IND Process and Review Procedures (Including Clinical Holds)

CONTENTS

PURPOSE
REFERENCES
DEFINITIONS
POLICY
GENERAL REVIEW PRINCIPLES
RESPONSIBILITIES AND PROCEDURES
EFFECTIVE DATE

PURPOSE

This MAPP describes:

- General review principles for investigational new drug applications (INDs).
- Policies and procedures for issuing and overseeing clinical holds of INDs.
- Policies and procedures for processing and responding to sponsors' complete responses to clinical holds.

REFERENCES

Guidance for Industry, *Content and Format of Phase I Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products, November 1995.*

Letter from Donna Shalala, Secretary, Health and Human Services, to Senator Jeffords, Chairman, Committee on Labor and Human Resources Committee, United States Senate, November 12, 1997.

Guidance for Industry, *Submitting and Reviewing Complete Responses to Clinical Holds,* April 1998.

Section 117 of the FDA Modernization Act of 1997.

DEFINITIONS

Clinical Hold: An order issued by FDA to the sponsor of an IND to delay or to suspend a clinical investigation. A *clinical hold* may 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.

Commercial IND: An IND for which the sponsor is usually either a corporate entity or one of the institutes of the National Institutes of Health (NIH). In addition, CDER may designate other INDs as *commercial* if it is clear the sponsor intends the product to be commercialized at a later date.

Division: All references in this MAPP to *divisions* or to *division* directors, reviewers, and project managers are to new drug review divisions (ODEs) unless otherwise specified.

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

CDER's Response to a Sponsor's Complete Response: A letter to the sponsor from CDER in response to a sponsor's complete response in which the sponsor is (1) 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., still a partial hold), or (3) the sponsor is informed that studies under the IND still may not proceed. In the last two cases, the letter should explain to the sponsor why the clinical hold has been maintained. This letter should issue within 30 calendar days of receipt by CDER of the sponsor's complete response

to the clinical hold.

Review Team: The team composed of members of different disciplines (e.g., the medical officer, project manager, chemist, pharmacologist, microbiologist, biopharmaceutist, statistician) who review and make recommendations concerning the IND.

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

POLICY

General

- CDER will review all initial INDs and, within 30 calendar days of receipt of the original IND, will contact the sponsor when a clinical hold is being imposed. If a clinical hold is imposed, the specific reasons for the clinical hold should be clearly specified in the clinical hold letter to the sponsor of the IND. For clinical holds issued for other than initial IND submissions, the specific reasons for the clinical hold should also be clearly specified in the clinical hold letter to the sponsor of the IND.

- The regulations require that, where FDA concludes there may be grounds for imposing a clinical hold, FDA will "attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order." [21 CFR 312.42(c)] CDER experience is that most potential holds, particularly those based on inadequate patient monitoring, can be resolved through such discussion.

- Any discussion of the planned protocol or other aspects of the application with the sponsor to resolve IND "hold" concerns must first be cleared by the appropriate team leader and appropriately documented. If IND "hold" concerns cannot be resolved and a clinical hold is to be imposed or retained, the Division Director or Acting Division Director must be involved.

- CDER will review and respond in writing to the sponsor's complete response to an IND clinical hold within 30 calendar days of receipt of the sponsor's complete response.

- If the sponsor's response to an IND clinical hold letter does not address all the

clinical hold issues, the sponsor will be so notified, and the 30-day response clock will not start until a complete response is received.

Authority

- Authority to impose, release, and retain clinical holds on INDs has been delegated to division directors or acting division directors. This authority cannot be further down delegated.

Tracking

- CDER will maintain a monthly tracking system to track IND submissions, IND clinical holds, sponsor complete responses to clinical holds, and CDER responses to sponsor complete responses to clinical holds.

- PDUFA performance goals for CDER's responses to sponsors' complete responses to clinical holds will apply only to commercial INDs, although the 30-day clock applies to *all* IND clinical hold complete responses and will be so tracked for Modernization Act reporting.

