OFFICE OF MEDICAL POLICY

Clinical Hold/Refusal-to-File Committee

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PURPOSE

- This MAPP outlines the procedures and responsibilities of the Clinical Hold/Refusal-to-File Committee in the Center for Drug Evaluation and Research (CDER).

BACKGROUND

- The Clinical Hold and Refusal-to-File (RTF) Committee (the committee) was established by the issuance of two *Federal Register* notices dated October 2, 1991 (56 FR 49894), and May 18, 1993 (58 FR 28983). At that time, the purpose of the committee was to assess the scientific and procedural quality of the clinical hold and RTF decisions being made. The committee was to consist of CDER senior officials, a Center for Biologics Evaluation and Research (CBER) senior official, and the Food and Drug Administration (FDA) Ombudsman. Initially, the applications were selected either randomly or at the request of the sponsor of the drug subject to a clinical hold or RTF (the basis for the choice was not revealed to the committee members or meeting attendees). In recent years, there has been an attempt to identify cases of special interest, including those where the clinical hold or RTF was considered but **not** imposed.

  In June 2006, a meeting was held with the Center Director and the directors from the Office of New Drugs to discuss the future of these committee meetings. There have been fewer clinical hold and RTF meetings in the past year, and it seemed to be a suitable time to discuss the value of these meetings. It was also noted that RTF decisions had become very infrequent, about 5 per year, although clinical hold decisions were fairly frequent, about 286 per year.

  It was decided that these meetings, like regulatory briefings and other meetings that share divisional experiences, were very helpful as a means of teaching and learning. It was suggested that we should attempt to increase attendance by inviting all CDER reviewers

to attend, not only those reviewers from the presenting division. Instead of choosing applications at random, review divisions would suggest applications for discussion, including those where a clinical hold or RTF was considered but not imposed.[1] These procedures apply to investigational new drug applications (INDs), new drug applications (NDAs), and biologic license applications (BLAs).

REFERENCES

- Investigational New Drugs; Procedures to Monitor Clinical Hold Process; Meeting of Review Committee and Request for Submissions (56 FR 49894, October 2, 1991)

- New Drug Applications; Refusal to File; Meeting of Review Committee (58 FR 28983, May 18, 1993)

RESPONSIBILITIES AND PROCEDURES

Participants

- **The committee members include:**

  - CDER Deputy Director
  - Director, Office of Medical Policy (OMP) (co-chair)
  - Director, Office of New Drugs (OND) (co-chair)
  - Directors, Offices of Drug Evaluation I, II, and III
  - Director, Office of Antimicrobial Products
  - Director, Office of Nonprescription Products
  - Director, Office of Oncology Drug Products
  - Director, Office of New Drug Quality Assessment
  - Associate Director of Pharmacology and Toxicology, OND
  - Two directors from an OND review division
  - Director, Office of Biostatistics
  - Director, Office of Clinical Pharmacology
  - Chief Mediator and Ombudsman Staff, Office of the Commissioner
  - Center for Biologics Evaluation and Research representative

- All reviewers are invited to attend.

Selection of Applications

- **The Office of Medical Policy will:**

  - Contact the Division Director and the Chief, Project Management Staff, of two review divisions to request a topic, either a clinical hold or an RTF decision of interest. Each of the two review divisions will be asked to present its clinical hold or

[1] Sponsors can still request review of their clinical hold or RTF experiences through FDA's Chief Mediator and Ombudsman, as described in the two FR notices cited previously.

RTF decision at the next Clinical Hold/RTF Committee meeting. The committee meetings are held approximately six times a year and are scheduled during one of the weekly CDER Regulatory Briefing time slots. The review divisions will be contacted in alphabetical order as follows:

- Anesthesia, Analgesia, and Rheumatology Products
- Anti-Infective and Ophthalmology Products
- Antiviral Products
- Biologic Oncology Products
- Cardiovascular and Renal Products
- Dermatology and Dental Products
- Drug Oncology Products
- Gastroenterology Products
- Medical Imaging and Hematology Products
- Metabolism and Endocrinology Products
- Neurology Products
- Psychiatry Products
- Pulmonary and Allergy Products
- Reproductive and Urologic Products
- Special Pathogen and Transplant Products

After the first two review divisions on the list are contacted for a committee meeting, the next two divisions will be contacted for the next committee meeting, and so on. All the review divisions will be contacted once before being contacted again alphabetically. Each division should expect to be contacted and asked to present a clinical hold or RTF issue approximately every 18 months.

