POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: Clinical Consultative Review of Drugs Regulated Within OND

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PURPOSE

- This MAPP describes the clinical consultative review process in the Office of New Drugs (OND) within the Center for Drug Evaluation and Research (CDER) for investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), and supplemental NDA and BLA applications. The procedures in this MAPP are intended to ensure quality and consistency in clinical consultative reviews. This MAPP also describes the sign-off policies and procedures for INDs, NDAs, BLAs, and supplements for drugs regulated in OND that require consults from other divisions or offices within OND.

- This MAPP does not describe consultative interactions between OND and the Office of Surveillance and Epidemiology. Those interactions are described in other documents.

- This MAPP does not describe the interactions between the Division of Nonprescription Clinical Evaluation and specific subject matter review divisions (SSMRDs) relating to the review of over-the-counter applications. Those interactions are described in other documents.

- This MAPP is one in a series of MAPPs designed to document good review practices (GRPs) for review staff in accordance with MAPP 6025.1 *Good*

Review Practices. General policies, responsibilities, and procedures regarding all GRPs are contained in MAPP 6025.1 and apply to this MAPP.

BACKGROUND

- INDs, NDAs, and BLAs for drugs regulated in OND are assigned to SSMRDs by indication. Frequently, however, the evaluation of a submission requires the expertise of a second review division or a second office within OND, either because of that division's or office's familiarity with the drug for other uses or because of its expertise in the disease or involved organ system. There is a trend for INDs to be opened with trials of increasing complexity, such as late phase 2 or phase 3 clinical trials that are intended to be part of an NDA or BLA submission or phase 2 trials that will affect the design of subsequent pivotal trial protocols, after completion of early phase clinical trials in non-U.S. sites. Drugs may be developed for multiple indications, and the experience and expertise of the initial review division may be important for another review division evaluating a second indication.

- OND's consult request process is well-established. This MAPP describes the nature of the consultative interaction for all drugs regulated in OND. MAPP 6020.13 *Good Review Practice: Clinical and Consultative Review of Drugs to Reduce the Risk of Cancer* describes consultative interactions that are specific to the review of cancer prevention drugs. The Office of Hematology and Oncology Products is responsible for the review of products to reduce the risk of cancer, and consults SSMRDs with particular expertise in the involved organ system or other uses of a drug. These two MAPPs therefore describe complementary processes.

POLICY

- The policies and procedures outlined in this MAPP apply to clinical consultative interactions between SSMRDs and offices within OND.

- Consults are appropriate when another division or office has expertise that could contribute to the assessment of the safety or efficacy of a drug under review.

  – Consults should make optimal use of the expertise of the consulted SSMRD or office by providing specific questions for the consultants. Such expertise may include the SSMRD evaluation of endpoint measurement, the premarketing safety monitoring of a pharmacologically similar drug approved for another indication by the SSMRD, or

experience with other uses of the drug under review. Consults should not request a global evaluation of the submission.

- Although consults may not be necessary for an IND for a new molecular entity (NME) or one that proposes a *first-in-human* trial, the review team should consider the need for a consult when a new IND is submitted and throughout the drug development cycle. For example, a consult should be considered for an NME that is a member of a class of drugs approved in another division, when a special protocol assessment (SPA) is requested, when pivotal phase 3 trials are submitted, and at other critical junctures in development.

- When consults are requested from another SSMRD, the assigned review division/office has primary review responsibility and retains sign-off authority. However, every effort should be made to perform a cooperative review in which careful consideration is given to consultant recommendations.

PROCEDURES

New INDs

- The 30-day IND review clock may not allow sufficient time to evaluate a complex clinical trial submitted as a new IND, especially if a consultative review is needed. When the assigned review division becomes aware of this circumstance through prior communication with a sponsor, it should encourage the sponsor to schedule pre-investigational new drug application/end-of-phase 2 (pre-IND/EOP2) meetings before submitting the IND.

  - To facilitate coordination and documentation of reviews, pre-IND meeting minutes, and correspondence, divisions should assign a pre-IND number for drugs without established applications when a sponsor requests a pre-IND meeting.