GENERAL REVIEW PRINCIPLES

- It is generally uphelpful to sponsors and a waste of CDER resources to perform Phase 1 IND reviews such that long lists of "NDA-type" deficiencies are sent to sponsors. Sponsors can be assumed to realize that the NDA submission should be more detailed than an initial IND submission. Identification of items that need to be addressed prior to submission of an NDA, but which are not needed to determine the safety of a proposed trial, is usually not necessary or appropriate for a Phase 1 IND review. This does not suggest that developing the manufacturing and controls aspects of a drug is not important during the IND phase or that potentially troublesome aspects of manufacturing and controls submission should not be identified when detected. Sponsors should generally be encouraged to schedule End-of-Phase 2 meetings at which such specific issues can be more appropriately discussed. An exception to this general policy would be for a drug whose first U.S. submission occurs late in development or for drugs likely to have wide early use under expanded access programs.

- The review of an IND from a manufacturing perspective should concentrate on determining if there are any reasons to believe the manufacturing or controls for

the clinical trial product present unreasonable health risks to the subjects in the initial IND trials. Such risks could arise from, for example, (1) a product made with unknown or impure components; (2) a product possessing chemical structures of known or highly likely toxicity; (3) a product that cannot remain chemically stable throughout the testing program proposed; (4) a product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard; or (5) a poorly characterized master or working cell bank.

- In reviewing Phase 1 INDs, chemistry, biopharmaceutic, medical, statistical, microbiologic, and pharmacology/toxicologic reviewers ordinarily should not request data in addition to those listed in the *Guidance for Industry: Content and Format of Phase 1 Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products.* If a reviewer believes information not discussed in the guidance is needed, this should be discussed, first, with ***the appropriate discipline team leader*** and then with ***the division director*** before a request is made of a sponsor. That such consultation with both the team leader and the division director has taken place should be made clear to sponsors at the time any such additional request for information for a Phase 1 IND is made. All requests to the sponsor for such approved additional data should be made either by the project manager or by the involved reviewer along with the project manager. Documentation of such requests, including the reasons for the request, shall be included in the IND file.

RESPONSIBILITIES AND PROCEDURES

- **RECOMMENDING A CLINICAL HOLD (COMPLETE OR PARTIAL)**

Review Team will:

a. Participate in team meetings as appropriate.

b. Clearly note any recommendation for a clinical hold and the reasons for that recommendation in their IND review.

Discipline Team Leaders will:

Clearly note concurrence or disagreement with the primary reviewer's recommendation(s) and the reason(s) for concurrence or disagreement.

Project Management Staff will:

a. Schedule a team meeting, if appropriate, to discuss whether to place the IND on clinical hold.

b. Forward the recommendations of both the primary reviewer and the team leaders to the division director for input into the decision.

c. Ensure that a clear record is created, signed, or initialed by the division director, which documents the basis for the clinical hold, referencing specific discipline reviews, meetings, or other bases for the clinical hold.

d. Ensure that copies of the IND hold recommendation documents are filed in the IND file.

Division Directors will:

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

- **ISSUING A CLINICAL HOLD (COMPLETE OR PARTIAL)**

For a Commercial Sponsor:

Division Directors will:

a. Along with the project manager, call the appropriate sponsor representative and inform the sponsor 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 or, if the sponsor prefers, at a convenient time within the next several days when appropriate sponsor personnel are available to understand and discuss hold issues.

b. At the request of the Office Director, discuss details of the clinical hold with the Office Director.

Project Management Staff will:

a. Arrange and sit in on calls to commercial sponsors where clinical hold decision area discussed.

b. Ensure that the teleconference is appropriately documented with a memorandum of the teleconference between the commercial sponsor,

Division Director, and Project Manager, and ensure it is filed in the IND, and a copy is sent to the Office Director.