- Contact the sponsor of any application chosen for presentation to ask whether the sponsor wishes to attend and participate in the meeting. If the recommended application is one for which a clinical hold or RTF decision was considered but not imposed, the sponsor of the application would not be contacted.

- Generate and distribute the agenda and post the background material on the OMP Intranet Web site.

- **The review division will:**

  - Forward the recommended application information, including sponsor contact, to the Office of Medical Policy.

  - Prepare an executive summary (see Attachment A for template) and provide any relevant background (reviews, correspondence, minutes of meetings, and for clinical holds, the study protocol) 1 to 2 weeks before the meeting. **Note:** If any of the documents, such as the reviews, are lengthy, the division may elect to forward a cover memo, attaching only the relevant sections of the document and not the entire document.

  - Provide a copy of any presentations 1 to 2 days before the meeting.

- The project manager of the review division will prepare the minutes (see Attachment B for the memorandum format).

Note: Any review division, including those not within the Office of New Drugs, may request that an application with clinical hold or RTF issues be reviewed and discussed by the committee. If a review division has an application it wishes to have the committee review out of sequence, the Project Manager for that application should contact Sandra Benton (301-796-1042, sandra.benton@fda.hhs.gov).

- **The Co-Chair(s) will:**

  - Assign the application scheduled for discussion to a committee member. The committee member will be responsible for summarizing the key issues and lessons learned from that application at the conclusion of the discussion.

Format of Meetings

- Committee meetings will be held approximately six times a year and are scheduled during one of the weekly CDER Regulatory Briefings.

- If the application is the subject of an RTF action or the IND is placed on hold, the sponsor of the application will be invited to present and, if the sponsor chooses to attend, will be asked to provide a 15-minute summary of its perspective, including a description of the sponsor's interactions with the review division (or divisions) concerning the application.

- Each meeting will be scheduled for 2 hours and two applications will be discussed. The presentations and discussion of each application will be scheduled as follows:

  - 30 minutes for dialogue and discussion with the review division about the basis for the clinical hold/RTF decision, with an emphasis on the critical scientific and regulatory issues raised during the review. Only FDA personnel may attend this part of the meeting.

  - 15 minutes for the sponsor, if in attendance, to join the meeting and present its summary and comments.

  - 15 minutes for the committee member assigned to the application to summarize the key issues and lessons learned and for additional discussion and/or comments by the committee and those attending. Only FDA personnel may attend this part of the meeting.

- After the committee discussion of the application is completed, the review division representatives attending the meeting will meet with the sponsor to share the committee's evaluation.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT A

Clinical Hold/Refusal-to-File Committee Meeting
Executive Summary

Meeting Date:

IND/NDA:

Product:

Proposed Indication:

Sponsor/Applicant:

Review Division:

Discipline-Specific Deficiencies Resulting in clinical hold/refusal-to-file decision (chemistry, clinical, pharmacology/toxicology):

Brief Summary of Key Issues Resulting in Decision:

Note: This should be no more than two paragraphs, highlighting key issues of interest.

Summary, Regulatory History:

Example: Date of receipt of original IND, 30-day safety meeting, initial contact with sponsor, date of clinical hold/refusal-to-file, significant subsequent interactions with sponsor or actions taken on application.

Resolution/Current Status:

ATTACHMENT B

Clinical Hold/Refusal-to-File Committee Meeting
Memorandum of Minutes

Meeting Date:
Application:
Sponsor/Applicant:
Type of Meeting:
Meeting Chair:
Meeting Recorder:

Committee Attendees:

Sponsor Attendees:

Background:

Presentation and Discussion:

Lessons Learned/Outcome:

ATTACHMENT C

Number of Clinical Hold/Refusal-to-File
Meetings Held Each Year

Year	Clinical Hold	Refuse to File
2005	1	0
2004	2	1
2003	4	2
2002	3	2
2001	3	2
2000	4	2
1999	4	2