  - When a pre-IND meeting request and package are submitted, the medical team leader or assigned medical reviewer should determine the need for a consult from another SSMRD. If appropriate, the SSMRD consultant should be identified and should participate in the pre-IND/EOP2 meeting.

  - If a sponsor opens a new IND with a late phase 2 or phase 3 trial, the sponsor should be informed by the IND acknowledgement letter that only the safety review will be completed within 30 days of receipt. The trial's ability to fulfill the regulatory requirements for demonstrating

effectiveness will depend on further review and a possible consultation with a second SSMRD or office, which could result in further internal discussion and review. The sponsor also should be informed that it should submit a request for an EOP2 meeting to ensure full review and comment on the adequacy of the trial to support the proposed development plan. The EOP2 meeting may result in a request for an SPA submission.

- The medical team leader and/or assigned medical reviewer will evaluate the IND to determine the need for a consult from another SSMRD or office as soon as possible, but no later than 2 business days after receipt from the document room. For new INDs, it is critical that this determination for consultation be made as soon as possible (but no later than 2 business days after receipt from the document room) to permit sufficient time for review within the 30-day safety review period.

- A consult should focus on a disease-specific issue or endpoint assessment and should not include open-ended requests for a global assessment of the safety and efficacy of a drug for the stated indication. The consult form and submission material (i.e., the volume submitted by the sponsor or link to the submission in the electronic document archive) should be sent to the consulting SSMRD as soon as the need for a consult is identified and should not be delayed while detailed questions to the consultant are formulated. This procedure is designed to minimize time delays associated with paper submissions and their transit between divisions. It is expected that the medical reviewer will write and send, preferably by e-mail, specific questions to the consultant as soon as possible, but no later than 2 business days following the consult request.

- The regulatory project manager (RPM) will facilitate completion and archiving of consult forms and transmission of supporting information to the consulting SSMRD. Use of electronic transmission whenever possible is encouraged.

- Standard procedures will be used for documenting, archiving, and tracking consult requests and reviews. The SSMRD should acknowledge receipt of the consult request and send the name and contact information of the SSMRD reviewer to the RPM in the requesting division.

- The SSMRD should make every effort to complete its consult by day 20 (after FDA receipt) and forward it to the requesting division electronically. The standard procedures for sign-off within the SSMRD should be followed.

  - If the consult or sign-off process cannot be completed by day 20 because of late receipt of IND materials for review or other reasons, at a minimum, the SSMRD should provide any potential hold issues to the primary

reviewers in the requesting division in writing by day 20. These comments should consist of well-formulated statements that have been reviewed by the appropriate SSMRD leadership and can be transmitted to the sponsor.

- If additional time is needed, the requesting division and the SSMRD will negotiate a date for completion of the requested consult that extends beyond day 30. The IND sponsor will be notified by the requesting division RPM that additional nonhold comments may result from the ongoing review.

- If the consult is complete, has been reviewed and approved by division management, but awaits sign-off in CDER's corporate electronic document archive, the draft consult may be sent via e-mail to the requesting division to facilitate communication of relevant issues to the sponsor. This procedure is consistent with the current policy that sign-off in CDER's corporate electronic document archive is encouraged but not required to take action on an IND. However, the review must be signed off as soon as possible.

- The medical reviewer will evaluate the SSMRD's consult, call the consultant to discuss if needed, and incorporate accepted recommendations into the IND review. If major recommendations are not accepted, the medical reviewer and team leader should call the SSMRD consultant to discuss these concerns further. Division management should be included in the decision for not accepting a major recommendation. Justification for not accepting major recommendations made by the consultant should be included in the review and will be communicated to the consultant in the final review, sent through CDER's corporate electronic document archive.

- Final reviews by the primary reviewers will be entered into CDER's corporate electronic document archive in accordance with standard CDER procedures, and the SSMRD consultants should be included on the routing list. Sign-off will follow standard CDER procedures.

- The assigned division's RPM will facilitate the management of and communications concerning INDs.

