SOPP 8201: Administrative Processing of Clinical Holds for Investigational New Drug Applications

Version #4

Effective Date: May 19, 2014

I. Purpose

The purpose of this Standard Operating Policy and Procedure (SOPP) is to provide guidance to the Center for Biologics Evaluation and Research (CBER) staff on the policies and procedures 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 is received from the sponsor.

II. Scope

This SOPP applies to INDs regulated by CBER. It does not apply to Investigational Device Exemptions (IDEs) regulated by CBER.

III. Background

Title 21 of the Code of Federal Regulations (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. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug or tested using the investigational biological *in vitro* diagnostic (IVD) product. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

IV. Definitions

A. Biologics Investigational and Related Applications Management Systems (BIRAMS) - The system used to track and manage INDs, IDEs, Master Files (MFs), and Emergency Use Authorizations (EUAs).

B. 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.

C. Complete Clinical Hold - A delay or suspension of all clinical work requested under the IND.

D. Complete Response – A response from the sponsor to a clinical hold which is determined by CBER to be adequate for a decision to be made on lifting or continuing the clinical hold.

E. Incomplete Response – A response from the sponsor to a clinical hold, which is intended to be a complete response, yet CBER determines that it is incomplete; the response is inadequate for a decision to be made on lifting or continuing the clinical hold.

F. Partial Clinical Hold - A delay or suspension of only part of the clinical work requested under the IND, i.e., a specific protocol is not allowed to proceed; however, other protocols under the IND are allowed to proceed.

G. Partial Response – A response from the sponsor to a clinical hold, which is identified by the sponsor as a partial response with more data to follow, or that is not identified by the sponsor as partial, but CBER determines that it is partial.

V. Policy

A. CBER will review all original INDs, and within 30 calendar days of receipt of the original IND, contact the sponsor by telephone (or other means of rapid communication) when a clinical hold is being imposed, to briefly explain the basis for the action.

B. If a clinical hold order is imposed, the specific reasons for the clinical hold are to be clearly specified in a clinical hold letter to the IND sponsor, as soon as possible and not later than 30 days after imposition of the clinical hold. (21 CFR 312.42(d))

C. Grounds for imposing a clinical hold of a Phase 1 study (21 CFR 312.42(b)(1)):

1. Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

2. The clinical investigators are not qualified by reason of their scientific training and experience;

3. The investigator brochure is misleading, erroneous, or materially incomplete;

4. The IND does not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies;

5. The IND is intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring).

D. Grounds for imposing a clinical hold of a Phase 2 or 3 study (21 CFR 312.42(b)(2)):

1. Any of the conditions in paragraphs C. 1 through 5 in this section apply, or,

2. The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

E. Additional grounds for imposing a clinical hold under an IND:

1. An IND submitted under 21 CFR 50.24 or 21CFR 50.23(d), involving a waiver from informed consent, may be placed on clinical hold if the conditions outlined in 21 CFR 312.42(b)(5) are met.

2. An expanded access IND or expanded access protocol may be placed on clinical hold if the conditions outlined in 21 CFR 312.42(b)(3) are met.

3. A proposed or ongoing investigation that is not designed to be adequate and well-controlled may be placed on clinical hold if the conditions outlined in 21 CFR 312.42(b)(4) or 312.42(b)(6) are met.

F. Where it is determined there are grounds for imposing a clinical hold, regulations require that FDA attempt to discuss and satisfactorily resolve the matter with the sponsor ***before*** issuing the clinical hold order. (21 CFR 312.42(c))

Note: If it is determined there are any resolvable issues that may prevent the clinical hold, the review committee should identify them well in advance of the 30 day goal date so there is ample time to review them, i.e., complete by review week 2 or 3.

G. Any discussion of the planned protocol or other aspects of the submission with the sponsor to resolve IND "hold" concerns are conducted by the review committee and appropriately documented. If IND "hold" concerns cannot be resolved and a clinical hold is imposed or retained, the Division Director must be involved.

H. A complete response, from the sponsor, to clinical hold issues is reviewed and a decision as to whether the study or studies may or may not proceed is made well in advance of the 30 day goal date so there is ample time to issue a letter to the sponsor, within 30 days from receipt of the sponsor's complete response. (21 CFR 312.42(e))

I. An incomplete or a partial response from the sponsor is not subject to the 30-day calendar response time. A sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted. (21 CFR 312.42(e))

J. Responses to any non-hold review items conveyed in the clinical hold letter submitted in the same amendment as the complete response to the clinical hold are not required to be reviewed within 30 days of receipt.

VI. Responsibilities

A. **Regulatory Project Manager (RPM)** – Manages the review of the IND and all related submissions, ensuring review timelines are met. Schedules review committee meetings as

needed and informs management of clinical hold issues and the review committee's recommendation on clinical hold/no hold. Prepares clinical hold correspondence and ensures data entry into the appropriate system. Serves as primary contact with the sponsor on clinical hold decisions.

