PROGRAM DESCRIPTION

PHARMACOLOGY AND TOXICOLOGY

Management of CDER Executive Carcinogenicity Assessment Committee and Communication of Committee Proceedings

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PURPOSE

This MAPP describes:

- The role, responsibilities, structure, and function of the Center for Drug Evaluation and Research (CDER) Executive Carcinogenicity Assessment Committee (Exec CAC)

- The procedures for committee meetings, including the preparation, review, archiving, and distribution of meeting minutes and communication of committee proceedings to the sponsor or applicant

BACKGROUND

- The Exec CAC was established to ensure consistency in recommendations and conclusions regarding protocols for and results of carcinogenicity studies across review divisions. The written recommendations on study design, conduct, and outcomes assist the review divisions and office directors in study interpretation when making risk-benefit decisions about drugs.

- The Exec CAC meets regularly to review all carcinogenicity protocols and final study reports. Sponsors usually submit the protocols in requests for special

protocol assessments (SPAs), which CDER must complete within 45 days. For SPAs for carcinogenicity protocols, the minutes of the Exec CAC meeting constitute CDER's SPA letter.

- The CAC and Exec CAC are separate committees with different memberships, responsibilities, roles, and procedures. Management of the CAC is described in MAPP 7412.2 Rev.1 *Management of CDER Carcinogenicity Assessment Committee and Communication of Committee Proceedings*.

RESPONSIBILITIES

- **The Exec CAC will:**

  1. Provide concurrence to sponsors on protocols for carcinogenicity studies, including dose selection (either as proposed by the sponsor or as revised by the committee)

  2. Provide nonconcurrence to sponsors on protocols for carcinogenicity studies when there is insufficient information to select doses

  3. Provide consultations to review divisions on whether a carcinogenicity study for a biologic is warranted or if there is sufficient information to write labeling for carcinogenic potential without requiring additional testing

  4. Provide CDER conclusions about carcinogenicity study findings

  5. Review questions that will be included in the briefing package for CAC meetings; provide advice for follow-up queries from sponsors after CAC meetings as needed

  6. Respond promptly with concurrence or suggestions to the review division regarding CDER response to sponsor queries

- **The Chair of the Exec CAC will:**

  1. Lead the meeting

  2. Sign the minutes

- **The Executive Secretary will:**

  1. Schedule meetings.

  2. Distribute documents.

3. Maintain files to facilitate continuing assessment of carcinogenicity study design and analysis issues. Facilitate access to files for reviewers on request.

4. Track comments and concurrences on draft Exec CAC minutes prepared by the review division, enter minutes for electronic signature, and send minutes, or the content therein, for protocols to the sponsor according to timelines as determined by applicable regulations and deadlines. Notify the division through the electronic file system when the minutes have been finalized.

- **The Review Division Pharmacologist/Toxicologist Responsible for the Drug Under Consideration in Consultation With His or Her Supervisor or Team Leader will:**

  Prior to the Meeting

  1. Email the Executive Secretary the information needed to schedule an Exec CAC meeting (see Procedures)

  2. Ask the assigned review division project manager to send a statistics consult for review of completed studies

  3. Review the appropriate studies and submissions

  4. Prepare and circulate background information, including a summary coversheet and review(s), at least 1 week before the Exec CAC meeting to the members listed on the meeting calendar

  At the Meeting

  1. Present a concise summary of relevant points and address questions raised by the committee

  Following the Meeting

  1. Promptly (usually within a day or two, depending on the deadline) prepare brief minutes of the Exec CAC meeting, obtain supervisory or team leader concurrence, and circulate the minutes to the Exec CAC for edits and concurrence. The pharmacologist/toxicologist reviewer will be available, or will arrange for the supervisor, to promptly address any questions or queries from the Exec CAC and to incorporate edits to the minutes because there usually is a tight deadline for finalizing the minutes. The pharmacologist/toxicologist reviewer will address comments and questions from the committee as needed and will circulate a final draft.

2. Review queries from the sponsor submitted to the review division regarding protocol changes during the conduct of carcinogenicity studies that may include requests to change doses, stop dosing, or terminate groups early. The pharmacologist/toxicologist reviewer, with supervisory concurrence, will then promptly draft a response and circulate this response by email to the members of the Exec CAC. The review division project manager will convey the response to the sponsor and will enter either the written response or a memo of the conversation into the electronic file system (with a link to the appropriate sponsor submission(s) (e.g., SPA)) so that the response will become a part of the permanent record.

PROCEDURES

Meetings

- The Exec CAC should evaluate data generated from the dose selection studies, the proposed carcinogenicity protocols, and the carcinogenicity study results. Generally, meetings of the Exec CAC should be held weekly. A request for an Exec CAC meeting to discuss a carcinogenicity protocol should be made as soon as possible after receipt of a request for SPA. The meeting generally should be held at least 1 week before the SPA due date. A request for an Exec CAC meeting to discuss final study results should be made several months ahead of the anticipated date for completing the review to ensure that regulatory deadlines can be met.

- Based on the information provided by the reviewer and the results of committee discussions, the Exec CAC members should provide at the meeting:

  – Recommendations on the dose selection for the carcinogenicity protocols, when adequate data are available. If the sponsor follows the protocol as accepted or as modified by the Exec CAC and reflected in the minutes, and the study is conducted properly without confounding issues, such as infections or animal mishandling, the study will be accepted.

  – Recommendations on other aspects of the carcinogenicity protocols, when appropriate.

  – Conclusions on the carcinogenicity study findings. The labeling should reflect the conclusions of the Exec CAC on what neoplasms were drug related in the animals in carcinogenicity studies.

- The Exec CAC meetings provide a forum for discussion of how assessment and labeling of carcinogenicity potential of biologics should be addressed. Pharmacology/toxicology supervisors and/or team leaders should be invited, and those addressing similar drug issues should be invited to listen and discuss, although they will not be presenting.

- Three members other than the reviewer and supervisor must be present to constitute a quorum. Members must reach a consensus.

Briefing Package

- For the Exec CAC meetings, the review division pharmacologist/toxicologist should prepare a briefing package containing:

  – The carcinogenicity protocol coversheet or results coversheet (a template is available on the Reviewer Tools and Templates web page of the 21st Century Review intranet website)

  – A detailed review and an overview of the relevant data for evaluation by the committee

  – The division's preliminary pharmacology/toxicology recommendations

- The briefing package for Exec CAC meetings should be reviewed by the pharmacology/toxicology supervisor or team leader and then distributed to committee members at least 1 week before the meeting.

Meeting Minutes

- The pharmacology/toxicology reviewer should promptly prepare meeting minutes, obtain supervisory or team leader concurrence, and then circulate the minutes to the Executive Secretary and the Exec CAC members for edits and concurrence.

- The minutes should contain a list of attendees with affiliations, a brief background, a brief summary of the committee discussion, and the Exec CAC conclusions.

- The Executive Secretary (or designee) should track and collate comments (because the meetings are often held shortly before the due dates, tracking should be done by the Executive Secretary to expedite the process to ensure that deadlines are met). The presenting reviewer and/or supervisor should address any additional questions or issues and the Executive Secretary (or designee) should enter minutes for electronic sign off by the Exec CAC Chair

(or designee), with copies sent to the Executive Secretary, pharmacology/toxicology reviewer, pharmacology/toxicology supervisor or team leader, and project manager.

- For protocol evaluations, this generally should occur within 45 days of the receipt date of the protocol submission, in accordance with time goals for completion of SPAs

- For evaluation of final study results, this generally should occur within 30 days of the meeting if not sooner

Communication of Committee Proceedings to Sponsor or Applicant

Protocol review meetings:

- The minutes generated from the Exec CAC meetings on the dose selection and study design for proposed carcinogenicity studies represent CDER conclusions on these matters. The minutes should be communicated to the sponsor promptly, generally within 45 days of the receipt date of the protocol submission in accordance with time goals for completion of SPAs. To facilitate this communication, the minutes of the Exec CAC meeting should be sent by the Executive Secretary or a designee to the sponsor after they are signed by the Associate Director for Pharmacology and Toxicology or a designee.

- For protocols submitted as postmarketing requirements (see MAPP 6010.9 *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*), the following text should be added to the minutes when they are drafted and communicated to the sponsor:

  "Because this study is being conducted as a postmarketing requirement, this protocol, including the alterations recommended by the Exec CAC, is considered the final study protocol."

- Any subsequent correspondence concerning the protocol or protocol amendments (i.e., clarifications, or decisions on requests for protocol modifications) should be sent to the sponsor by the review division.

Study result review meetings:

- The Exec CAC minutes of the evaluation of carcinogenicity study results represent CDER's conclusion about the potential carcinogenicity of a drug, including specific drug-related findings or absence of findings. These minutes aid clinical divisions in weighing risks and benefits associated with use of that drug for specific indications. The minutes of the Exec CAC meeting should

be available 30 days after the meeting. When requested by the sponsor, the Exec CAC meeting minutes should be sent by the review division after ensuring the removal of any confidential information (e.g., proprietary data on other drugs). The division may add a cover letter with a statement that the findings of the Exec CAC reflect CDER's judgment on the potential carcinogenicity of a drug, but are not a measure of the approvability of an application.

REFERENCES

1. MAPP 6010.9 *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments* (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm)

2. MAPP 7400.1 Rev. 2 *Management of the CDER Pharmacology/Toxicology Coordinating Committee and Its Associated Subcommittees and Working Groups* (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm)

3. Guidance for industry *Special Protocol Assessment* (https://www.fda.gov/RegulatoryInformation/Guidances/default.htm)

4. International Conference on Harmonisation guidances (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

ORGANIZATION

The Exec CAC meets regularly to review protocols and final study results.

1. **Chair** — The Associate Director for Pharmacology and Toxicology in the Office of New Drugs (OND) or designated representative

2. **Executive Secretary** — The Chair may act as Executive Secretary or appoint either a full-time or part-time Executive Secretary to the Exec CAC

3. **Members** — Voting members of the Exec CAC include the Chair and office of drug evaluation associate directors for pharmacology/toxicology (the permanent members), a representative from one OND review division (e.g., pharmacology/toxicology supervisor or team leader appointed monthly on a rotating basis), and the pharmacology/toxicology supervisor or team leader and the reviewer from the division responsible for the drug under consideration

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
12/4/13	Rev. 2	MAPP 7412.1 *Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive CAC* and MAPP 7412.2 *Distribution of Final Reports From the Carcinogenicity Assessment Committee (CAC) and Executive CAC* have been reorganized and renamed. MAPP 7412.1 Rev. 2 covers the Exec CAC and MAPP 7412.2 covers the CAC. The MAPPs have also been updated to reflect 45-day special protocols and current terms (e.g., OND instead of ORM). Wording was modified to clarify procedures and to address biological products. The templates for cover sheets and minutes have been detached and are posted on an internal website.
06/08/18	Rev. 2	MAPP was recertified