- The SSMRD consultants, in addition to completing the consult, should be invited to attend safety meetings for new INDs as appropriate, all clinical hold meetings, teleconferences, and applicable division meetings through the initial 30-day review process.

Subsequent IND Submissions

- Similar procedures with appropriate timelines should be applied to protocols accepted for an SPA, for late phase 2 or phase 3 trials designed to support approval, and other significant submissions to the IND after the initial 30-day review period.

- The SSMRD consultants, in addition to completing the consult, should be invited to attend any applicable division meetings throughout the IND drug development phase.

NDAs and BLAs

- The standard CDER procedures will be followed for distribution, assignment, and review of NDAs, BLAs, and supplements.

- The assigned division's medical reviewer and medical team leader should determine the need for a consult from another SSMRD or office during the pre-NDA/BLA stage. If appropriate, the SSMRD consultant should be identified and involved in the review and meetings at this stage. If a pre-NDA/BLA meeting is not held, the need for consultation should be determined before the filing meeting (per the guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* (GRMP guidance)) so that consultants may participate in this first milestone meeting.

  – If the assigned division consulted another SSMRD during the IND stage of drug development, the division should consider whether the SSMRD should be re-consulted for review of the marketing application. If a consult is not needed, the rationale for this decision should be reflected in the regulatory section of the medical review.

  – If the SSMRD is re-consulted, if possible the consultant who wrote the IND consult should complete the NDA/BLA consult to preserve continuity.

- The RPM will facilitate completion and archiving of consult forms and transmission of supporting information to the consulted SSMRD or office. Use of electronic transmission is encouraged.

- Standard procedures will be used for documenting, archiving, and tracking consult requests and reviews.

- The timeline in the 21st Century Review process should be followed to facilitate review, communications, and accomplishment of target review and action goals.[1]

- The medical reviewer will evaluate the SSMRD's consult, call the consultant to discuss if needed, and incorporate accepted recommendations into the NDA/BLA review. If major recommendations are not accepted, the medical reviewer and team leader should call the SSMRD consultant to discuss these concerns further. Division management should be included in the decision for not accepting a major recommendation. Justification for not accepting major recommendations made by the consultant should be included in the final review and will be communicated to the SSMRD when the final review is entered into CDER's corporate electronic document archive.

- Final reviews by the primary reviewers will be entered into CDER's corporate electronic document archive in accordance with standard CDER procedures, with appropriate copies sent to the SSMRD. Sign-off will follow standard CDER procedures.

- The SSMRD consultant should be invited to attend meetings on the application as documented in the GRMP guidance.

- The assigned RPM will facilitate the management of and communications concerning NDAs, BLAs, and supplements.

Dispute Resolution

- The responsible signatory authority may accept or reject consultative advice. This MAPP requires the division with regulatory responsibility for the drug to discuss rejection of major recommendations with the SSMRD. If the SSMRD feels strongly that rejection of a major recommendation will affect the assessment of safety or efficacy of the drug under review, it is encouraged to try to resolve these disagreements with clear communication and discussion in telephone calls or meetings with the assigned review division.

- If further discussion does not substantially resolve the disagreement and serious concerns about the assessment of safety and efficacy persist, the SSMRD may proceed with dispute resolution according to the procedures in MAPP 4151.1 Rev. 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain* and MAPP 4151.2 Rev. 1 *Resolution of*

[1] See the Desk Reference Guide at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf.

Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.

REFERENCES

1. Guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

2. MAPP 6020.13 *Good Review Practice: Clinical and Consultative Review of Drugs to Reduce the Risk of Cancer*, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

3. MAPP 4151.1 Rev. 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*

4. MAPP 4151.2 Rev.1 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.*

5. MAPP 6025.1 *Good Review Practices*

DEFINITIONS

- Drug — for the purposes of this MAPP, refers to a drug or a therapeutic biological product regulated by CDER

- Specific subject matter review division (SSMRD) — OND review divisions with primary oversight of a group of prescription drugs used to treat physiologically categorized disease entities (e.g., the Division of Cardiovascular and Renal Products, the Division of Transplant and Ophthalmology Products)

EFFECTIVE DATE

This MAPP is effective upon date of publication.