CLINICAL PHARMACOLOGY

OCP Prioritization, Triage, and Review Process for INDs and Pre-INDs

CONTENTS

PURPOSE

- This MAPP describes the policies, responsibilities, and procedures for the triage and prioritization of investigational new drug (IND) and pre-IND submissions for review in the Office of Clinical Pharmacology (OCP) conducted in conjunction with the policies and procedures of the Office of New Drugs (OND) and Office of Pharmaceutical Science (OPS).

- This MAPP applies to formal and informal requests for reviews or consults.

BACKGROUND

- OCP's scientific and regulatory work during the pre-IND and IND period is intended to encourage the sponsor's presentation of an integrated plan for clinical pharmacology and biopharmaceutics studies and also to optimize OCP's input on prospective submission of study protocols.

- With the intent of improving the value of OCP input into drug development plans and protocols, OCP conducted a study of its current IND process, including surveys within OND, OPS, and segments of the pharmaceutical industry to measure the perceived value of the current IND review practices. (See REFERENCES.) This MAPP implements improvements in the process suggested as a result of the survey.

REFERENCES

- OCP IND Process Study Report, July 27, 1999
- Project Manager Resource Manual, Section 2: IND Process and Review Procedures
- ODE IV Pre-IND Consultation Program
- MAPP 4000.4 Clinical Pharmacology and Biopharmaceutics Review Template

DEFINITIONS

- **OCP Pre-IND and IND Prioritization, Triage, and Review Process**. The policies and procedures used by OCP to triage, prioritize, review, and critically evaluate IND submissions. The process is conducted in coordination with OND and OPS and includes OCP communication to IND sponsors.
- **Criteria for Value-Added IND Review**. A method of scientific review that (1) takes an integrated approach to the review of INDs by focusing on a sponsor's development plans, as well as individual studies, study protocols, and results; (2) is intended to make drug development plans more informative with respect to efficiently derived clinical pharmacology and biopharmaceutics data; and (3) is used to prioritize the order in which IND submissions are reviewed to maximize the contribution of reviewer's time to the collective knowledge about the drug and drug product.
- **Formal Assignment and Consultation**. An assignment recorded in CDER's electronic database for tracking IND and new drug application (NDA) assignments and submissions. These assignments represent OCP's responsibility to evaluate the clinical pharmacology, biopharmaceutics, pharmacokinetic (PK) and pharmacodynamic (PD) information in INDs, as set forth in 21 CFR parts 312 and 320.
- **Informal Assignment and Consultation.** A request for OCP reviewers' and team leaders' technical expertise that is not or cannot be reasonably captured in CDER'S electronic database for tracking IND and NDA/biological license application (BLA) submissions and assignments.
- **The Question-Based Review (QBR).** A new review approach to guide the assessment of clinical pharmacology and biopharmaceutic data in an application. The QBR consists of three steps: a review of the studies submitted by the sponsor, a description and analyses of the data from these studies, and a description of the important questions and whether or not the data in the application address them. See MAPP 4000.4 for a full discussion of the QBR.

POLICY

- Responding to requests for assistance in reviewing drug development plans and specific study protocols is a priority for OCP.

- The OCP prioritization, triage, and review process described in this MAPP is essential to meeting the needs of our stakeholders and optimizing OCP resources.

- The OCP IND prioritization, triage, and review process will focus on:

    - overall drug development plans
    - IND submissions that may have major impact on product approval or labeling

- Pre-IND and IND reviews will be conducted in a manner consistent with OCP's philosophy of Good Review Practices related to the question-based review (QBR).

    - Reviews will focus on information and data needed to address specific questions about the clinical pharmacology and/or biopharmaceutics attributes of the drug and drug product under consideration.

    - OCP will provide advice and guidance on fulfilling regulatory requirements when necessary even in the absence of a specific question from the sponsor.

- OCP will continue to streamline the process for its pre-IND and IND reviews and will periodically review the criteria established to prioritize the review of pre-IND and IND submissions.

- OCP's pre-IND and IND prioritization, triage, and review process will follow the procedures outlined below.

RESPONSIBILITIES

The Director of the Office of Clinical Pharmacology or designee will:

- Coordinate with the Center's OND and OPS Directors on determining and developing policies, responsibilities, and procedures described in this MAPP and ensure appropriate implementation.

- Ensure that the OCP scientific review management and staff understand the policies, responsibilities, and procedures described in this MAPP.

- Ensure that this MAPP is reviewed periodically and updated as necessary to reflect current policies and operating procedures.

OCP Division and Staff Directors will:

- Implement this MAPP at the Division and Staff level.

- Coordinate with OND and OPS Division Directors and Deputy Division Directors when needed to facilitate the implementation of this MAPP.

