NDAs as well as to the submission of supplements and amendments to NDAs.
- "Providing Regulatory Submissions in Electronic Format--General Considerations" (January 28, 1999). This guidance includes a description of the types of electronic file formats that the agency is able to accept to process, review, and archive electronic documents. The guidance also states that documents submitted in electronic format should enable the user to: (1) Easily view a clear and legible copy of the information; (2) print each document page by page while maintaining fonts, special orientations, table formats, and page numbers; and (3)

copy text and images electronically into common word processing documents.

- “Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format” (November 12, 1999). This guidance provides information to assist applicants in submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license application (ELA).
- "Providing Regulatory Submissions in Electronic Format-—Prescription Drug Advertising and Promotional Labeling" (January 31, 2001). This draft guidance discusses issues related to the electronic submission of advertising and promotional labeling materials for prescription drug and biological products.
- "Providing Regulatory Submissions in Electronic Format-—ANDAs" (June 27, 2002). This guidance discusses issues related to the electronic submission of ANDAs and supplements and amendments to those applications.
- "Providing Regulatory Submissions in Electronic Format-—Annual reports for NDAs and ANDAs" (August 2003). This guidance discusses issues related to the electronic submission of annual reports for NDAs and ANDAs.
- "Providing Regulatory Submissions in Electronic Format-—Postmarketing Periodic Adverse Drug Experience Reports" (June

2003). This guidance discusses general issues related the electronic submission of postmarketing periodic adverse drug experience reports for NDAs, ANDAs, and BLAs.

- "Providing Regulatory Submissions in Electronic Format-—Human Pharmaceutical Product Applications and Related Submissions" (August, 2003). This draft guidance discusses issues related to the electronic submission of ANDAs, BLAs, INDs, NDAs, master files, advertising material, and promotional material.
- "Providing Regulatory Submissions in Electronic Format-—General Considerations" (October 2003). This draft guidance discusses general issues common to all types of electronic regulatory submissions.
- "Providing Regulatory Submissions in Electronic Format-—Content of Labeling" (February 2004). This draft guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biological products.

These guidance documents are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm.

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 25, 2006 (71 FR 30142), FDA published a notice requesting comment on this information

collection. No comments were received pertaining to the information collection.

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 312.130 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) in 2004 and 2005, CDER estimates that approximately 88 responses are submitted annually from approximately 67 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 2004 and 2005, CBER estimates that approximately 92 responses are submitted annually from approximately 60 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	67	.76	88	284	24,992
CBER	60	1.53	92	284	26,128
Total					51,120

There are no capital cost 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 $ 2,556,000.

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

The change in burden estimates (from 46,576 hours to 51,120 hours) is based on more recent data reflecting the number of receipts.

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.

PAPERWORK REDUCTION ACT SUBMISSION

Please read the instructions before completing this form. For additional forms or assistance in completing this form, contact your agency's Paperwork Clearance Officer. Send two copies of this form, the collection instrument to be reviewed, the supporting statement, and any additional documentation to: Office of Information and Regulatory Affairs, Office of Management and Budget, Docket Library, Room 10102, 725 17th Street NW, Washington, DC 20503.

1. Agency/Subagency originating request FDA	2. OMB control number b. [x] None a. 0910 - 0445___
3. Type of information collection (*check one*) a. [ ] New Collection b. [ ] Revision of a currently approved collection c. [x] Extension of a currently approved collection d. [ ] Reinstatement, without change, of a previously approved collection for which approval has expired e. [ ] Reinstatement, with change, of a previously approved collection for which approval has expired f. [ ] Existing collection in use without an OMB control number For b-f, note Item A2 of Supporting Statement instructions	4. Type of review requested (*check one*) a. [x] Regular submission b. [ ] Emergency - Approval requested by at close of comment period c. [ ] Delegated 5. Small entities Will this information collection have a significant economic impact on a substantial number of small entities? [ ] Yes [x] No 6. Requested expiration date a. [X] Three years from approval date b. [ ] Other Specify:____/_
7. Title Submitting and Reviewing Complete Responses to Clinical Holds; Guidance for Industry	
8. Agency form number(s) (*if applicable*)	
9. Keywords sponsors, drugs. clinical investigation	
10. Abstract Guidance to assist sponsors in submitting responses to clinical holds so that they may be identified as complete responses and the agency can track the time to respond.	

11. Affected public (*Mark primary with "P" and all others that apply with "x")* a. ___ Individuals or households b. _x__ Business or other for-profit c. ___ Not-for-profit institutions d. ___ Farms e. ___ Federal Government f. ___ State, Local or Tribal Government	12. Obligation to respond (*check one*) a. [x] Voluntary- (guidance document) b. [ ] Required to obtain or retain benefits c. [ ] Mandatory
13. Annual recordkeeping and reporting burden a. Number of respondents - _____ b. Total annual responses - _ 1. Percentage of these responses collected electronically - none c. Total annual hours requested - 51,120_ d. Current OMB inventory - 46,576_____ e. Difference 4,544 _____ f. Explanation of difference 1. Program change _____ 2. Adjustment - Change in recent submission data _____	14. Annual reporting and recordkeeping cost burden *(in thousands of dollars)* a. Total annualized capital/startup costs ___0_____ b. Total annual costs (O&M) ___0_____ c. Total annualized cost requested ___0_____ d. Current OMB inventory ___0_____ e. Difference ___0_____ f. Explanation of difference 1. Program change _____ 2. Adjustment _____
15. Purpose of information collection (*Mark primary with "P" and all others that apply with "X"*) a. __ Application for benefits b. __ Program evaluation c. __ General purpose statistics d. __ Audit e.__ Program planning or management f.__ Research g. x Regulatory or compliance	16. Frequency of recordkeeping or reporting *(check all that apply)* a. [ ] Recordkeeping b. [ ] Third party disclosure c. [x] Reporting 1. [x] On occasion 2. [ ] Weekly 3. [ ] Monthly 4. [ ] Quarterly 5. [ ] Semi-annually 6. [ ] Annually 7. [ ] Biennially 8. [ ] Other (describe) _____
17. Statistical methods Does this information collection employ statistical methods [ ] Yes [x] No	18. Agency Contact (person who can best answer questions regarding the content of this submission) Name: Karen Nelson Phone: 827-1482