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# Manual of Standard Operating Procedures and Policies

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## Investigational New Drugs

### Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications

SOPP 8201

Version #3

April 27, 1999

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#### 1. Purpose

Provides guidance to CBER staff on the procedures to be used for placing a study or studies submitted as part of an Investigational New Drug Application (IND) on clinical hold and for removing or maintaining the hold once a complete response has been received from the sponsor.

#### 2. Background

Title 21 of the *Code of Federal Regulations*

(21 CFR) Section 312.42 describes a clinical hold as an "order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation." This order can apply to one or more of the studies covered by an IND. Among the grounds listed for imposing a clinical hold are that subjects would be exposed to unreasonable and significant risk; the investigator brochure is misleading, erroneous, or incomplete; the clinical investigators are not qualified; or the IND does not contain sufficient information to assess the risks to subjects of the proposed studies. For Phase 2 or 3 trials a plan or protocol that is clearly deficient in design to meet its stated objectives is also a reason for placing a study on hold. An IND submitted under 21 CFR 50.24, involving a waiver from informed consent, may be placed on clinical hold if the sponsor fails to satisfy or submit the criteria under that section.

21 CFR Part 312.42 (d) allows that the hold may be relayed to the sponsor by phone or other rapid means of communication and that no more than 30 days following the IND being placed on hold, a written explanation of the basis of the hold is to be provided to the sponsor.

The FDA Modernization Act of 1997 states that a sponsor's request to remove a clinical hold will be reviewed and a response will be issued in writing within 30 days of the receipt of the request.

#### 3. Policy

It is the policy of CBER that a written explanation will be provided to a sponsor whose study or studies have been placed on clinical hold as soon as possible after notification of the hold by phone or other method of rapid communication, but no later than the 30 day time limit specified in 21 CFR 312.42(d).

It is also the policy of CBER that a complete response from the sponsor to clinical hold issues will be reviewed and a decision as to whether the study or studies may or may not proceed will be made within 30 days of receipt of the complete response. The decision will also be relayed to the sponsor, in writing, within this 30 days.

#### 4. Definitions

##### **CLINICAL HOLD**

An order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing clinical investigation.

##### **COMPLETE CLINICAL HOLD**

A delay or suspension of all clinical work requested under the 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, the IND will not be considered to have been on 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 is not allowed to proceed; however, other protocols are allowed to proceed under the IND,). If only part of a protocol is allowed to proceed, with progress to the next part contingent upon FDA review/approval of additional data, this is also a partial hold. In contrast, if the Agency has told a sponsor that the sponsor needs to review results of a clinical study (or pre-clinical data) before proceeding, there is no clinical hold.

##### **SPONSOR'S COMPLETE RESPONSE TO AN IND CLINICAL HOLD**

A response in which all issues which were the basis for the clinical hold have been addressed, whether adequately or not.

##### **RESPONSE TO A SPONSOR'S COMPLETE RESPONSE**

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

##### **THIRTY DAY RESPONSE CLOCK**

FDA is required under the modernization act to respond in writing to the sponsor's complete response to a clinical hold within thirty days of receipt of the response.

##### **BIOLOGICS IND MANAGEMENT SYSTEM (BIMS) CODES**

BIMS is the computer system used to track and manage IND submissions. The system is dependent on the proper assignment of codes for the identification of type and status of submissions and correspondence. The codes used in the system pertinent to this SOP are listed below.

##### ***IND Status***

##### **Hold**

*No*

clinical studies under the IND (21 CFR 312.42) or IDE (21 CFR 812.30) are allowed to proceed. IDE applications use "disapproval" or "withdrawal of approval".

Change of status from Pending or In Effect should be based on a telephone call date (documented with a memorandum), or if no call is made, on a clinical hold letter issuance.

**Pt Hold (Partial Hold)**

One or more studies under the IND (or IDE) are allowed to proceed while one or more other studies are on hold. Also includes situations where a study may have substantial restrictions imposed pending resolution of safety or design issues. Examples include instances in which two different protocols are submitted to an IND, and one is approved but the other is placed on clinical hold, or for a single protocol, the investigation may go forward with restrictions proposed by the Agency and further progress of the protocol may not occur until additional data have been submitted and reviewed by FDA.

Change of status from Pending, or In Effect should be based on a telephone call date (documented with a memorandum) or if no call is made, on a partial clinical hold letter issuance. Change of status from Hold should be based on a letter issuance. This letter type will receive both the RH and PH codes (see below).

***Amendment type*****Response to Clinical Hold**

Amendments to INDs that are identified by the sponsor as being in response to a clinical hold telephone call or letter. There are 4 subtypes.

**Unknown**

The sponsor does not indicate whether or not this is a complete response to the clinical hold issues. This is the default subtype for the system and should be changed as soon as the type is identified.

**Complete**

The sponsor identifies the response as complete and we concur.

**Incomplete**

The sponsor identifies the response as complete and we do not concur.

