POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

IND Clinical Holds

Table of Contents

PURPOSE

This MAPP describes:

- Policies and procedures for issuing and overseeing clinical holds of investigational new drug applications (INDs)

- Policies and procedures for processing and responding to sponsors' complete responses to clinical holds

BACKGROUND

- An IND goes into effect 30 calendar days after FDA receives the IND, unless FDA notifies the sponsor that the trials described in the IND are subject to a clinical hold, or on earlier notification by FDA that the trials may proceed (21 CFR 312.40(b)).

- A clinical hold is an order issued by FDA to the sponsor of an IND to delay a proposed clinical trial or suspend an ongoing trial. The hold may apply to one or more trials covered by an IND (21 CFR 312.42(a)). The regulations under 21 CFR 312.42(d) specify that a clinical hold order may be made by telephone or other means of rapid communication or in writing, and that FDA will provide to

the sponsor a written explanation of the basis for the hold no more than 30 calendar days after the hold is imposed.

- The regulations under 21 CFR 312.42 describe the grounds for imposing a clinical hold, as well as the requirements pertaining to the imposition and removal of a clinical hold order.

- The authority to impose, lift, and retain clinical holds on INDs has been delegated to division directors or acting division directors. This authority will not be further down delegated.

- For complete responses to clinical holds (responses that address all the deficiencies identified in the clinical hold letter), FDA has 30 calendar days to respond in writing. FDA's response will either remove the hold or maintain the hold, and will provide the reason for such a determination (21 CFR 312.42(e)).

- A trial may resume only after the sponsor has been notified by FDA that the trial may proceed. Resumption of the trial will be authorized by FDA when the sponsor corrects the deficiencies identified by FDA when the hold was imposed or otherwise satisfies FDA that the investigation(s) is safe to proceed. FDA's determinations are as follows:

  – The information provided in the submission does not resolve all of the deficiencies identified in the clinical hold letter or new deficiencies are identified in the complete response and the trials under the IND may not proceed (hold is continued); or

  – Trials under the IND are allowed to proceed with specific restrictions (i.e., full hold is lifted, partial hold is imposed); or

  – All trials under the IND are allowed to proceed (hold is lifted)

POLICY

- Because the regulations specify that an IND goes into effect 30 calendar days after FDA receives the IND (unless FDA imposes a clinical hold), the Center for Drug Evaluation and Research (CDER) will review all original INDs and, within 30 calendar days of receipt, determine whether there may be grounds for imposing a clinical hold.

- If CDER concludes there may be grounds for imposing a clinical hold, CDER will "attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order"[1] by explaining the concerns identified by the review team with the sponsor unless patients are exposed to immediate and serious risk. The discussion must include a manager at the team leader level or higher and must be appropriately documented.

- CDER will identify in the clinical hold letter, which is provided to the sponsor no more than 30 calendar days after the hold is imposed, the specific reasons for the clinical hold decision and the steps the sponsor must take to address the issues.

- CDER will identify any additional *nonhold* issues, which will be designated as nonhold issues, at the end of the hold letter, or relay these issues to the sponsor in a separate communication.

- If all the trials covered by an IND are delayed or suspended, CDER will impose a *full clinical hold*. If only certain (or *some*) trials covered by an IND (e.g., a specific protocol or part of a protocol) are not allowed to proceed, but other protocols or parts of a protocol are allowed to proceed without delay, CDER will impose a *partial clinical hold*. A partial clinical hold may also be imposed when the trials currently proposed under the IND are allowed to proceed, but additional trials submitted to the IND may not proceed until deficiencies identified by FDA in the partial clinical hold letter have been met.

- CDER will review and respond in writing (i.e., by letter) to the sponsor's complete response to a clinical hold within 30 calendar days of receipt of the sponsor's response.

  – CDER may notify the sponsor of its decision as to whether to retain or lift the hold earlier than calendar Day 30 by rapid means of communication; however, a letter must be issued within 30 calendar days.

