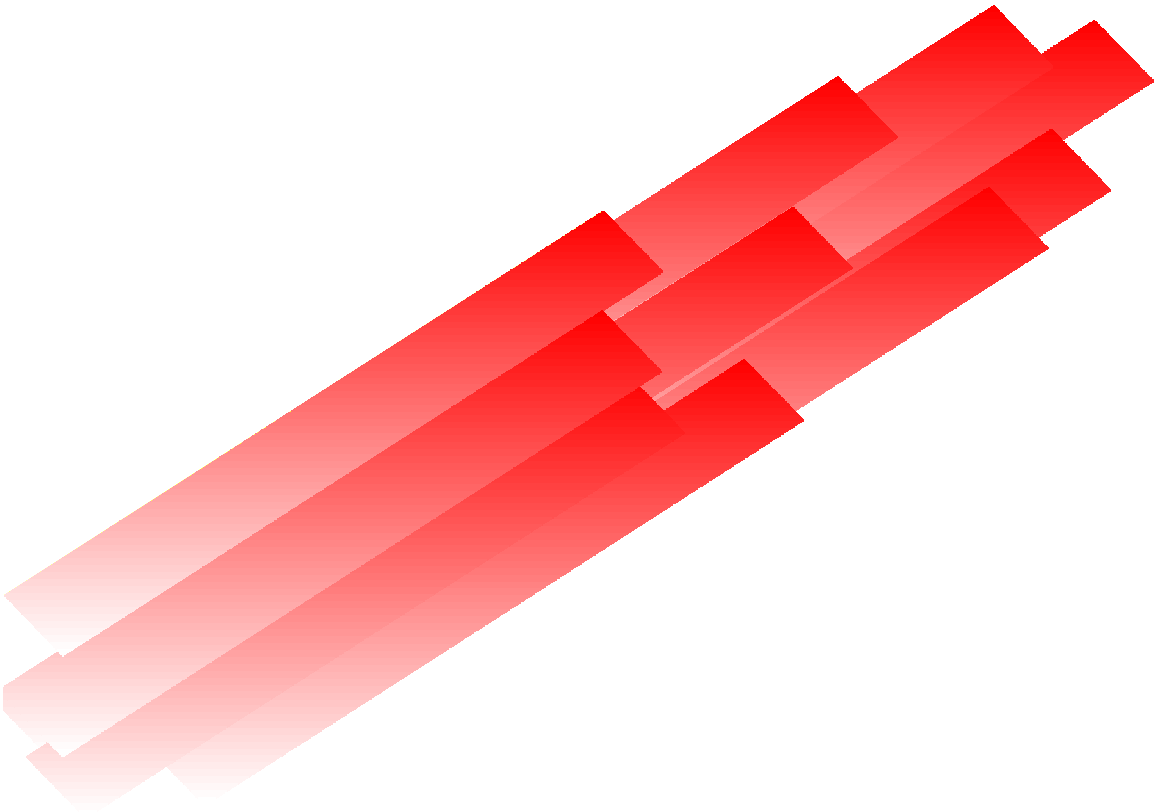
Guidance for Industry

Submitting and Reviewing Complete Responses to Clinical Holds



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Comments and suggestions regarding this document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the guidance. All comments should be identified with the docket number provided at the beginning of the notice. Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

After the comment period closes, comments should be provided in writing to the Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857; or Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, Md. 20852-1448.

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The Drug Information Branch (HFD-210),Center for Drug Evaluation and Research (CDER),
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Submitting and Reviewing Complete Responses to Clinical Holds

I. INTRODUCTION

Under the Food and Drug Administration (FDA) regulations, an investigational new drug application (IND) is either allowed to proceed or placed on clinical hold (21 CFR 312.42). A clinical hold is an order issued by the FDA to the applicant to delay a proposed clinical investigation or to suspend an ongoing investigation. A clinical hold may be either a *complete clinical hold* or a *partial clinical hold*. An applicant may then respond to the clinical hold. Once the applicant has submitted a complete response to the clinical hold, the Agency must evaluate the response and decide whether to lift the hold.

