OFFICE OF CLINICAL PHARMACOLOGY

An Integrated Genomics, Pharmacometrics, and Clinical Pharmacology Review Process

CONTENTS

PURPOSE

- This MAPP establishes a review process for genomics, pharmacometrics, and clinical pharmacology, referred to as the *integrated review process* (IRP), for the evaluation of new drug applications (NDAs) and biologics license applications (BLAs) for new molecular entities (NMEs), and applications or supplements for pediatric indications in the Office of Clinical Pharmacology (OCP).
- The guiding principle is that reviewers from the Divisions of Clinical Pharmacology, Genomics, and Pharmacometrics work collaboratively on OCP reviews.

BACKGROUND

- Reviewers in the Office of Clinical Pharmacology (OCP) are charged with managing quality and consistency of all clinical pharmacology reviews for CDER as described in MAPP 4000.4, "Clinical Pharmacology and Biopharmaceutics NDA Review Template."
- The staff of the Divisions of Clinical Pharmacology within OCP will be referred to as Clinical Pharmacology (CP) reviewers.
- The Pharmacometrics Staff is charged with managing quality and consistency of pharmacometric reviews within OCP. The primary focus of pharmacometrics is on NDA/BLA reviews for NMEs and Pediatric Supplements. Pharmacometrics review encompasses usage of population modeling and simulation analyses of exposure-response data to answer specific trial design, evidence of effectiveness, and/or dose selection questions. These models often consider variability (due to intrinsic/extrinsic factors) in exposure and its influence on effectiveness and safety endpoints. An important part of the review includes communicating complex modeling and simulation results in plain language so members of OCP and other interdisciplinary scientists can understand the results and potential impacts.

- The Genomics Group Staff is charged with managing quality and consistency of genomics reviews within OCP. The primary focus is on NDA/BLA reviews for NMEs. The genomics reviews include assessment of genomic, genetic, proteomic, and metabolomic data. The breadth of the review can vary considerably depending on the context of use of these data. In general, genomics reviews include the analysis of the impact of genetic/genomic biomarkers on efficacy and/or safety endpoints, and on doses and dosing intervals. These data may include, but are not limited to, correlation (genotype-phenotype) of gene expression or polymorphisms in certain genes (e.g., Cytochrome P450 metabolism genes) to adverse events in the context of the drug under review. The review may lead to recommendations to alter the dose of the drug or to avoid use of the drug in a subgroup of patients for efficacy or safety reasons.
- The Good Review Management Principles (GRMP) initiative has redefined the timelines and deliverables during the review process, thereby creating early deadlines. Successful overall OCP review depends on the integration of pharmacometrics, genomics, and clinical pharmacology reviews early in the review process. However, the expectations for all OCP staff are increasing with the new GRMP for NDAs/BLAs, and development and adherence to the IRP is critical for providing high quality and informative reviews and more efficient management of the review process. (See CDER MAPP 6025.3 rev. 1, below.)

REFERENCES

- CDER MAPP 4000.4 Clinical Pharmacology and Biopharmaceutics Review Template 6/27/04.
- CDER MAPP 5120.1 rev. 1 Office of Clinical Pharmacology Briefing Criteria and Attendance Policies 11/2/09.
- CDER MAPP 6025.3 rev.1 Good Review Practice: Consultative Review of Drugs Regulated Within OND 7/16/07.
- CDER MAPP 4151.1 Resolution of Disputes: Roles of Reviewers, Supervisors, and Management: Documenting Views and Findings and Resolving Differences 8/19/96.

DEFINITIONS

- **The Primary Pharmacometrics and/or Genomics Staff Reviewer:** The reviewers on the Pharmacometrics Staff or Genomics Staff who perform the primary pharmacometrics and/or genomics review and are an integral part of the clinical pharmacology and CDER review teams.