For an Individual Investigator IND:

Project Management Staff will:

a. Call the sponsor and inform the sponsor that the IND has been placed on clinical hold, briefly explain the reason(s) for the hold, and offer to arrange a teleconference with the division director to discuss the hold more fully if so desired by the sponsor.

b. Prepare a memorandum of the teleconference between Project Manager and sponsor, and ensure that a copy is filed in the IND, and a copy is sent to the Office Director.

For Both Commercial INDs and Individual Investigator INDs:

Project Management Staff will:

a. Ensure that a letter, signed by the division director or acting division director is sent to the sponsor detailing the reasons for the clinical hold within 7 calendar days from the date of the teleconference communicating the clinical hold to the sponsor. The primary purpose of this letter is to identify clearly the specific reasons for the clinical hold decision. Additional "non-hold" issues regarding the IND that the Division wishes to communicate to the sponsor may be added to the end of the hold letter provided these are clearly marked as non-hold issues, or sent to the sponsor in a separate letter.

b. Ensure the correct categories for the clinical hold are designated. The categories should be listed after the cc page of the clinical hold letter.

H1 Medical Risk
H2 Pharm/Tox
H3 Chemistry
H4 Microbiology
H5 Protocol Design
H6 Target Population
H7 Dose/Duration
H8 Route of Administration
H9 Other (specify briefly)

HW Waiver of Informed Consent for emergency research under 21 CFR 50.24

c. Ensure that the following language is used in clinical hold letters:

"Please identify your response to the clinical hold issues as a **CLINICAL HOLD COMPLETE RESPONSE** and, in your cover letter, clearly indicate whether or not your response is a complete response to all issues raised in the clinical hold letter. Responses to non-hold issues should be addressed in a separate amendment to the IND."

- **MONITORING CLINICAL HOLDS (COMPLETE OR PARTIAL)**

Reports Data Management team will:

Provide monthly reports of IND submissions, clinical holds, clinical hold resubmissions, and clinical hold removals to the Deputy Center Director (Review Management), Deputy Center Director (Pharmaceutical Sciences), Office of Review Management (ORM) Office Directors, Associate Directors for Regulatory Affairs, Division Directors, Chiefs, Project Management Staffs, Center Project Management Director, and Office of Pharmaceutical Sciences (OPS) Office of New Drug Chemistry (ONDC) Office Director and Division Directors and Office of Biopharmaceutical Sciences (OBS) Office Director and Division Directors.

New Drug Review Office Directors will:

Review at each division Administrative Rounds any clinical hold (complete or partial) that still remains in effect more than 60 calendar days.

Clinical Holds Peer Review Committee will:

a. Meet quarterly to review all commercial IND clinical holds (complete or partial) issued during the previous quarter even if the IND clinical hold has been released prior to the meeting of the committee.

b. Give sponsors the opportunity to appear before the committee when their IND is discussed and to offer their views, under proceedings similar to those used for the Refuse-to-File Review Committee.

- **RESOLUTION OF CLINICAL HOLDS/ACTING ON SPONSOR RESPONSES TO A CLINICAL HOLD**

Project Management Staff will:

a. Consult with the review team about whether or not the sponsor's submission is a complete response. If the sponsor has designated a submission to be a complete response, but FDA does not believe it is a complete response, call the sponsor and inform the sponsor that their response is not complete and that the 30-day clock will not be started. A memorandum of the teleconference will be prepared by the project manager and placed in the IND file.

b. If FDA agrees that the resubmission is a complete response, write a "receipt of complete response" acknowledgment letter informing the sponsor of the due date for action on the submission.

Review Team will:

a. Review the sponsor's submission and determine whether or not it is a complete response to the clinical hold issues identified in the clinical hold letter.

b. Review the sponsor's submission and determine whether it resolves the reasons for the clinical hold.

c. Clearly document in the review of the response whether they believe the clinical hold should or should not be lifted.