- If FDA determines that the sponsor's response to an IND clinical hold letter does not address all the clinical hold issues (i.e., is not a *complete* response to a clinical hold), the CDER review division (i.e., the Office of New Drugs regulatory project manager (RPM)) will notify the sponsor of this determination within 14 calendar days. The submission will not be subject to the 30-calendar-day review clock unless determined to be a complete response.

[1] 21 CFR 312.42(c)

RESPONSIBILITIES AND PROCEDURES

Recommending a Clinical Hold (Complete or Partial)

Reviewers will:

- Participate in team meetings, as appropriate.
- Determine whether the investigational drug and/or proposed clinical trial(s) meet the criteria for imposing a clinical hold. (In general, reviewers should not identify *marketing application type* deficiencies at this stage of development.)
- Note the reasons for the recommendation and the information needed to address any deficiencies identified in an IND review.
- Disciplines recommending a clinical hold for an original IND should finalize their review in the electronic archive system by calendar Day 30 of IND receipt. If a discipline recommending a clinical hold is unable to finalize their review by calendar Day 30, the discipline may finalize a memo that describes the deficiencies in the electronic archive system by calendar Day 30, followed by a full review in the electronic archive system by calendar Day 60. *(Disciplines not recommending a hold should finalize their review in the electronic archive system by calendar Day 60 of IND receipt.)*

Discipline Team Leaders will:

- Sign the primary review in the electronic archive system, noting their concurrence or disagreement with the primary reviewer's recommendation(s). If the team leader disagrees with the primary reviewer's recommendation(s), the team leader should file a separate review in the electronic archive system that documents the reasons for disagreement.

Regulatory Project Management Staff will:

- If the review team has identified concerns that could lead to a hold, schedule a team meeting, if needed, to discuss whether to place the IND on clinical hold
- Ensure that the recommendations of both the primary reviewer(s) and the team leader(s) are forwarded to the division director for input into the decision
- Coordinate communication with the sponsor of any potential hold issues identified before calendar Day 30 of an original IND in an effort to resolve issues in advance of a hold decision, as appropriate

- Confirm that all reviews recommending clinical hold for original INDs have been filed in the electronic archive system within 30 calendar days of receipt of the original IND

Division Directors will:

- Make the final decision on whether to issue a clinical hold

Issuing a Clinical Hold (Complete or Partial)

Division Directors will:

- Discuss the clinical hold with the office director, if the office director's input is needed, before the division communicates with the sponsor.

- For commercial INDs, if the hold is communicated initially by telephone, participate in the call to the sponsor, along with the RPM and, if necessary and based on division policy, appropriate review team members to inform the sponsor that the IND has been placed on clinical hold within 30 calendar days of receipt for original INDs. The reasons for the hold should be discussed with the sponsor at the time the hold is imposed.

- If the hold will be communicated initially by facsimile or secure email, review and clear the communication (in sufficient time for it to be sent to the sponsor within 30 calendar days of receipt, if an original IND).

Regulatory Project Management Staff will:

For a Commercial IND

- Schedule and facilitate calls to commercial sponsors where clinical hold decisions are discussed.

- If the hold is communicated initially by facsimile or secure email, send the cleared facsimile/email to the sponsor (within 30 calendar days of receipt for an original IND). Request confirmation of receipt of the clinical hold communication. File the communication in the electronic archive system.

- If the hold is communicated initially by telephone, file a memorandum of the teleconference in the electronic archive system, with a copy to the division and office director.

For a Sponsor-Investigator IND

- If the hold is to be communicated initially by telephone, call (along with appropriate review team members, if needed) the sponsor-investigator on behalf of the division director (on or before calendar Day 30 of receipt for the original IND) and inform the sponsor-investigator that the IND has been placed on clinical hold. The reasons for the hold should be discussed with the sponsor at the time the hold is imposed. The RPM will file a memorandum of the teleconference in the electronic archive system.

