REVIEW MANAGEMENT

Clinical Review of Drugs to Reduce the Risk of Cancer

CONTENTS

PURPOSE

- This MAPP describes:
  - The clinical review process in 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 sign-off policies and procedures for INDs, NDAs, BLAs, and supplements for drugs to reduce the risk of cancer.
- These procedures are intended to ensure quality and consistency in the review of these drugs.
- The policies and procedures outlined in this MAPP apply to interactions between the Office of Oncology Drug Products (OODP) and consultants residing in other CDER divisions and other offices or centers.

BACKGROUND

- Drugs to reduce the risk of cancer have become an increasingly 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, and other important stakeholders, as well as coordination of cross-center work, is critical in facilitating the development and review of these drugs. These factors were some of the considerations that lead to the creation of the new OODP and the transfer of existing cancer prevention drugs, with the exception

of drugs to reduce the risk of nonmelanoma skin cancer, to this office. Existing cancer prevention applications were transferred to OODP in December 2004 and January 2005. Transferred applications are listed at http://www.fda.gov/cder/cancer/appl_assignment.htm. Nonmelanoma skin cancer therapies will continue to be reviewed in the Division of Dermatology and Dental Products (DDDP), because these common lesions are usually diagnosed and treated exclusively by dermatologists. All drugs to reduce the risk of cancer, except those intended to reduce nonmelanoma skin cancer, will be reviewed within the OODP.

REFERENCES

- NCI and FDA Announce Joint Program to Streamline Cancer Drug Development, May 30, 2003, http://www.fda.gov/bbs/topics/NEWS/2003/NEW00912.html
- Challenge and Opportunity on the Critical Path to New Medical Products, March 16, 2004, http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf
- FDA to Establish New Cancer Office and Program: Changes Designed to Improve Efficiency and Consistency of Cancer Product Reviews, July 16, 2004, http://www.fda.gov/bbs/topics/news/2004/NEW01091.html
- FDA Office of Oncology — Questions and Answers, July 16, 2004, http://www.fda.gov/oc/initiatives/oncology/questions.html
- Assignment of Applications for Products to Reduce the Risk of Cancer, March 8, 2005, http://www.fda.gov/cder/cancer/appl_assignment.htm
- Office of New Drugs Reorganization, June 22, 2005, http://www.fda.gov/cder/cderorg/ond_reorg.htm

DEFINITIONS AND ACRONYMS

- BLA — biologics license application
- DDDP — Division of Dermatology and Dental Products
- Drug — for the purposes of this MAPP, refers to a drug or a therapeutic biological product regulated in CDER.
- EOP2 — end-of-phase 2
- IND — investigational new drug application
- NDA — new drug application
- ODS — Office of Drug Safety

- OODP — Office of Oncology Drug Products

- pre-IND — pre-investigational new drug application

- 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.

- RPM — regulatory project manager

- SPA — special protocol assessment

- SSMRD — specific subject matter review division: Office of New Drugs (OND) review divisions with primary oversight of a group of prescription drugs used to treat physiologically categorized disease entities (e.g., Cardiovascular and Renal Products, Anti-Infective and Ophthalmologic Products). For the purposes of this MAPP, this term distinguishes this group of review divisions from the review divisions contained within the OODP. 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., Office of Drug Safety (ODS), Center for Devices and Radiological Health, Center for Food Safety and Applied Nutrition, or Center for Biologics Evaluation and Research).

POLICY

- The OODP will have regulatory responsibility for drugs developed to reduce the risk of cancer. **Exception:** *Drugs to prevent nonmelanoma skin cancer will be regulated by the DDDP and are not discussed in this MAPP.*

  – Existing INDs that include studies for cancer risk reduction and studies for other indications will be administratively split into separate INDs. Sponsors will be notified of the split and requested to direct their submissions accordingly.

  – 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 preclinical information as a new IND to the OODP.

- 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 OODP. Information previously submitted to the Agency 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.

- A supplement for a new cancer risk reduction indication for a previously approved drug will be assigned to OODP, 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 the OODP has primary review responsibility and retains sign-off authority. Although the OODP is responsible for the application, every effort should be made to perform a cooperative review, in which careful consideration is given to consultant recommendations.

  - The OODP will consult the appropriate SSMRD for all cancer prevention NDAs, BLAs, efficacy supplements, phase 3 studies, *pivotal* chemoprevention trials, and special protocol assessments (SPAs), as appropriate. The OODP 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 the OODP 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 Reproductive and Urologic Products for risk reduction strategies using oral contraceptives regardless of cancer site; ODS for an approved drug now planned

for use for cancer prevention). The OODP 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 and Allergy Products for adequacy of bronchoscopic measurements for a lung cancer endpoint) or safety monitoring of a drug approved for a noncancer prevention indication (ODS for review of postmarketing safety data).

- The OODP 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

- All new cancer prevention applications will be assigned to the OODP, except for applications for drugs to reduce the risk of nonmelanoma skin cancer, which will be submitted to the DDDP.

- 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.

