POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: Clinical and Consultative Review of Drugs to Reduce the Risk of Cancer

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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 for drugs to reduce the risk of cancer. 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 to reduce the risk of cancer.

- The policies and procedures outlined in this MAPP apply to interactions between the Office of Hematology and Oncology Products (OHOP) and consultants residing in other CDER divisions and other offices or centers.

- This MAPP does not describe consultative interactions between OND and the Office of Surveillance and Epidemiology (OSE). 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

- Drugs to reduce the risk of cancer are an important focus of drug development. Expertise in cancer epidemiology and pathophysiology, in the design and analysis of chemoprevention trials, and in assessment of adverse events and toxicity in a healthy but at-risk population is important for the evaluation of the safety and efficacy of these drugs in CDER. In addition, collaboration with sponsors, oncology professional societies, clinical trial participants and advocates, the National Cancer Institute (NCI), and other important stakeholders, as well as coordination of cross-center work, is critical in facilitating the development and review of these drugs. For these reasons, all drugs to reduce the risk of cancer, except those intended to reduce nonmelanoma skin cancer, are reviewed within OHOP.[1]

- Frequently, the evaluation of a cancer prevention application requires the expertise of a review division or office outside of OHOP, either because of that division's or office's familiarity with the drug for other uses or because of its expertise in the involved organ system. Input is particularly helpful because 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 at non-U.S. sites.

- OND's consult request process is well-established. MAPP 6025.3 *Good Review Practice: Clinical Consultative Review of Drugs Regulated Within OND* describes consultative interactions between specific subject matter review divisions (SSMRDs) in OND. This MAPP describes the consultative review process specific to cancer prevention drugs.

POLICY

- OHOP has regulatory responsibility for drugs developed to reduce the risk of cancer. **Exception:** *Drugs to prevent nonmelanoma skin cancer are regulated by the Division of Dermatology and Dental Products (DDDP) and are not discussed in this MAPP.*

  – Regulatory project managers (RPMs) should instruct sponsors who intend to develop a new molecular entity for cancer risk reduction to submit the protocol and required nonclinical information as a new IND to OHOP.

[1] Nonmelanoma skin cancer therapies are reviewed in the Division of Dermatology and Dental Products, because these common lesions are usually diagnosed and treated exclusively by dermatologists.

- RPMs should instruct sponsors who plan to develop drugs with an established IND for a new indication of cancer risk reduction to submit the risk reduction protocol as part of a new IND to OHOP. Information previously submitted to the FDA for this drug may be cross-referenced from the existing application. Because of the 30-day review clock for INDs, the FDA should strongly encourage sponsors to include summaries of the key information used to support the cancer prevention protocol in the IND and to provide the corresponding serial number of the original application if more detailed information is required by the reviewing or consulting division. Only the safety review will be completed within 30 days of receipt; review of the adequacy of the trial to support the proposed indication generally will require additional time. Sponsors should be encouraged to submit a special protocol assessment (SPA) for phase 3 prevention trials, even when the trial is used to open a new IND.

- A supplement for a new cancer risk reduction indication for a previously approved drug will be assigned to OHOP, not to the SSMRD that reviewed the original application. Required information may be incorporated by specific reference (application number, date of submission, type of information).

- Jurisdiction for INDs that contain a single protocol with dual co-primary endpoints, one for cancer risk reduction and one for a noncancer risk reduction indication, will be determined by the relevant division directors and adjudicated, if necessary, by the respective office directors. If the office directors cannot reach agreement on drug assignment, the Director of OND will assign jurisdiction. Dual endpoint applications should be reviewed either consultatively or collaboratively, depending on the specific trial design and results.

- Review of cancer risk reduction applications (INDs, NDAs, BLAs, supplements) will be based on a consultative review process, when an SSMRD may be consulted but OHOP has primary review responsibility and retains sign-off authority. Although OHOP is responsible for the application, every effort should be made to perform a cooperative review, in which careful consideration is given to consultant recommendations.

  - OHOP will consult the appropriate SSMRD for all cancer prevention NDAs, BLAs, efficacy supplements, phase 3 trials, *pivotal* chemoprevention trials, and SPAs, as appropriate. OHOP may use its judgment as to whether a consult is required when one drug is submitted for investigation in several INDs, all with similar trial designs and safety issues. In this situation, if an SSMRD completed a consult for the first IND and the second and third INDs (or the second and third protocols

submitted to the IND) address substantially the same issues, formal consultation may not be needed.

- The SSMRD and other offices and centers will be consulted as needed for other submissions (e.g., labeling supplements with clinical data).

- In some instances (e.g., a breast cancer application), a relevant SSMRD outside of OHOP may not exist based on the site of the cancer. In such cases, consultation with an SSMRD or another office or center may be warranted on the basis of expertise in related efficacy or safety issues (e.g., Division of Bone, Reproductive, and Urologic Products for risk reduction strategies using oral contraceptives regardless of cancer site; OSE for an approved drug now planned for use for cancer prevention). OHOP may use its judgment as to whether a consult is needed.