  Secondary Pharmacometrics/Genomics Reviewer: The OCP Reviewer who will perform the secondary review for scientific quality and consistency of the Primary Pharmacometrics/Genomics Reviewer's review. The Secondary Pharmacometrics/Genomics Reviewer will always be a member of the Pharmacometrics/Genomics Staff.
- **Lead QBR Author:** The OCP Reviewer responsible for completing the question based review (QBR), with input from the other OCP reviewers. The lead QBR author also collates the QBR with clinical pharmacology, pharmacometric, and genomics reviews and recommendations. The Clinical Pharmacology Reviewer typically will be the lead QBR author. Team leaders will decide which reviewer will be the lead QBR author based on the relative contribution of each discipline to the overall OCP review. For example, the Primary Clinical Pharmacology Reviewer is most likely lead

QBR author for NDA or BLAs for NMEs; however, it is likely that the Primary Pharmacometrics Reviewer will be the lead QBR author for pediatric submissions, which have a small number of PK studies and one or more effectiveness and safety trials requiring pharmacometrics analyses. Similarly, the Primary Genomics Reviewer may be the lead QBR author for sNDAs that deal with relabeling based on genomic/genetic tests needed to avoid adverse events associated with the drug. The secondary review process will remain the same in all cases. The Clinical Pharmacology Team Leader is always responsible for getting OCP reviews of high quality completed by the OCP team and within the agreed upon timelines.

POLICY

- All reviewers within OCP will comply with the integrated genomics, pharmacometrics, and clinical pharmacology review process to ensure an efficient and impactful reviews.

RESPONSIBILITIES

- The Primary Clinical Pharmacology (i.e., Divisions of Clinical Pharmacology), Pharmacometrics, and Genomics Reviewers are jointly responsible for the OCP recommendations derived from the integrated Clinical Pharmacology/Pharmacometrics/Genomics reviews. They are responsible for their respective parts of the QBR.
- While the Primary Pharmacometrics or Genomics Reviewer is often a member of the Pharmacometrics and/or Genomics Staff, this is not mandatory. Interested and qualified reviewers from the Clinical Pharmacology therapeutic team can serve as the Primary Pharmacometrics and/or Genomics Reviewers. Pharmacometrics and/or Genomics Staff will consider the complexity of the review/analysis, experience, and workload in determining the Primary Pharmacometrics/Genomics Reviewer, in consultation with the Clinical Pharmacology Team Leader. The standard processes (to be disseminated separately) pertaining to data analysis, review, slides and meeting preparation, and archival of data and/or reviews for pharmacometrics/genomics reviews will apply to all those designated as the Primary Pharmacometrics/Genomics Reviewers.

Members of the Divisions of Clinical Pharmacology (DCP) are responsible for the following:

The Clinical Pharmacology Team Leader (TL) provides timely notification (see Procedures section) on:

- All NDAs and BLAs for NMEs and applications or supplements for pediatric indications (usually within 2 weeks of receipt of the submission by OCP)
- Other types of submissions that have a potential need for a pharmacometrics/genomics review as judged by DCP soon after or before the filing meeting

The Primary Clinical Pharmacology reviewer, Clinical Pharmacology Team Leader, DCP Division Director, or Deputy Director participates in OCP scoping meetings (see Scoping Meetings).

The Clinical Pharmacology TL manages pre-filing, pre-mid-cycle, pre-briefing, and briefing meetings within OCP. For submissions without need for pharmacometrics/genomics review, DCP will manage the scoping meeting.

Pharmacometrics/Genomics Staff is responsible for the following:
Managing scoping meetings where pharmacometrics/genomics review need has been identified.

