PHARMACOLOGY AND TOXICOLOGY

MANAGEMENT OF CDER CARCINOGENICITY ASSESSMENT COMMITTEE (CAC) AND EXECUTIVE CAC

CONTENTS

PURPOSE This MAPP describes:

- The role and responsibilities of the Carcinogenicity Assessment Committee (CAC);
- The structure and function of the committee;
- The procedures to be used for committee meetings; and
- The guidance documents used by the committee.

BACKGROUND

The CDER Carcinogenicity Assessment Committee (CAC) serves as the primary consulting body on carcinogenicity issues within the Center for Drug Evaluation and Research. The CAC provides a tertiary review of carcinogenicity studies submitted to the Reviewing Division under an IND or NDA and provides written recommendations on study designs, conduct, and outcomes to assist the review Divisions and Office Directors in study interpretation. In general, all carcinogenicity studies submitted to CDER should be evaluated by the CAC or CAC Executive Committee.

REFERENCES

- CDER MAPP 7400.1, *Management of CDER Pharmacology/Toxicology Coordinating Committee*, July 1, 1996.
- CDER MAPP 7412.2, *Distribution of Final Reports from the Carcinogenicity Assessment Committee (CAC) and the Executive CAC*.
- CDER MAPP 7412.3, *Submission of Preclinical Carcinogenicity Protocols and Study Results*.

ORGANIZATION

The following descriptions and explanations should be applied on a general basis. There may be some variability in the implementation due to workload demands:

- **CAC**

  1. **Chair** - The Center's Senior Pharmacologist/Toxicologist in the Office of Review Management or delegated representative.

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

  3. **Members** - Voting members of the CAC include the Chair, Executive Secretary (with appropriate scientific credentials), each Office of Drug Evaluation (ODE) review division Pharmacology Team Leader or designate, and the Associate Director for the Office of Epidemiology and Biostatistics. One scientific expert within the Office of Testing and Research, Office of Pharmaceutical Sciences maybe designated by the Chair with full voting priveledges.

  4. **Other Participants** - Non-voting observers and consultants from other Divisions/Centers or Federal government organizations may be included in the deliberations at the request of the Review Division, or at the discretion of the Chair.

- **Executive CAC**

1. **Chair -** The Center's Senior Pharmacologist/Toxicologist in the Office of Review Management or delegated representative.

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

3. **Members** - One ODE review division Pharmacology Team Leader (appointed monthly on a rotating basis) and the Pharmacology Team Leader from the division responsible for the drug under consideration. One scientific expert within the Office of Testing and Research, Office of Pharmaceutical Sciences maybe designated by the Chair. All are full voting members.

RESPONSIBILITIES

- **CAC and Executive CAC**

  1. Provide consultation on carcinogenicity study designs;

  2. Assure consistency and high quality in the analysis and interpretation of animal carcinogenicity studies of pharmaceuticals;

  3. Monitor scientific developments and trends to ensure that scientific standards of design and interpretation are promoted and implemented.

- **The Executive Secretary is responsible for:**

  1. Arrange and organize meetings;

  2. Distribute documents;

  3. Maintain files to facilitate continuing assessment of carcinogenicity design and analysis issues for pharmaceuticals;

  4. Prepare minutes and final reports [meeting minutes will be made available electronically to every committee member; minutes shall be filed on the shared common drive]; and

  5. Maintain reference documents and other relevant publications for committee members. The following reference documents generally represent accepted practices in the area of carcinogenicity study designs

and results:

- National Toxicological Program (NTP), Board of Scientific Counselors. *Report of the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation.* Department of Health and Human Services: August 17, 1984.

- National Cancer Institute, Division of Cancer Control and Prevention, Carcinogenesis Bioassay Program. *Guideline for Carcinogen Bioassay in Small Rodents.* NCI-CG-Technical Report-1, 1976.

- National Cancer Institute, Interagency Regulatory Liaison Group, Work Group on Risk Assessment. "Scientific Basis of Identification of Potential Carcinogens and Estimation of Risk," 63:242-268, 1979.

- U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. "Toxilogical Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Redbook II)." Draft, 1993.

- Office of the President, Office of Science Technology Policy (OSTP). "Chemical Carcinogens; A Review of the Science and its Associated Principles," *Environmental Health Perspectives*, 67:201-282, 1986. (See also the *Federal Register,* Vol. 50, No. 50, p. 10372.)