**Partial**

The sponsor identifies the response as not complete. There is no time frame for review of these as individual amendments, although the 30 day clock will start when the amendment that completes the response to the clinical hold is received.

***Letter types*****HO Clinical Hold**

Notification that *all* studies under the IND have been placed on clinical hold and may not resume until FDA so informs the sponsor (312.42). In almost all cases, the sponsor has already been notified of the clinical hold by telephone.

**PH Partial Hold**

Notification that the IND has been placed on partial hold. The letter identifies the extent to which studies may proceed and the restrictions on further progress of the IND. In almost all cases the sponsor has already been notified of the partial hold by telephone.

**HC Continue Clinical Hold**

Notification that the existing hold has not been lifted.

**HR Clinical Hold/Remove Hold**

The sponsor is notified that the IND had been placed on hold, but the hold had been removed. Details of the reasons for the hold are included. This occurs when the sponsor has responded to the hold before a hold letter was issued.

### **RH Remove Hold**

FDA notification that *all* studies under the IND placed on clinical hold may resume (312.42).

### **RP Remove Hold/Partial**

FDA notification that studies under the IND placed on partial clinical hold may begin or resume.

### ***Telecon categories***

#### **HO Hold**

Notification that *all* studies under the IND have been placed on clinical hold and may not resume until FDA so informs the sponsor (312.42).

#### **PH Partial Hold**

Notification that one or more, but not all, studies under the IND have been placed on clinical hold and may not resume until FDA so informs the sponsor (312.42), or substantial restriction has been placed on a study, e.g., the next stage may not begin until certain conditions are met.

#### **RH Remove Hold**

FDA notification that *all* studies under the IND placed on clinical hold may resume (312.42).

#### **RP Remove Hold/Partial (RP)**

FDA notification that studies under the IND placed on partial clinical hold may begin or resume

## **5. Procedures**

- If issues are identified that may justify imposition of a clinical hold, appropriate individuals in the office with product responsibility should attempt to discuss and satisfactorily resolve the matter before issuing the clinical hold order, as required by 21 CFR 312.42(c). However, any study that is not allowed to proceed must be placed on clinical hold.
- A decision whether or not to place an IND on hold or allow it to proceed will be made by the appropriate individuals in the Office with product responsibility within 30 days of its receipt.
- The sponsor will be notified of a decision to place the study or studies on clinical hold, by phone or other method of rapid communication. This notification will be documented in writing for the file and the status of the IND in the Biologics IND Management System (BIMS) will be updated.
- A letter containing a written explanation of the basis for the hold will be prepared and sent to the sponsor as soon as possible, but no later than 30 calendar days after this notification.
- Additional review comments may also be contained in the hold explanation letter if they are clearly designated as separate issues and are available within the 30 day timeframe so as not to delay the issuance of the hold explanation.
- Further review comments not available at the time the written explanation of the basis for the clinical hold is sent can follow in an information request letter at a later date. In this case the following statement should be included in the clinical hold explanation letter.

"Additional comments and questions on your IND studies and/or product which are not a basis for clinical hold but which should be addressed, will be sent to you in a separate letter."

- A submission to an IND that is identified by the sponsor as a response to a clinical hold, but does not indicate whether the response is complete or partial, should be quickly evaluated to determine its proper category.
  - If it is determined that the response is not complete it should be identified in BIMS as a partial response and reviewed as resources permit.
  - If it is identified as a complete response it should be identified in BIMS as a complete response and reviewed according to the procedures outlined below.
- A submission to an IND that is identified by the sponsor as a complete response to a clinical hold will be evaluated immediately.
  - If it is determined that the submission is not a complete response to the clinical hold issues, the Agency contact for that IND will, as soon as possible and no later than 30 days after receipt of the response, inform the sponsor by telephone or other means of rapid communication that the 30 day clock will not start until a complete response is received. The proper BIMS code will be entered into the system for that submission.
  - If the submission is a complete response, the proper BIMS code will be entered into the system for that submission. The complete response will be reviewed. A decision whether or not to allow the study to proceed will be made and relayed to the sponsor, in writing, within 30 days of receipt of the complete response. If the decision is to maintain the clinical hold, the remaining issues will be identified in the letter. The status of the IND in BIMS will be updated when the letter is issued.
- Responses to non-hold items submitted in the same amendment as the complete response to the clinical hold, need not be reviewed within 30 days of receipt of that amendment.
- Further complete responses to clinical hold issues will be processed as above.

## 6. Effective Date

April 27, 1999

## 7. History

Written/Revised	Approved	Approval Date	Version Number	Comment
RMCC	R. Devine	April 27, 1999	3	Incorporates changes resulting from comments to the Guidance to Industry - Submitting and Reviewing Complete Responses to Clinical Holds. Replaces version 2, issued 4/14/1998
RMCC (Review Management Coordinating Committee)	R. Devine	April 14, 1998	2	Updates the content to conform with FDA Modernization act of 1997
Applications Policy Task Force	R. Devine	August 20, 1996	1	First Issuance

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