B. **Review Committee Members –** Reviews the IND including clinical protocol(s) and all related submissions. Participates in review committee meetings, conferring with the RPM and other review members to determine if the IND may proceed or should be placed on clinical hold. Assists the RPM with identifying any resolvable issues that would prevent the clinical hold. Each review committee member is expected to document their review, including their concurrence or disagreement with the clinical hold recommendation, citing the reasons for clinical hold, when applicable. Participates in the hold telecon with the sponsor, when appropriate.

C. **Division Director or designee** – Makes the final decision on whether to issue a clinical hold on the IND, and for those which have received a complete response, whether the clinical hold should be lifted, modified, or remain on hold. May participate in the clinical hold telecon with the sponsor. Serves as signatory authority for letters to sponsors conveying clinical hold decisions.

VII. Procedures

A. Review IND (as well as solicited amendments and new clinical protocols received) to determine if issues are identified that may justify imposing a clinical hold. If issues are identified, notify RPM to schedule a meeting. **[Review Committee Members]** Note: Review committee meetings may be face to face, via telecon or by email discussion.

B. Schedule a review committee meeting to determine a Hold/No Hold recommendation, and identify any potentially resolvable issues to avoid a clinical hold. **[RPM]**

C. Conduct team meeting to discuss whether to place the IND on clinical hold. Attendees should include all review committee members and Division Director or designee. **[RPM]**

D. Discuss whether there are any issues that may be resolvable and could prevent the clinical hold or result in a partial hold. **[Review Committee Members]**

E. Email the review committee's recommendation, including the rationale on clinical hold/no hold, at least two business days prior to the 30-day due date for original INDs to the Division Director or his/her designee. Note: this email should be part of the file and can be used as a meeting summary. **[RPM]**

F. Review the review committee's recommendation and decide whether a clinical hold/partial hold should be ordered. Email the decision to the RPM. **[Division Director or designee]**

G. Notify the sponsor of the decision to place the study(-ies) on clinical hold or partial hold, by telephone or other means of rapid communication no later than the 30-day due date. If

the 30-day due date falls on a weekend, notify the sponsor on the Friday prior to the due date **[RPM and Review Committee Members, as appropriate]**

H. Document the clinical hold notification in writing for the file and enter it into BIRAMS as a *Clinical Hold Notification ('Hold' or 'Partial Hold')* telecon. **[RPM]**

Note: The *Clinical Hold Notification* must be entered into BIRAMS on the day the sponsor is notified. This starts the 30-day hold letter clock and changes the status of the IND in BIRAMS from *'Pending'* to *'Hold'*.

I. Issue a letter to the sponsor containing an explanation of the basis for the clinical hold as soon as possible, and no later than 30 calendar days after the initial hold notification to the sponsor. **[RPM]**

1. 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.

2. Further review comments not available at the time the written explanation of the basis for the clinical hold is sent in an information request letter at a later date.

J. Enter the Clinical Hold letter into BIRAMS and upload the letter into the EDR**. [RPM]**

K. Evaluate the response to clinical hold to designate whether the response is complete, incomplete, or partial. See Section IV for definitions. **[RPM and Review Committee Members]**

1. If the sponsor identified the response as complete, yet you determine that the response is not complete, it should be identified in BIRAMS as an incomplete response.

2. If the sponsor identified the response as a partial response with more data to follow or the submission has not been identified by the sponsor as either complete or partial, yet you determine that the response is a partial response, it should be identified in BIRAMS as a partial response.

3. If you determine that the response is complete and allows for a decision to be rendered (i.e., lift or continue hold), it should be identified in BIRAMS as a complete response.

L. Evaluate any submission to an IND that is identified by the sponsor as a complete response to a clinical hold as soon as possible and not later than 30 days. **[RPM and Review Committee Members]**

1. If you determine that the submission is not a complete response to the clinical hold issues, the RPM for that IND will, as soon as possible and no later than 30 days after receipt of the response, inform the sponsor that the 30 day clock will not start until a complete response is received.

2. If you determine that the submission is a complete response to the clinical hold issues, the RPM initiates review of the complete response. A decision whether or not to allow the study to proceed is 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 are identified in the letter.

M. Sign letter conveying partial hold, continued hold, remove hold, or a combination of these. Issue letter within 30 days from the date of receipt of the complete response to clinical hold. **[Division Director or designee]**

N. Enter the letter into BIRAMS and upload the letter into the EDR**.** Ensure the correct IND Status is captured in BIRAMS, based on the communication entered. **[RPM]**

VIII. Appendix

N/A

IX. References

A. The Reference below is located on CBER's Intranet Web Page (unless otherwise noted)

BIRAMS Data Dictionary (accessed via BIRAMS Help Menu)

B. Web links to the references below can be found in the list following the History Table.

1. Guidance for Industry – Submitting and Reviewing Complete Responses to Clinical Holds
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078764.pdf

2. Guidance for Industry – Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf

X. History

Written/Revised	Approved By	Approval Date	Version Number	Comment
C. Vincent	Christopher Joneckis, PhD	May 12, 2014	4	Updated to reflect legislative changes since the last revision in 1999. Added Responsibilities Section.
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