- International Committee on Harmonisation (ICH) agreements and other related guidelines including new guidelines initiating from efforts of the above organizations.

- **Review Division Pharmacologist and/or Team Leader**

  The review of a carcinogenicity study design and results should be initiated by the review division.

  The Division pharmacology reviewer, in consultation with the pharmacology Team Leader, should review:

  1. All completed carcinogenicity studies submitted to the IND or NDA, regardless of whether any issue has been identified by the review

division, and

2. All proposed carcinogenicity study protocols and supporting data if the sponsor has requested concurrence on dose selection and /or study design.

PROCEDURES

Meetings

- **CAC** - Meetings of the full CAC are held at the request of a reviewing division or based on a determination by the Executive committee that the studies reviewed raise policy issues or distinct scientific problems that require broader discussion.

  When a full CAC meeting is scheduled for a specific pharmaceutical, the sponsor or applicant should be notified by the Review Division and given the opportunity to participate in the committee review process. In most cases, they should be advised 3 to 4 weeks prior to the full CAC meeting of issues and problems identified for discussion by the committee. If requested, the sponsor/applicant should prepare and submit a background package reflecting their perspective on these issues for consideration by CAC members 2 weeks prior to the meeting. Sponsors should prepare a brief presentation of relevant data and interpretation, limiting the discussion to data previously submitted to the Review Division. In general, sponsors should limit attendance to 2-3 experts in the areas of concern who can best discuss the data and answer questions.

  The sponsor should not be present during the final Committee deliberations and voting. Proprietary data on related or relevant products may be discussed at this time (e.g. data on other members of a drug class).

- **Executive CAC** - Generally, meetings of the Executive committee are held every 2 weeks (bimonthly). The Executive CAC evaluates data generated from the dose selection studies, the proposed carcinogenicity protocols, and the carcinogenicity study results. Based on the data furnished in the briefing package, the committee provides:

  1. Concurrence and/or recommendations on the dose selection for the carcinogenicity protocols, when adequate data are available;

2. Concurrence on the carcinogenicity study findings; or

3. Recommendations that the carcinogenicity data and/or the dose selection data should be evaluated at a full CAC meeting when the study results raise policy issues or distinct scientific problems.

Voting

- **CAC** - At least 75% of the voting members of the CAC should be present to constitute a quorum. If unanimous agreement is not reached on a particular issue, areas of differing viewpoints should be documented carefully in the CAC report.

- **Executive CAC** - All members of the Executive committee (or designated alternates) must be present to constitute a quorum.

CAC and Executive CAC Briefing Package

- The reviewing division should prepare a briefing package containing:

  1. Carcinogenicity coversheet (the form is available electronically on the shared common drive) (see Attachment A);

  2. An overview of the relevant data for evaluation by the committee; and

  3. The review division's preliminary recommendations.

- This package should be distributed to Committee members approximately 1 week prior to the meeting. The meeting format and agenda should be determined by the Chair in conjunction with the Executive Secretary.

Reports

- The Executive Secretary or CAC Chair (or designate) should prepare a report of the Committee's deliberations. The reviewing pharmacologist may draft the report when the Executive committee recommendations agree completely with the preliminary division recommendations.

- The report should contain a summary of the material reviewed by the Committee, a statement of the issues addressed, results of any votes, and consensus recommendations to the division. The report should also provide a summary of any issues not fully resolved including alternative views expressed

during committee deliberations.

- A draft report should be circulated to all voting and non-voting members for comment and concurrence prior to approval of the final report and sign off by the CAC Chair.

    1. All comments from the review division should be provided through the team leader to the chair and executive secretary.

    2. Comments submitted which provide additional considerations or alternative views expressed by Committee members or Committee consultants, not presented during the Committee deliberations, may be appended to the final report, if received during the 14-day comment period.

    3. All written comments will be included in the CAC file for the application.

    4. The CAC file should include the final report, all data submitted to and reviewed by the Committee, and any written comments provided in response to the Committee report.

- The final report of the CAC deliberations should be sent to the sponsor/applicant in accordance with MAPP 7412.2, *Distribution of Final Reports from the Carcinogenicity Assessment Committee (CAC) and the Executive CAC*. Any comments on the final report received from the sponsor will be forwarded to the CAC and included in the CAC file.