Discipline Team Leader will:

Review the primary reviewer’s assessment of the sponsor’s submission and clearly document whether the team leader concurs or disagrees with the primary reviewer with respect to the disposition of the clinical hold.

Division Directors will:

a. Review the review team’s recommendation and decide whether the clinical hold should be lifted, modified, or remain on hold.

b. If the review team will not meet the 30-day deadline, telephone the sponsor and discuss the review progress to date, and what is being done to facilitate completion of the review.

- **WHEN THE DECISION IS TO RETAIN OR MODIFY THE HOLD:**

Project Management Staff will:

a. For a commercial IND, schedule and sit in on a teleconference with the Division Director and the sponsor so that the decision to retain or modify the clinical hold can be communicated by the Division Director.

b. Ensure that the teleconference is appropriately documented by a memorandum of the teleconference and ensure that a copy is placed in the IND file and in the "Continue Clinical Hold" package that is sent to the Office Director. In addition, the project manager should ensure that an e-mail or telephone call to the Office Director is made to inform him/her of the decision on the day of the teleconference with the sponsor.

c. For an individual investigator IND, call the sponsor and communicate the decision to retain or modify the clinical hold, and briefly explain the reasons. Offer to arrange a teleconference with the division director to discuss the continued clinical hold, and ensure that a memorandum of the teleconference is prepared and placed in the IND file and in the "Continued Clinical Hold" package that is sent to the Office Director.

d. For both commercial and individual INDs, ensure that a response from FDA is communicated to the sponsor in writing within 30 calendar days of CDER's receipt of the sponsor's complete response.

e. Prepare a "Continued Clinical Hold" review package for the Office Director's review. The package should include the following items and be forwarded to the Office Director within 7 calendar days of the sponsor's notification of the decision to retain or modify the clincial hold.

    1. A copy of the teleconference and letter documenting the retention or modification of the clinical hold, and the reasons for the decision.

    2. A copy of the review(s) of the sponsor's response to the original clinical hold.

    3. A copy of the sponsor's complete response to the clinical hold. This may be provided in the original review jackets.

    4. A copy of the original hold teleconference memorandum and letter.

    5. A copy of the review(s) applicable to the original hold issues.

The sponsor's initial submission(s) relevant to the original hold issues should be available on the Office Director's request.

Office Directors will:

a. Review any instance in which a clinical hold is maintained or modified by the division.

b. Communicate the result of his/her review to the division by memorandum within 14 calendar days after receipt of the IND "Continued Clinical Hold" package from the division.

- **WHEN OFFICE DIRECTOR'S DECISION DIFFERS FROM THE DIVISION'S DECISION TO RETAIN HOLD.**

For Commercial and Individual Investigator INDs

Project Manager will:

a. Schedule and sit in on a teleconference with the Division Director to call the sponsor and communicate the Office Director's decision. This teleconference should occur within 2 working days of the Office Director's decision.

b. Ensure that the teleconference is appropriately documented with a memorandum of the teleconference between the sponsor, Division Director, and Project Manager, concerning the Office Director's conclusions, and ensure it is filed in the IND and a copy is sent to the Office Director.

c. Ensure that a letter reflecting the Office Director's decision is signed by the Division Director, is sent to the sponsor within 7 calendar days of the teleconference, a copy is filed in the IND, and a copy is sent to the Office Director.

Division Director will:

Communicate the Office Director's decision to the sponsor by telephone and then in a letter.

- **WHEN THE DECISION IS TO LIFT THE CLINICAL HOLD**

Project Management Staff will:

For Commercial and Individual Investigator INDs:

a. Telephone the sponsor's representative and communicate the decision to lift the clinical hold.

b. Prepare a memorandum of the teleconference, and ensure that it is placed in the IND file.

c. Write a letter for the Division Director's signature confirming that the hold has been lifted. Ensure that letter issues within 30 calendar days of the receipt of the sponsor's complete response to the clinical hold.

EFFECTIVE DATE

This MAPP is effective upon date of publication.