- Because the 30-day IND review clock may not permit sufficient time to evaluate a complex phase 3 prevention study submitted as a new IND, the OODP should encourage sponsors to schedule pre-investigational new drug application/end-of-phase 2 (pre-IND/EOP2) meetings before submitting the IND.

  - Divisions are encouraged to establish 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 OODP medical team leader should determine the need for a consult from the SSMRD. If appropriate, a consult reviewer should be identified and should participate in the pre-IND/EOP2 meeting.

- Sponsors should be encouraged to submit an SPA for phase 3 prevention studies, even when the trial is used to open a new IND.

  - Sponsors should be informed that the safety review of a phase 3 study submitted in a new IND will be determined within 30 days of its receipt. However, they should also be informed that the study's ability to fulfill the regulatory

requirements for a new cancer risk reduction indication will depend on any needed consultation with an SSMRD, office, or center, which could result in further internal discussion and review. Such an outcome usually requires the full 45-day review clock of an SPA.

- New cancer prevention submissions for drugs with previously established applications for a different indication require a new IND. The RPM and medical team leader are responsible for identifying prevention protocols incorrectly submitted to an existing IND (either in the OODP 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 the OODP.

- The OODP medical team leader will evaluate the IND as soon as possible but no later than 2 days after receipt from the document room to determine the need for a consult with an SSMRD, other office, or other center. For new INDs, it is critical that this determination for consultation be made as soon as possible (but no later than 2 days after document room receipt) 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 product for the stated indication. The consult form and submission material should be sent when 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 OODP reviewer will write and send specific questions to the consultant as soon as possible, but no later than 2 days following the consult request.

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

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

- The SSMRD should make every effort to complete its consult by day 20 (after FDA receipt) and forward it to the OODP division electronically. The standard procedures for sign-off within the SSMRD should be followed. If it is not possible because of late receipt of IND materials for review or other reason to complete the consult or complete the management clearance process for the consult by day 20, at a minimum, the SSMRD should provide any potential hold issues to the primary reviewers in the OODP division by day 20. These comments should consist of well-formulated statements that have been reviewed by the appropriate SSMRD division leadership and can be transmitted to the sponsor. The OODP division and the SSMRD will negotiate a date for completion of the requested consult that extends beyond day 30 if additional time is needed. The IND sponsor will be notified by the OODP division RPM that additional nonhold suggestions may be contained in the pending consult which will be conveyed to the sponsor if accepted by the OODP reviewers. If the consult is complete, has been reviewed and approved by division management, but awaits sign-off in the corporate electronic document archive, the draft consult may be

sent via e-mail to the OODP division to facilitate communication of relevant issues to the sponsor. This procedure is consistent with the current policy that sign-off in the corporate electronic document archive is encouraged but not required to take action on an IND.

- The medical reviewer will evaluate the SSMRD's consult, call the consultant to discuss if needed, and incorporate accepted recommendations into the IND review. Justification for not accepting major recommendations made by the consultant should be included in the review. This will be communicated to the consultant through CDER's corporate electronic document archive.

- Final reviews by the primary reviewers will be entered into CDER's corporate electronic document archive with appropriate copies sent to the SSMRD, other reviewers and team leaders on the review team, consultants in other centers, and the RPM as per standard CDER procedures. Sign-off will follow standard CDER procedures.

- Management of and communications concerning prevention INDs rests with the assigned OODP RPM.

- The SSMRD should be invited to attend safety meetings for new INDs, as appropriate, and all clinical hold meetings, telecons, and applicable division meetings through the initial 30-day review process and through the IND drug development phase.

- Similar procedures with appropriate timelines should be applied to protocols accepted for an SPA and for *pivotal* phase 3 trials designed to support approval.

Cancer Prevention NDAs and BLAs

- All cancer prevention NDAs, BLAs, and supplements (except for nonmelanoma skin cancer risk reduction) will be assigned to the OODP, 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 the OODP will be assigned to the OODP 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 OODP medical reviewer and medical team leader should determine the need for a consult with the SSMRD, other office, or other center during the pre-NDA/BLA stage. If appropriate, a consult reviewer 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 (as per the good

review manufacturing practices (GRMP)) so that consultants may participate in this first landmark meeting.

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

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

- The GRMP timeline should be followed to facilitate review, communications, and accomplishment of target review and action goals.

- Final decisions regarding prevention NDAs/BLAs/supplements rest with the OODP.

- Management of and communications concerning prevention NDAs/BLAs/supplements rests with the assigned OODP RPM.

- The OODP 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

- Any disagreements with the recommendations for INDs, NDAs, or BLAs will be handled according to the procedures for resolution of internal disputes (see MAPP 4151.1, *Resolution of Disputes: Roles of Reviewers, Supervisors, and Management Documenting Views and Findings and Resolving Differences*).

- If the SSMRD and the OODP differ in their recommendations for an NDA or BLA action and these differences persist despite division- and office-level meetings, the OODP office director has decision-making authority.

- If the SSMRD feels strongly that its recommendation regarding an NDA or BLA action should be accepted and the OODP office director does not agree, the SSMRD may request input by the director of OND.

EFFECTIVE DATE

This MAPP is effective upon date of publication.