Section 117 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act) provides that "Any written request to the Secretary from the applicant of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor [sic], within 30 days after receipt of such request." In addition, in conjunction with the reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA), the Agency committed to user fee performance goals incorporating the same response time. In her letter to Congress regarding reauthorization of PDUFA, the Secretary of Health and Human Services committed the Agency to respond to an applicant's complete response to a clinical hold within 30 calendar days of the Agency's receipt of the applicant's complete response. Beginning in fiscal year (FY) 1998, the Agency has committed to respond to at least 75 percent of complete responses within 30 calendar days of receipt of the complete response. In FYs 1999-2002, the Agency will respond to at least 90 percent of the complete responses within 30 calendar days of receipt of the complete response.

The purpose of this guidance document is to describe 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 response.

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[1] This guidance has been prepared by the Review Management Working Group comprising individuals from the Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on submissions of responses to clinical holds. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

II. DEFINITIONS

Clinical Hold: An order issued by FDA to the applicant of an IND to delay a proposed clinical investigation or to suspend an ongoing clinical investigation. A clinical hold can be either a *complete clinical hold* or a *partial clinical hold*.

- **Complete Clinical Hold**. A delay or suspension of all clinical work requested under an IND. If a sponsor submits an initial IND and within the first 30-day period FDA and the sponsor agree on an alternative protocol that is allowed to proceed, this does not constitute a clinical hold provided there are no specific FDA contingencies that require FDA review/approval before further studies are started.

- **Partial Clinical Hold:** A delay or suspension of only part of the clinical work requested under the IND (e.g., a specific protocol or part of a protocol is not allowed to proceed; however, other protocols or parts of the protocol are allowed to proceed under the IND). If FDA requires that progress to the next study is contingent (1) on FDA review of additional data and (2) subsequent specific permission for the study to proceed, this represents a partial clinical hold. On the other hand, if the sponsor does not need to wait for FDA review ***and*** authorization to proceed before initiating a new protocol, then this is not a partial hold, even if additional data have been requested.

Applicant's Complete Response to an IND Clinical Hold: A response from the applicant in which all clinical hold issues identified in the clinical hold letter have been addressed.

Agency's Response to an Applicant's Complete Response: A letter to the applicant from the Agency in response to an applicant's complete response in which the applicant (1) is allowed to proceed under the IND as proposed by the applicant (i.e., the clinical hold is lifted), (2) is allowed to proceed with specific restrictions not proposed by the applicant (i.e., a partial hold), or (3) is informed that studies under the IND may still not proceed. In the latter two cases, the letter will set forth why the clinical hold is being maintained. This letter should be issued to the applicant within 30 calendar days of receipt of the applicant's complete response.

30-day Response Clock: The FDA is required by the Modernization Act to respond in writing to the applicant within 30 calendar days after receipt of the applicant's complete response to a clinical hold.

III. POLICIES AND PROCEDURES

A. The Agency's letter to an applicant placing an IND on clinical hold will state that the 30-day response clock will not begin until a complete response to the clinical hold is submitted by the IND applicant.

B. Applicants should ensure that their complete responses to clinical holds contain no material related to issues other than the IND clinical hold. Responses to non-hold issues that the applicant wishes to communicate to FDA should be submitted in a separate amendment.

C. To facilitate the timely review of a clinical hold response, it is recommended that the applicant send the response by a method that ensures the applicant that it has been received by the appropriate FDA document room. A copy of the cover letter should be faxed to the FDA contact responsible for the IND. The responsible FDA contact will be identified in the clinical hold letter.

D. When the applicant believes it has responded to all issues raised in a clinical hold letter (i.e., that a complete response has been submitted to the Agency), it should be so stated in the cover letter to the IND submission.

E. The applicant should clearly state in large, bold type at the top of the cover sheet of the complete response: **IND CLINICAL HOLD COMPLETE RESPONSE**.

F. If the applicant has designated a response to be a complete response, but FDA does not believe it is a complete response, FDA will inform the applicant, by phone or other means of rapid communication, that until FDA receives a complete response to the clinical hold, the 30-day clock will not start.

G. Within 30 calendar days after the receipt of a complete response to a clinical hold, the FDA will respond in writing, indicating whether the hold is lifted and, if not, specifying the reasons why not.

H. After an IND has been placed on clinical hold, until the applicant has received a communication (via phone, fax, letter, e-mail) from the Agency allowing the study to proceed, the study may not be initiated (21 CFR 312.42(e)). Such communication, if other than by original letter, will be followed by an original letter.

I. If the review team believes that it will not meet the 30-day deadline, the Agency will telephone the applicant and discuss the review progress to date and what is being done to facilitate completion of the review.