- Consults should be focused on the expertise of the SSMRD or office/center with specific questions for the consultants and should not request a global evaluation of the submission. Such expertise may include the SSMRD evaluation of endpoint measurement (e.g., Division of Pulmonary, Allergy, and Rheumatology Products for adequacy of bronchoscopic measurements for a lung cancer endpoint) or safety monitoring of a drug approved for a noncancer prevention indication (OSE for review of postmarketing safety data).

- The OHOP Office Director will sign the action letter for the NDA, BLA, or supplement for the first cancer prevention indication for a drug. Sign-off for subsequent cancer prevention indications will follow standard CDER practices.

PROCEDURES

Cancer Prevention INDs (original and amended)

- All cancer prevention INDs (except for nonmelanoma skin cancer risk reduction) will be assigned to OHOP, using the standard document receipt and processing procedures.

- Applications for prevention indications will be tracked in the appropriate databases using the specific therapeutic classification code for cancer prevention (5010210).

- Standard procedures will be followed for document receipt, processing, assignment, and distribution.

- The procedures in MAPP 6025.3 should be followed for all consults to SSMRDs for cancer risk reduction INDs.

- New cancer prevention submissions for drugs with previously established applications for different indications require new INDs. The RPM and medical team leader are responsible for identifying prevention protocols incorrectly submitted to an existing IND (either in OHOP or in another division). The RPM will inform the sponsor of the need to resubmit the protocol as a new IND to the appropriate division within OHOP.

Cancer Prevention NDAs and BLAs

- All cancer prevention NDAs, BLAs, and supplements (except for nonmelanoma skin cancer risk reduction) will be assigned to OHOP, using the standard document receipt and processing procedures.

- Applications for prevention indications will be tracked in the appropriate databases using the specific therapeutic classification code for cancer prevention (5010210). A supplement for a new cancer prevention indication for a drug with an established NDA or BLA for an indication that is reviewed outside of OHOP will be assigned to OHOP rather than to the SSMRD that reviewed the original application.

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

- The procedures in MAPP 6025.3 should be followed for all consults to SSMRDs for cancer risk reduction marketing applications.

- The OHOP Office Director will sign the first prevention claim for a drug, regardless of whether the drug has been previously approved for another indication. Subsequent applications for additional cancer prevention claims will follow standard CDER procedures.

Dispute Resolution

- The OHOP signatory authority may accept or reject consultative advice. This MAPP requires OHOP 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 OHOP.

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

REFERENCES

1. NCI and FDA Announce Joint Program to Streamline Cancer Drug Development, May 30, 2003, https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM152305.pdf

2. The Critical Path Initiative: Report on Key Achievements in 2009, https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UCM221651.pdf

3. FDA announces changes in drug center's oncology office, September 12, 2011, https://wayback.archive-it.org/7993/20170114063407/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm271501.htm

4. Office of Hematology Oncology Products (OHOP) Reorganization: Information for IND, NDA, and BLA Sponsors, September 12, 2011, https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm271326.htm

5. Assignment of Applications for Products to Reduce the Risk of Cancer, March 8, 2005, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/CancerDrugs/ucm091859.htm

6. MAPP 6025.3 *Good Review Practice: Clinical Consultative Review of Drugs Regulated Within OND*, https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

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

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

9. MAPP 6025.1 *Good Review Practices*

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

DEFINITIONS

- Drug — For the purposes of this MAPP, refers to a drug or a therapeutic biological product regulated in CDER.

- Prevention — For the purposes of this MAPP, refers to drugs to reduce the risk of cancer, not other diseases. It may include primary (reducing the risk of cancer in at-risk individuals) or secondary (reducing the risk of a second cancer in a cancer survivor) cancer risk reduction. It does not imply that cancer will never occur in a treated individual. In addition, the term *prevention applications* excludes the nonmelanoma skin cancer applications regulated in the DDDP.

- Prevention IND — An IND for the development of a drug intended to reduce the risk of cancer.

- Prevention NDA — An NDA, or supplement, for a drug intended to reduce the risk of cancer.

- Prevention BLA — A BLA, or supplement, for a drug intended to reduce the risk of cancer.

- 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). For the purposes of this MAPP, this term distinguishes this group of review divisions from the review divisions contained within OHOP. In some cases, reviewers with expertise regarding the potential safety or effectiveness of a drug to reduce the risk of cancer may reside in other offices or centers (e.g., OSE, Center for Devices and Radiological Health, Center for Food Safety and Applied Nutrition, or Center for Biologics Evaluation and Research).

EFFECTIVE DATE

This MAPP is effective upon date of publication.