- Guide and train team leaders and reviewers on the triage and prioritization process for IND submissions.

OCP Team Leaders will:

- Implement this MAPP within their team by
    - ensuring that OCP reviewers are familiar with and comply with this MAPP and
    - training team members to provide input into drug development plans and specific study protocols using the criteria of added value.

- Brief affected stakeholders (e.g., OND and OPS reviewers and team leaders) on the OCP IND prioritization, triage, and review process described in this MAPP.

- Monitor pre-IND and IND submissions to
    - ensure appropriate assignment and referral of IND submissions to OCP staff
    - consult with their OCP Division Director as appropriate.

- Conduct secondary reviews of primary IND submission reviews and sign those reviews using CDER's Division File System (DFS) or equivalent method.

- Review and sign-off on a primary OCP reviewer OCP Tracking/Action Sheet (in the absence of detailed review) for Formal/Informal Consults using CDER's DFS or an equivalent method.

- Monitor the OCP process described in this MAPP and evaluate it for continued improvement.

- Identify and recommend to Division Officials and reviewers the best review practices and ways to further improve OCP review processes during the IND period to ensure reaching OCP goals.

OCP Reviewers will:

- Become familiar with this MAPP, follow the guidance and training given by the team leader, and carry out the policies and procedures of the process.

- Conduct scientific and regulatory reviews and provide input into the sponsor's development of an integrated plan to obtain efficiently derived clinical pharmacology and biopharmaceutics data.

- Focus attention on priority IND submissions as described in this MAPP and overall development plans based on added value criteria. (Refer to the OCP IND Triage Criteria below.)

- Use the OCP Tracking/Action Sheet for Formal/Informal Consults, save it in DFS, and submit it to the Team Leader for sign-off using the prioritization and triage criteria described in this MAPP.

- Identify the nature of the review using keywords (refer to the OCP IND Triage Criteria below) when submitting the review in DFS.

- Identify and communicate to the team leaders ways to improve our processes to make application review and drug development more complete with respect to clinical pharmacology and biopharmaceutics information.

OCP Project Manager will:

- Brief all affected CDER project managers, document room personnel, and Office of Information Management personnel regarding the OCP IND process for triaging and prioritizing IND submissions for review (including the OCP Triage Criteria), as needed.

- Serve as liaison between OCP staff members and CDER project management staff to facilitate the implementation of this MAPP, evaluate the process for improvements as needed, and facilitate the implementation of any improvements.

- Ensure all affected CDER project managers, document room personnel, and Office of Information Management personnel receive periodic continuing education on the OCP IND process as needed.

THE OCP IND PRIORITIZATION, TRIAGE, AND REVIEW PROCESS

General

- The submission comes to OCP from the CDER project manager in OND or OPS responsible for each pre-IND or IND. The OND or OPS project manager first triages the submission (using the OCP IND Triage Criteria) and then forwards the document to the OCP team leaders (or to the reviewer, if identified in CDER's electronic database for tracking IND and NDA submissions).

- OCP team leaders and reviewers conduct, write, and sign-off on scientific and regulatory reviews according to the OCP pre-IND and IND prioritization, triage, and review process described in the following section.

OCP IND Triage Criteria

The OND or OPS project manager triages and, in a timely manner, forwards to the OCP reviewer or team leader the following types of documents:

- Meeting packages for Pre-INDs, End-of-Phase IIA (EOP2A), End-of-Phase II (EOP2), pre-NDA, and other meeting packages relevant to OCP reviewers

- Pre-IND or initial IND packages (submission packages numbered 000)

- Phase I study protocols, protocol changes, or reports that address:
  - Pharmacokinetics (PK)
  - Absorption, distribution, metabolism and/or excretion (ADME)
  - Mass balance
  - Dose proportionality
  - Bioavailability (BA) e.g., for absolute or relative BA, formulation or dosage form changes or different routes of drug administration
  - Bioequivalence (BE) e.g., for manufacturing or formulation changes
  - Food effects
  - Drug-drug interactions
  - Pharmacodynamics (PD)
  - Pharmacokinetics and/or Pharmacodynamics for specific populations such as pediatrics, geriatrics, gender, patients with hepatic or renal disease

- Other study protocols, protocol changes, or reports that address:
  - Dose ranging
  - Population PK and/or PD
  - Exposure response
  - Allometric scaling
  - Pharmacogenomics/Pharmacogenetics
  - QT related protocols

- Phase 2 and phase 3 protocols or protocol changes

- In vitro study protocols, protocol changes, or reports that address:
  - Protein binding
  - Metabolism
  - Transporters
  - Drug-drug interactions
  - Permeability studies

The OCP team leader and reviewer will determine the level of review.

OCP IND Prioritization

Due to limited resources, OCP will review and provide timely comments for the various IND submission categories described below in order of priority.

- Emphasis will be to review the submissions that have a significant clinical pharmacology impact on drug development, including overall drug development plans, dose finding protocols, and quantitative methods protocols.

- Reviews of low priority submissions should be undertaken only if there is significant regulatory justification or a direct request from another discipline with agreement from the OCP team leader and OCP Division Director.

Priority Groupings by IND Categories
(Refer to Attachment B for definitions of IND Codes)

High Priority Group:

- Pre-INDs requiring OCP input, initial INDs (# 000) that already have human data, EOP2A, EOP2 and pre-NDA submissions for meetings with sponsors.
- Study protocols for biopharmaceutics and clinical pharmacology studies where the sponsor is seeking comments from OCP <u>before</u> initiating the study.
- Pivotal phase 2 and phase 3 protocols.
- Submissions at any stage of drug development (including pre-IND) where input on use of quantitative drug development methods (i.e., exposure-response, PK/PD modeling, drug-disease modeling, genomic analysis, etc.) can be influenced.
- Any other pre-IND or IND submissions for which the OND or OPS Division requires a timely response due to a pending decision (by the sponsor, OND, or OPS) based completely, or in part, on OCP review.
- Special Protocol Assessment submissions and pediatric protocols
- Continuing Marketing Applications (CMA) submissions
- Counter-terrorism submissions

Low Priority Group:

- Initial IND submissions (# 000) not containing human data or issues relevant to OCP.
- Protocols for study types for which FDA guidances have been issued. This may be dependent on the type of protocol and indication.
- Completed IND study reports of drugs that are likely to be submitted as NDAs, such as reports after phase 2. It is possible that the review may be deferred until the NDA is submitted.
- Non-Commercial INDs, unless they meet criteria for high-priority review.
- Phase 2 and phase 3 protocols not likely to contribute to a regulatory decision.

Communicating OCP Recommendations

Principles

- Communications between the sponsor, the clinical division, OPS, and OCP should occur as often as necessary to ensure timeliness and value of OCP's input into the sponsor's drug development program as well as specific study protocols.

- Recommendations and comments on drug development programs should encourage clinical pharmacology and biopharmaceutics studies that will provide the information and data anticipated to facilitate a question-based review (QBR) of the NDA.

- OCP reviewers will use the most efficient and effective method available to communicate recommendations and comments to sponsors, OND, and OPS divisions when completing IND review assignments. The complexity and importance of comments are factors to consider when communicating OCP's recommendations and comments.

Procedures

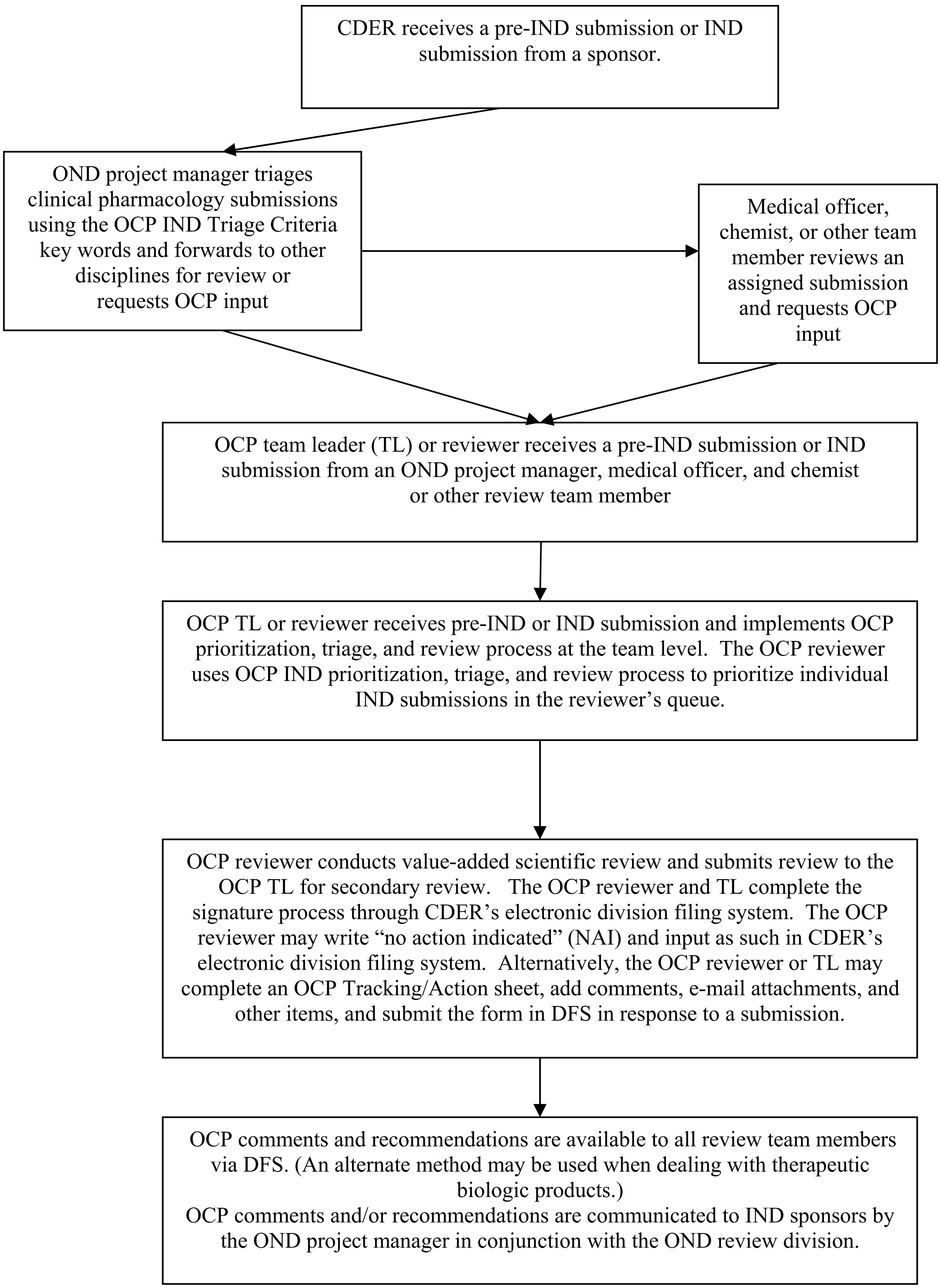
- IND reviews can be communicated to clinical divisions by:
  - "No Action Indicated" or "NAI" on the IND jacket
  - Tracking/Action Sheet for Informal Reviews
  - email attachment
  - memorandum of telephone conversation
  - memorandum of meeting
  - facsimile
  - formal written reviews. If a formal review is requested, the review will be concise and informative.

- All informal and formal IND review assignments must be documented and recorded in DFS.
  - Completion of formal assignments will be documented and recorded on the tracking form provided with the submission.
  - Informal assignments (including comments on submissions provided by e-mail) will be recorded on the Tracking/Action Sheet for Informal Reviews, which will be dated at completion and entered into CDER's electronic document filing system.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

ATTACHMENT A
OCP IND Review Process within CDER Clinical Divisions



ATTACHMENT B: DEFINITIONS OF IND CODES

These codes can be found in the section 1.D of the Project Manager Resource Manual available on the CDER intranet at

http://cdernet/pmcc/Project%20Manager%20Resource%20Manual/Section%201/defcod.htm .

I. INCOMING IND CODES

II. OUTGOING IND DOCUMENT & ACTION CODES

ATTACHMENT C

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults

From: doubleCLICKhere, Enter Your Name, TAB to the next field	**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**

DATE: **MM/DD/YY**	IND No.: Serial No.:	NDA No.	DATE OF DOCUMENT	

NAME OF DRUG **[ ]**	PRIORITY CONSIDERATION **S or P**	Date of Informal/Formal Consult:	

NAME OF THE SPONSOR: [ ]

TYPE OF SUBMISSION
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED TOPIC

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
- ☐ PHASE III PROTOCOL
- ☐ DOSING REGIMEN CONSULT
- ☐ PK/PD- POPPK ISSUES
- ☐ PHASE IV RELATED
- ☐ DISSOLUTION/IN-VITRO RELEASE
- ☐ BIOAVAILABILITY STUDIES
- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☐ OTHER *(SPECIFY BELOW)*:
  [ ]

REVIEW ACTION

- ☐ NAI (No action indicated)
- ☐ E-mail comments to:
  ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro
  ☐ Pharmacometrics ☐Others (Check as appropriate and attach e-mail)
- ☐ Oral communication with
  Name: [ ]
- ☐ Comments communicated in meeting/Telecon. see meeting minutes dated:
  [ ]
- ☐ Formal Review/Memo (attached)
- ☐ See comments below
- ☐ See submission cover letter
- ☐ OTHER *(SPECIFY BELOW)*:
  [ ]

REVIEW COMMENT(S)
☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:
[ ]

SIGNATURE OF REVIEWER: ____________________ **SIGNATURE OF TEAM LEADER: __________________**	Date _______________ Date _______________
CC.: HFD # [ ]; TL: [ ]; DD: [ ]	**Project Manager: _______________ Date**