If the pharmacometrics/genomics review need has been identified, the Pharmacometrics/Genomics Staff will:

- Provide a written plan on the questions to be addressed, roles assigned, and timelines, as described in the OCP Scoping Meeting Form (see Attachment at end of this MaPP)
- Provide a precise and clearly written pharmacometric/genomic review that follows the pharmacometric/genomic review template and related review processes which are available at http://eroom.fda.gov/eRoom/CDER5/CDEROCPPharmacometrics/0_162dd.
- Participate in pre-filing, pre-mid-cycle, pre-briefing, and final briefing meetings within OCP
- Participate in meetings with the CDER review team (including filing, mid-cycle, labeling), pharmaceutical sponsors, and advisory committees

PROCEDURES

Submission Notifications and Pharmacometric/Genomics Review Requests

The following procedures should be followed when notifying Pharmacometric and Genomic Staff of an NDA, BLA, or pediatric submission.

NDA/BLA for NMEs and pediatric submissions

- Within 2 weeks of receipt of a submission, the Clinical Pharmacology TL will send a notification for NDAs or BLAs for NMEs and applications or supplements for pediatric indications by e-mail to both pharmacometrics@fda.hhs.gov and cderocpbgenomics@fda.hhs.gov.
- The e-mail notification should include the application number, drug name, the link to the electronic document room (EDR) (if available), and whether the submission is for an NME or pediatric indication. A Pharmacometric/Genomic Review Request Form will not be necessary for these submissions.

Other types of NDA/BLA submissions

- Requests for a pharmacometrics review should be submitted to pharmacometrics@fda.hhs.gov using the Review Request Form located on the OCP Web site (http://cdernet/ocpb/pm/ReviewRequest/). Requests for a genomics review should be submitted to the Genomics Staff using the review request form at http://intranetapps.fda.gov/scripts/OCP%5FApps/GenomicsReview/entry/.

OCP Pre-Filing Meetings for NDA/BLAs for NMEs

The Clinical Pharmacology Team Leader or designee will invite the Pharmacometric TL and Genomics Reviewer associated with that therapeutic area to the pre-filing meetings.

Purpose:

- From the pharmacometrics perspective, the meeting is to determine the need for a pharmacometric review.

- The Pharmacometrics TL will decide, in consultation with the review team, on the need for a pharmacometrics review. Typically, the need is driven by availability of appropriate data and/or whether the pharmacometric analysis has the potential to influence approval, dosing, and/or labeling decisions.
- If there is no need for a pharmacometrics review, then Pharmacometrics Staff will not be involved with the remainder of the review process.

- From the genomics perspective, the meeting is to determine the need for a Genomics Review.
  - The Genomics Reviewer, in consultation with the review team, will decide on the need for a genomics review.
  - If there is no need for a review, then Genomics Staff will not be involved with the remainder of the review process.
- From the clinical pharmacology review perspective, there may be additional objectives, such as to understand the clinical relevance of potential drug-drug interactions and exposure changes in special populations.

Scoping Meetings

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.

All NMEs will have a scoping meeting. Scoping meetings are optional for submissions where standard QBR questions apply. The decision to have a scoping meeting will be made by the team leaders.

The Pharmacometrics Project Manager will schedule the scoping meeting to occur approximately 2 weeks after the CDER filing meeting for submissions needing a pharmacometrics review. If a genomics review is needed, the Genomics Project Manager will schedule the scoping meeting. The DCP will manage the scoping meetings for submissions that do not require pharmacometrics/genomics review.

Purpose - To identify the key questions, to identify the lead QBR author, and to agree to timelines and deliverables.

Required participants (for scheduling purposes)

- Primary Clinical Pharmacology, Pharmacometrics, and Genomics Reviewers, and their respective Team Leaders
- Primary Medical Reviewer
- DCP Director or Deputy Director (whichever is available, but not necessarily both)
- Pharmacometrics or Genomics Project Manager

Optional Participants (for scheduling purposes)

- OCP Director or Deputy Director (for NMEs only)
- DCP Director or Deputy Director
- Pharmacometrics Director
- Medical Team Leader

Roles and Responsibilities of Participants:

Clinical Pharmacology Reviewer

- Review Clinical Pharmacology and Clinical Summaries and labeling before the meeting
- Develop clinical pharmacology questions requiring pharmacometrics/genomics input and discuss with Pharmacometrics/Genomics Reviewer before scoping meeting
- Provide a listing of draft key review questions with supporting rationale (slides or handouts, 5 slide limit)

Pharmacometrics/Genomics Reviewer

- Review Clinical Summaries and labeling before the meeting
- Develop initial pharmacometrics/genomics questions and discuss with Clinical Pharmacology Reviewer before meeting
- Provide a listing of draft key review questions with supporting rationale (slides or handouts, 5 slide limit)

Pharmacometrics/Genomics Project Manager

- Manage the scoping meeting
- Record key agreements in the Scoping Meeting Form (see Attachment)
- Send the completed Scoping Meeting Form to all meeting participants
- Archive the Scoping Meeting Form in the Pharmacometrics/Genomics eRoom

OCP Pre-Mid-Cycle Meetings

DCP will manage the OCP pre-mid-cycle meeting to discuss clinical pharmacology mid-cycle deliverables before presenting these findings outside OCP. Invite OCP Director or Deputy Director to mid-cycle meetings for NMEs with important OCP issues only.

- Participants:
  - Primary Clinical Pharmacology, Pharmacometrics, and Genomics Reviewers, and their respective Team Leaders
  - DCP Director or Deputy Director (whichever is available, but not necessarily both)

Communication During the Review

- Keeping the entire OCP review team informed of key findings is important throughout the review process. As needed, informal meetings (e-mail, phone, face-to-face) among Clinical Pharmacology, Pharmacometrics, Genomics, and Medical/Statistical Reviewers are encouraged. It is not required that all Primary OCP Reviewers (clinical pharmacology, pharmacometrics, and genomics) be present at all such informal meetings. However, all reviewers should be invited to participate. Important outcomes of interactions with reviewers outside OCP should be shared with the rest of the OCP Primary Reviewers (clinical pharmacology, pharmacometrics, and/or genomics). Important review findings that might influence approval or labeling decisions should be discussed among the OCP reviewers before discussing outside of OCP.

- The general expectation is that clinical pharmacology/pharmacometrics/genomics teams work together collaboratively during the review process.
- The standard processes (to be disseminated separately) pertaining to data analysis, review, slides and meeting preparation, and archival of data and/or reviews for pharmacometrics/genomics reviews will apply to all those designated as the Primary Pharmacometrics/Genomics Reviewers.
- Differences in opinions with respect to review and/or process should be resolved among the Clinical Pharmacology/Pharmacometrics/Genomics Reviewers and Team Leaders. For unresolved issues, the

corresponding Clinical Pharmacology/Pharmacometrics/Genomics Directors should resolve the differences together as per (see References.)

Integrated Question-Based Review Process and Timelines

- A single well-collated, integrated QBR is desired. The focus should be on resolving problems identified as important to the clinical assessment of benefit and risk. Reviews should be separately signed off only under certain circumstances, such as scientific disagreements.
- The Primary OCP Reviewers (clinical pharmacology, pharmacometrics, genomics) and their respective Team Leaders will be responsible for their respective sections of the QBR, as agreed to at the scoping meeting. If the primary Clinical Pharmacology Reviewer finds additional information that contributes to the questions addressed by Pharmacometrics or Genomics, then that information should be included and the Pharmacometrics or Genomics Reviewer should be informed.
- The Clinical Pharmacology, Pharmacometrics, and Genomics Reviewers will exchange respective reviews as MS Word documents The Lead Author will collate questions and write an integrated executive summary and listing of recommendations that reflect each individual review.
- The full pharmacometrics and genomics review will be included as an appendix to the QBR. To merge these documents, the final pharmacometrics and genomics review will be saved as an Adobe PDF file. The Lead Author will merge these PDF files together. The purpose of using PDF format is to avoid the Lead Author having to do painstaking, time-intensive reformatting of fonts, table/figure numbering, margins, headings, and table of contents.
- The final OCP review (PDF format) will be signed off by all the Primary Reviewers and their respective Team Leaders.
- The order of sign off is as follows: Lead Author, Contributing Author(s), Pharmacometrics/Genomics Team Leader, Clinical Pharmacology Team Leader, and Clinical Pharmacology Director (if applicable).
- The following table presents goal timelines for the different review milestones (see the Attachment for specific milestone dates that affect reviewers at scoping meetings).