  Final reports from the Executive CAC on the proposed dose selection for carcinogenicity studies should be provided to the review division in a timely manner in order that the review division may convey its recommendations within 60 days of the protocol receipt date.

- CAC and Executive CAC reports should be included in the administrative file for the IND/NDA and in NDA action packages.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment A

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

NDA: IND: DRUG CODE#:
CAS#: DATE:
DIVISION(s):
DRUG NAME(s):

SPONSOR:
LABORATORY:
P/T REVIEWER(s):
P/T REVIEW DATE:
CARCINOGENICITY STUDY REPORT DATE:
THERAPEUTIC CATEGORY:
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION:

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date):

MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay):

RAT CARCINOGENICITY STUDY (multiple studies? Std1; Std2 etc.):

RAT STUDY DURATION (weeks):
STUDY STARTING DATE:
STUDY ENDING DATE:
RAT STRAIN:
ROUTE:
DOSING COMMENTS:

No. Rats in Control 1 (C1): Control 2 (C2):
Low Dose (LD): Middle Dose (MD):
High Dose (HD): High Dose2 (HD2):

RAT DOSE LEVELS (mg/kg/day)

Rat Low Dose: Rat Middle Dose:
Rat High Dose: Rat High Dose2:

*Dose adjusted during study.

Basis for Doses Selected (MTD; AUC ratio; saturation; maximum feasible):

RAT CARCINOGENICITY (negative; positive; MF; M; F):

RAT TUMOR FINDINGS:

RAT STUDY COMMENTS:

MOUSE CARCINOGENICITY STUDY (multiple studies? Std1; Std2 etc.):

MOUSE STUDY DURATION (weeks):
STUDY STARTING DATE:
STUDY ENDING DATE:
MOUSE STRAIN:
ROUTE:
DOSING COMMENTS:

No. Mice in Control 1 (C1): Control 2 (C2)
Low Dose (LD): Middle Dose (MD):
High Dose (HD): High Dose2 (HD2):

MOUSE DOSE LEVELS (mg/kg/day)

Mouse LD: Mouse MD:
Mouse HD: Mouse HD2:
*Dose adjusted during study.

Basis for Doses Selected (MTD; AUC ratio; saturation; maximum feasible):

Prior FDA Concurrence (Div/CAC)? (y/n; Date):

MOUSE CARCINOGENICITY (negative; positive; MF; M; F):

MOUSE TUMOR FINDINGS:

ABBREVIATIONS FOR TUMOR SITE IDENTIFICATION*

Aden=adenoma
AG = adrenal gland
B = brain
BD = bile duct
Carc=carcinoma
CG = clitoral gland
CS = circulatory system (e.g. hemangioepithelioma/sarcoma)
HG = harderian gland
HS = hematopoietic system (e.g. leukemia; lymphoma)
I = intestine
IS = integumentary system (e.g. connective tissue)
K = kidney
L = liver
LU = lung
MG = mammary gland
MT = mesothelial tissue
N = nose
O = ovary
OC = oral cavity
OST= osteosarcoma in bone
PG = preputial gland
PTG= pituitary gland
S = stomach
SB = subcutaneous tissue
SK = skin
SP = spleen
TG = thyroid gland
TV = tunica vaginalis
U = uterus
ZG = zymbals gland

* R. W. Tennant and J. Ashby, Mutation Research, 257 (1991), 209-227.

Carcinogenicity Assessment Committee (CAC/CAC-EC) Cover Sheet
Review of Carcinogenicity Study Design/Dose Selection Proposals

Application (IND/NDA) number:
Division: CAS#:
Drug name:
Pharmacological Classification:
Sponsor/Applicant:
Sponsor/Applicant contact name:
Sponsor/Applicant telephone/fax number:
Date submitted:
45-day date:
Review completed:
Date of CAC review:
CAC members:

Summary of proposal for review
Species/strain:
Number/sex/dose:
Route:

	male	**female**
Doses proposed:	_____	_____
Basis of dose selection:		
MTD	_____	_____
AUC ratio	_____	_____
saturation	_____	_____
MFD	_____	_____

Kinetics submitted:	**rodent**	**human**
pharmacokinetics	_____	_____
metabolism	_____	_____
protein binding	_____	_____

Notable design features:

Summary of Recommendations to CAC

	male	**female**

Doses recommended:
Basis for recommendation:

CAC Concurrence (y/n):
CAC Recommendations:

Comments: