OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF NEW DRUGS

MULTI-DISCIPLINARY PROCEDURES FOR MANAGING END-OF-PHASE 2A MEETINGS

CONTENTS

PURPOSE

This MAPP establishes an integrated review process (IRP) for the multiple disciplines involved with End-of-Phase 2A (EOP2A) meetings. These meetings are Type C meetings (see Definitions). From past experience, staff from the Office of Translational Sciences (OTS) and Office of New Drugs (OND) have been primarily involved with these meetings.

BACKGROUND

CDER issued a (draft) Guidance to Industry on EOP2A Meetings in September 2009 (see References). The Guidance describes the scope of EOP2a meetings and the procedure for requesting such meetings.

The principal goal of EOP2A meetings is to improve the quality of late-phase drug development and regulatory submissions. The main focus of these meetings is for FDA scientists to engage in scientific discussions with industry on topics related to dose-finding and trial design. Recommendations from EOP2A meetings are influential but not binding.

Our pilot experience indicates that the success of EOP2A meetings is dependent on staff from OTS and OND working collaboratively. The major work undertaken at these meetings involves building and exploring quantitative models based on prior placebo and active treatment data to simulate future trials. The results of these explorations, together with practical considerations and clinical perspectives, form the basis for trial design choices for dose-range, endpoints, and analysis.

Typically, EOP2 meetings involve FDA staff answering regulatory questions pertaining to the potential acceptability of the design characteristics of registration trials and other information for the NDA. The experience from the pilot program is summarized by Wang et al (see References). The EOP2A meetings involve FDA staff answering scientific questions about future trial designs based on the information for the compound under development and prior trials in that area. Exploring alternative design and dosing strategies, where possible, would be a valuable contribution supporting the quality and efficiency of drug development.

Topics for discussion at an EOP2A meeting might include:

- Use of quantitative information for dose selection using mechanistic or empirical relationships among biomarker, surrogate endpoints or clinical endpoints for both effectiveness and safety

- Use of quantitative knowledge of drug effects in animals and human subjects to aid in both dose-ranging trial design and safety assessment. Examples may include: Effects in Placebo group, Disease severity (baseline) effect, or Disease endpoint variability and time course

- Use of available nonclinical and clinical exposure-response data and discussion of implications for dose-response trial design

- Contrasting alternative trial design strategies (e.g., parallel, cross-over, adaptive, randomized withdrawal) and analyses (e.g., Bayesian)

- Use of pharmacogenetic information from nonclinical studies and clinical trials and discussion of the implications of genetic factors on PK, PD, or both. The discussion might include a quantitative evaluation of genetic effects on dose selection and the use of genetics to inform assessments of drug safety and effectiveness in future trials

- Discussion of blood or DNA sampling strategies and other trial design features to optimize the usefulness of future studies

- Discussion of the utility of PK/PD data for dosing adjustments in special populations (e.g., pediatrics)

REFERENCES

- Guidance for industry on formal meetings with sponsors and applicants for PDUFA products. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf

- Guidance for industry on End of Phase 2A meetings. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079690.pdf
- Wang, Y., V.A. Bhattaram, P.R. Jadhav, L.J. Lesko, R. Madabushi, J.R. Powell, W. Qiu, H.Sun, D.S. Yim, J.J. Zheng, J.V.S. Gobburu, "Leveraging Prior Quantitative Knowledge to Guide Drug Development Decisions and Regulatory Science Recommendations: Impact of FDA Pharmacometrics During 2004-2006," *Journal of Clinical Pharmacology*, 48(2):146-156, 2008.
- CDER-EOP2A Meetings eRoom. http://eroom.fda.gov/eRoom/CDER9/CDEREndofPhase2AEOP2AMeetings

DEFINITIONS

- **Type C Meeting**: Guidance for industry on formal meetings with sponsors and applicants for PDUFA products defines a Type C meeting as any meeting other than a Type A or Type B meeting between FDA and a sponsor or applicant regarding the development and review of a product in a human drug application as described in section 735(1) of the Act.
- **Scoping Meeting**: A meeting of the review team early in the review cycle to discuss and agree on key questions for each discipline. This is part of the good review management practices. This is also referred to as 'Front Loading' meeting.

POLICY

The multi-disciplinary procedure for managing EOP2A meetings is applicable to all CDER staff.

Meeting acceptance criteria: EOP2A meetings are resource-intensive, yet can be very productive interactions between sponsors and FDA reviewers in terms of improving the quality of drug development. Current staffing in OND and OTS may preclude acceptance of some EOP2A meeting requests. FDA decisions about granting an EOP2A meeting, especially with multiple requests across CDER, depend on the following criteria (in order of priority):

1. Availability of review staff in OND and OTS to participate in the meeting.
2. Completeness of sponsor's submission: Priority will be given to meeting requests from sponsors who have performed a complete analysis and have well-developed questions related to drug development decisions. Meeting requests with purely technical questions related to quantitative analyses will not be given priority.
3. Importance of the indication: Priority will be given to meeting requests involving potential drugs to treat life-threatening diseases or diseases with important public health implications.
4. Prior experience: The availability of quantitative models plays a substantial role in the preparation for these meetings. Priority will be given to disease areas where rich prior experience exists. For example, the Office of Translational Sciences (OTS) has experience with disease models for Parkinson's Disease, HIV/HCV, Alzheimer's Disease, and non-small cell lung cancer.

To be successful, EOP2A meetings require close collaboration between OND and OTS staff. All EOP2A draft reviews will be managed and communicated using a central electronic forum, such as eRoom (see References). Reviewers can upload and edit draft reviews; send notifications to each other; make comments; maintain electronic links to the EDR; and easily archive completed reviews. The central management system also facilitates ready information on other ongoing EOP2A meetings across CDER. Formal documentation of the final reviews, correspondence with the sponsor, and meeting minutes will be archived in DARRTS by Regulatory Project Manager.

CDER policies pertaining to Equal Voice are applicable.

RESPONSIBILITIES

OND Divisions are responsible for:

- Assigning a Regulatory Project Manager (RPM) when an EOP2A meeting is requested.
- Notifying Directors of the Office of Biostatistics (OB) and Division of Pharmacometrics (DPM) of EOP2A meeting request within 2 days of receipt.
- Collaborating with the Director, DPM and the Director, OB on whether to grant the meeting and, if so, the timing of the meeting.
- Notifying the sponsor whether the meeting is granted or denied according to industry meeting timelines and established procedures (see References).
- Project-managing the scoping meeting, pre-meeting, and industry meeting; EOP2A meetings are considered to be type C meetings.
- Completing the relevant parts of the EOP2A Meeting Decision Form (Appendix A) (Division Director and RPM). The Decision Form is an internal tool to document our decision making for future use. It will be archived by DPM.
- Assigning an OND Clinical Reviewer for the EOP2A meeting, if the meeting is granted. The OND Division will be responsible for input on the clinical endpoints and general trial design issues, and any clarification on regulatory issues.
- Deciding on the key questions to be discussed at the meeting. These questions may be different from those posed by the sponsor.
- Communicating the draft responses and recommendations to the sponsor subsequent to the internal meeting.
- Working closely and collaboratively with the rest of the review team.

Director, DPM, will be the point of contact for OTS and is responsible for:

- Collaborating with the Director, OND Division and the Director, OB on whether to grant the meeting and, if so, the timing of the meeting.
- Working closely and collaboratively with the OND RPM and Division Director, and Director, OB to coordinate the EOP2A meeting process.

- Communicating with the Director, OB and discussing the potential role of OB reviewers. If the meeting topics involve statistical issues (e.g., primary statistical analyses for registration trials), discuss availability of OB review staff.
- Communicating receipt of the EOP2A meeting request within Office of Clinical Pharmacology (OCP) to the respective Divisions of Clinical Pharmacology and Genomics Group. Working closely with OCP staff during the EOP2A meeting process.
- Notifying the OND RPM within 2 days after receiving the meeting request of the name of the OTS Lead who will jointly decide with OND on whether to accept the meeting request or not. If the topics are predominantly pharmacometric in nature, then DPM will be the OTS Lead. If the topics are predominantly statistical in nature, then OB will be the OTS Lead.
- Assessing the information provided in the meeting request for availability of the appropriate exposure-response and placebo data to be used to plan the subsequent trials; and completeness of the modeling and simulation work as well as availability of OCP review staff.
- Completing the relevant parts of the EOP2A Meeting Decision Form (Appendix A).
- Coordinating granted meetings with Directors, Divisions of Clinical Pharmacology, DPM and Genomics Group to assign reviewers, as needed, from their respective staff, and notifying the OND RPM of reviewer assignments by day 14 after the meeting request is received to facilitate scheduling of the meetings. The Team Leader of the relevant Division of Clinical Pharmacology should be a member of the review team for all EOP2A meetings.
- Deciding the key questions or issues to be discussed at the EOP2A meeting. These questions may be different from those posed by the sponsor.
- Conducting a thorough analysis of the meeting package and preparing OCP draft responses to the sponsor to be discussed at the internal pre-EOP2A meeting.
- Preparing a detailed report of any additional analyses performed, followed by sign-off in DAARTS. The data, analyses, and output files related to the modeling and simulation will be archived in accordance with the standards determined by Division of Pharmacometrics.
- Working closely and collaboratively with the rest of the review team.

Directors, Office of Biostatistics (OB) and Office of Translational Sciences (OTS), are responsible for:

- Collaborating with the Directors, OND Division and DPM on whether to grant the meeting and, if so, the timing of the meeting.
- Assigning reviewer(s) who will be responsible for the statistics-related questions if the meeting is granted. The Director, OB, will notify the OND RPM of the assignments by day 14 after the meeting request is received to facilitate scheduling of the meetings.

- Deciding on the key questions to be discussed at the EOP2A meeting. These questions may be different from those posed by the sponsor.
- Preparing OB draft responses to the sponsor to be discussed at the internal pre-EOP2A meeting.
- Preparing a detailed report of any additional analyses performed and archive accordingly.
- Working closely and collaboratively with the OTS point of contact and the rest of the review team.

PROCEDURES

Work Management within CDER:

Table 1 provides a summary of the timelines and milestones for a typical EOP2A meeting and a detailed description is given below:

- Meeting requests are to be submitted by the sponsor to the Director of the OND Review Division. OND RPM will forward the meeting request to Directors of DPM, and OB promptly. Team Leader, DPM will complete the Decision Form (Appendix A). These forms will not be archived, but will be retained by the Office of Clinical Pharmacology.
- If the meeting is granted, sponsor will be requested to submit complete meeting package and any relevant data within a week. This will ensure adequate review time for FDA staff.
- **SCOPING MEETING:** If the meeting is granted, the project manager will schedule a scoping meeting. The purpose of the scoping meeting is to agree on the review deliverables, timelines, and reviewer responsibilities.
    - The scoping meeting will occur approximately two weeks after receiving the complete meeting package from the sponsor.
    - The multi-disciplinary review team will decide on the key questions for the EOP2A meetings at the scoping meeting. These questions may be different from those posed by the sponsor.
    - The Cross-Discipline Team Leader (CDTL) for the EOP2A meetings will be determined based on the key questions. The team leader of the discipline that will have the most substantial contribution, such as the Division of Pharmacometrics TL, to the EOP2A work will be a natural choice for the CDTL. This will ensure efficient use of our resources.
    - The RPM completes the EOP2A Scoping Form (Attachment B) at the scoping meeting. The purpose of this form is to identify the review team members, their responsibilities, and the key questions for review. There is no need to officially archive this form. Subsequent to the scoping meeting, the project manager sends a copy of the form (or a link to the document) to the review team.

- **DRAFT REVIEW AND INTERNAL PRE-EOP2A MEETING:**
  - Draft reviews from the reviewers are due to the CDTL one week before the EOP2A meeting. The CDTL will compile the draft recommendations and forward to the review team for discussion at the internal pre-EOP2A meeting.
  - Following the internal meeting, at least 48 hours before the EOP2A meeting, the CDTL will provide the RPM the draft recommendations to be forwarded to the sponsor.
  - A decision on whether an FDA presentation at the EOP2A meeting is necessary will be made at the pre-meeting. The decision will depend on whether our reviewers have identified new or substantially different findings from those submitted by the sponsor.
- **EOP2A MEETING:**
  - OND and OTS lead will co-chair the EOP2A meeting.
  - If necessary, a summary of new and substantial findings will be presented by the FDA reviewers and/or the Sponsor.
- The OND RPM and CDTL will compile draft meeting minutes based on input from the review team. The co-chairs of the meeting will approve and sign the meeting minutes.
- FDA and sponsors will be surveyed upon completion of the EOP2A meeting. The purpose of the survey is for the FDA to learn about the value of the meeting and aspects that can be improved for the future. DPM will administer and receive the survey using Attachment C. The completed form will not be archived, but will be retained by the OCP.

Types of interaction with the sponsor:

1. Not all EOP2A meetings require a face-to-face meeting. When the questions do not necessitate a face-to-face discussion with the sponsor, recommendations can be communicated to the sponsor via email or fax. When a brief and straightforward discussion or clarification is warranted, a teleconference may be more efficient than a face-to-face meeting. Face-to-face meetings should be reserved for requests that warrant discussion of new findings from the review team and/or when there are recommendations that might alter the drug development substantially.
2. During the EOP2A meeting preparation, the review team may need to interact with the sponsor on technical matters related to data submission, modeling, and simulation results, alternative simulation scenarios, and/or related study reports. In that case, the OCP or OB reviewers should forward written requests/questions to the sponsor via the CDTL and OND RPM. If there is a need for a follow-up teleconference, the RPM and CDTL are required attendees. There is no need to generate formal minutes.

Table 1. Timelines and milestones (in working days) for the EOP2A meeting process. Timelines are shown in days from the submission of the meeting request.

Task	Timeline, days	Responsibility
Receive meeting request from sponsor	0	Sponsor
Forward copies of meeting request to Directors of DPM, OB	2	OND RPM
Decide on OTS Lead and communicate to OND Director, RPM	4	Directors OB, DPM/OCP
Create eRoom entry and complete Decision Form (Appendix A)	7	OTS Lead
Enter discipline reviewer names on Scoping Form (Appendix B) & forward to OND RPM	14	Directors OB, DPM/OCP
Forward decision on granting meeting and date to OND RPM	19	Director OND, OTS Lead
Request sponsor to estimate the complete package submission date	19	OND RPM *This information will help us negotiate the EOP2A meeting date (if needed)*
Forward decision on granting meeting to sponsor	21	OND RPM
Schedule scoping meeting for 2 weeks after the estimated complete meeting package submission	21	OND RPM
Complete meeting package	35	Sponsor
Forward copies of complete meeting package to reviewers	37	OND RPM
Scoping meeting; Scoping Form (Appendix B)	49	Review team; OND RPM
Forward Scoping Form to review team	51	OND RPM
Draft discipline reviews to CDTL	68	Reviewers
Pre-meeting (internal)	68	Review team
Final draft responses to OND RPM	70	CDTL
Draft responses to sponsor	72	OND RPM
EOP2A Meeting	75	Review team, Sponsor

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment A (Will be provided electronically in eRoom)

Project Manager's Section: Submission# INSERT SUBMISSION # Submission Date MM/DD/YYYY Sponsor Requested Meeting Date MM/DD/YYYY Sponsor INSERT SPONSOR NAME Submission Type, Number ☐ IND ☐ NDA/BLA Insert Number Complete Package Submission INSERT DAYS AFTER MEETING GRANTED? (*ask sponsor for an estimate)* Drug Name Generic: INSERT GENERIC Brand: INSERT BRAND (if known)	**CDER EOP2A Decision Form** **To be filled-out in eRoom, by OTS Lead with input from OND, OTS** OND Section: A. Is the proposed indication of high public health importance and/or prone to high trial failure rate ☐ Yes ☐ No
OTS Section: (OTS Lead to complete this section) **OTS Lead** A. Investigators' brochure B. Modeling and simulation summary report C. Summary of future trial designs D. Drug development related questions E. Prior quantitative models available	 ☐ **OCP** ☐ **OB** ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No
Grant Meeting EOP2A Meeting Date	☐ Yes ☐ No MM/DD/YYYY

Attachment B (Will be provided electronically in eRoom)

Submission Date MM/DD/YYYY	**CDER EOP2A Scoping Form** **To be filled-out in eRoom by OND RPM at the Scoping Meeting**
Sponsor Requested Meeting Date MM/DD/YYYY	Submission Type, Number ☐ IND ☐ NDA/BLA Insert Number
Sponsor INSERT SPONSOR NAME	Drug Name Generic: INSERT GENERIC Brand: INSERT BRAND (if known)

Scoping Meeting Attendees:

OND RPM:	INSERT NAME OR NOT ATTENDED
OND Reviewer(s):	INSERT NAME OR NOT ATTENDED
OND TL:	INSERT NAME OR NOT ATTENDED
DPM/OCP Reviewer(s):	INSERT NAME OR NOT ATTENDED
DPM/OCP TL:	INSERT NAME OR NOT ATTENDED
DCP/OCP Reviewer(s):	INSERT NAME OR NOT ATTENDED
DCP/OCP TL:	INSERT NAME OR NOT ATTENDED
Genomics/OCP Reviewer(s):	INSERT NAME OR NOT ATTENDED
OB Reviewer(s):	INSERT NAME OR NOT ATTENDED
OB TL:	INSERT NAME OR NOT ATTENDED
Additional Attendees:	INSERT NAMES OR NONE ATTENDED

Key Questions:

1. Add text

Milestones and Timelines:

Milestone	Task	Date
Each discipline's draft responses to CDTL	Review team	
Draft responses along with summary of new results to RPM	CDTL	
EOP2A meeting	Review team	

Attachment C (Will be provided at the EOP2A Meeting)

EOP2A Meeting Date MM/DD/YYYY	**EOP2A Meeting Evaluation** **Send to Director, Division of Pharmacometrics, OCP**
Affiliation (Mark all that apply) ☐ FDA ☐ Sponsor ☐ Medical ☐ Pharmacometrics ☐ Statistics ☐ Clinical Pharmacology/PK ☐ Genomics ☐ Regulatory Affairs ☐ INSERT OTHER	Submission Type, Number ☐ IND ☐ NDA/BLA Insert Number Drug Name Generic: INSERT GENERIC Brand: INSERT BRAND (if known)
1. What was the overall value of this meeting to drug development decisions? Explain:	☐ None ☐ Supportive ☐ Pivotal
2. Did the meeting change development plans? Explain:	☐ Yes ☐ No
3. Person hours spent on this project?	INSET HOURS
4. Sponsor: Are you willing to share the EOP2A experience in a manuscript?	☐ No ☐ Yes with compound blinded ☐ Yes with compound unblinded

5. Suggestions for improving future EOP2A meetings