- If the hold is communicated initially by facsimile or secure email, send the cleared (by the division director) facsimile/secure email to the sponsor (within 30 calendar days of receipt, if an original IND). Request confirmation of receipt of the clinical hold communication. File the communication in the electronic archive system.

For Both Commercial INDs and Sponsor-Investigator INDs

- Ensure that a letter, signed by the division director, is sent to the sponsor detailing the reasons for the clinical hold within 30 calendar days from the date the sponsor is notified of the clinical hold.

Acting on Sponsor Responses to a Clinical Hold

When a Submission Identified as a Response to a Clinical Hold Is Received

Regulatory Project Management Staff will:

- Consult the review team on whether the sponsor's submission is a complete response

  – If the review team does not believe the submission to be a complete response:

    ▪ Notify the sponsor within 14 calendar days of receipt that the response is not complete and that the 30-calendar-day clock will not start

    ▪ Ensure that the submission is recoded to reflect that it is an incomplete response and document the communication with the sponsor in the electronic archive system using the appropriate standard template

  – For a complete response, in the rare event that the review team is unable to meet the 30-calendar-day deadline specified in 21 CFR

312.42(e), notify the sponsor and discuss the review progress to date, and what is being done to facilitate completion of the review. Archive the reason for missing the 30-day goal date and notification to the sponsor.

Reviewers will:

- Review the submission and determine whether it is a complete response to the clinical hold issues identified in the clinical hold letter. Communicate this determination to the RPM within 14 calendar days of receipt. If the submission is a complete response, review the submission and determine whether it resolves the reasons for the clinical hold within 30 calendar days of receipt of the submission.

- Document a recommendation as to whether the clinical hold should be lifted and file the review within 30 calendar days of receipt of the clinical hold response.

Discipline Team Leader will:

- Sign the primary review and:

  – Add signatory comment of concurrence in the electronic archive system if the team leader agrees with the primary review conclusions; or

  – Add signatory comment of nonconcurrence in the electronic archive system if the team leader does not agree with the primary review conclusions. File a separate memorandum in the electronic archive system that addresses any differences of opinion with that of the primary review and provide the rationale for the differences.

Division Director will:

- Evaluate the review team's recommendation and decide whether the clinical hold should be lifted, modified, or retained.

Communicating the Decision to Retain, Modify, or Lift the Hold

Regulatory Project Management Staff will:

- Communicate to the sponsor the decision to retain, modify, or lift the clinical hold within 30 calendar days of receipt of the complete response.

- If the notification of CDER's decision regarding the sponsor's response to clinical hold is carried out via rapid means of communication (e.g., telephone, secure email, facsimile), document the notification and file in the electronic archive system, and request confirmation of receipt of the clinical hold communication if via secure email or facsimile.

- Regardless of whether the initial communication of the decision is communicated via rapid means of communication, ensure that a letter, signed by the division director, confirming the decision to retain, modify, or lift the clinical hold is filed in the electronic archive system and issued within 30 calendar days of receipt of the sponsor's complete response.

REFERENCES

- MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review* (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm)

DEFINITIONS

Commercial IND: An IND for which the sponsor is usually a corporate entity. Other INDs may be designated as commercial if it is clear the sponsor intends the investigational drug to be commercialized at a later date. INDs from the National Institutes of Health (NIH) will not be classified as commercial INDs until such time as the division determines that commercial development is being pursued.

Sponsor-Investigator IND (i.e., Research IND): An IND for which the sponsor is usually an individual investigator or an academic institution or the NIH. The sponsor does not indicate that it intends to commercially develop and market the investigational drug being studied under the IND.

Sponsor's Complete Response to an IND Clinical Hold: A response from the sponsor in which all clinical hold deficiencies identified in the clinical hold letter have been addressed. (Note that this differs from whether all the clinical hold deficiencies identified in the clinical hold letter have been *resolved.*)

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
02/20/2018	Rev. 3	Revised and moved language within the Background section regarding responses to clinical holds.