Milestone	**Timeline in Calendar days (minimum)**
Finalize QBR and sign-off	+3
OCP Briefing	0
Dry run within OCP; exchange Clinical Pharmacology/Pharmacometrics/Genomics draft slides before dry run	-3
OCP Briefing Announcement with final draft QBR	-7
Clinical Pharmacology Team Leader QBR Concurrence	-8
Pharmacometrics/Genomics Team Leaders QBR Concurrence	-12
Clinical Pharmacology/Pharmacometrics/Genomics Team Leaders review final draft QBR	-14
Clinical Pharmacology/Pharmacometrics/Genomics Exchange reviews with Team Leader concurrence and Lead Author collates reviews	-21
Individual Clinical Pharmacology/Pharmacometrics/Genomics draft reviews to respective Team Leaders	TBD tentatively at Scoping Meeting

Date of OCP Briefing is dependent upon advisory committee meeting and PDUFA goals.

OCP Briefing

- DCP will schedule pre-briefing and briefing meetings
    - Lead QBR Author will issue the briefing announcement with final draft QBR.
    - Clinical Pharmacology, Pharmacometrics, and/or Genomics Primary Reviewers will be responsible for the slides to be presented at the briefing and any discussion around the respective topics.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT

Scoping Meeting Date MM/DD/YYYY	**OCP Scoping Meeting Form**

Review Type	Submission Type, Number and Date
☐ NME ☐ Pediatric ☐ Other: Provide Description	☐ NDA ☐ BLA Insert Number

Sponsor	Drug Name
INSERT SPONSOR NAME	Generic: INSERT GENERIC Brand: INSERT BRAND

Scoping Meeting Attendees:		Indicate Lead Author
Pharmacometrics Reviewer:	INSERT NAME OR NOT ATTENDED	☐
Clinical Pharmacology Reviewer:	INSERT NAME OR NOT ATTENDED	☐
Genomics Reviewer:	INSERT NAME OR NOT ATTENDED	☐
Pharmacometrics TL:	INSERT NAME OR NOT ATTENDED	
Clinical Pharmacology TL:	INSERT NAME OR NOT ATTENDED	
Clinical Reviewer:	INSERT NAME OR NOT ATTENDED	
Clinical TL:	INSERT NAME OR NOT ATTENDED	
DCP Division Director:	INSERT NAME OR NOT ATTENDED	
DCP Deputy Director:	INSERT NAME OR NOT ATTENDED	
Additional Attendees:	INSERT NAME OR NONE ATTENDED	

Key Review Questions:

1. Add text

Milestones and Timelines:

Milestone	Date
Pre- Mid-Cycle Meeting	
Mid-Cycle Meeting	
Clinical Pharmacology/Pharmacometrics/Genomics Team Leaders review final draft QBR Clinical Pharmacology Concurrence Pharmacometrics/Genomics Concurrence	
Clinical Pharmacology/Pharmacometrics/Genomics Exchange reviews and Lead Author Collates Reviews	
OCP Briefing Announcement with final draft QBR	
Dry run within OCP, exchange Clinical Pharmacology/Pharmacometrics/Genomics draft slides before dry run	
OCP Briefing	
Final QBR Sign-off	
(If applicable) Pre-Advisory Committee Meeting	
(If applicable) Advisory Committee Meeting	