
Guidance for Reviewers

Pharmacology/Toxicology Review Format

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Pharmacology/Toxicology**

May 2001

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Guidance for Reviewers¹

Pharmacology/Toxicology Review Format

I. INTRODUCTION

This document contains as attachments internal FDA review formats currently being used by pharmacology/toxicology reviewers in IND and NDA primary reviews. The attached format documents are being published to provide internal and external stakeholders with an understanding of the standard format and content of pharmacology/toxicology reviews. FDA uses the format documents for a number of reasons. First of all, standardization provides for unified communication amongst multiple audiences, including secondary reviewers, re-assigned reviewers, and ultimately the American public. Standardization also ensures that the most important information is captured in all reviews. In addition, the standard format makes it readily apparent what types of studies have and have not been reviewed, and assists other reviewers when reviews are referenced at later times. Reviewers use these formats for most original, supplemental, and amended applications. In some cases the formats may not be used, such as for safety studies or consults to other groups, where short response times restrict their use. These format documents are consistent with the ICH Common Technical Document (CTD) and will eventually be considered in the Center-wide Good Review Practices (GRP) initiative.

II. DISCUSSION

A. IND Review Format

For IND reviews, the reviewer should use only the headers for which there is data. Thus, in the majority of IND reviews, many of the headers will not be used.

B. NDA Review Format

For NDA reviews, the reviewer should use all the headers, including those for which there are no data. If there are no data, a note will be made that data were not submitted. Thus, for NDA reviews, all of the headers will be listed, with a brief note following the headers for which there are no data.

¹ This guidance has been prepared by the Associate Director for Pharmacology and Toxicology, Office of Review Management in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance document represents the Agency's current format used for pharmacology/toxicology reviews. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

III. ATTACHMENTS

A. IND Review Format

B. NDA Review Format

**ATTACHMENT A:
IND REVIEW FORMAT
PHARMACOLOGY/TOXICOLOGY**

IND number:

Review number:

Sequence number/date/type of submission:

Information to sponsor: Yes () No ()

Sponsor and/or agent:

Manufacturer for drug substance :

Reviewer name:

Division name:

HFD #:

Review completion date:

Drug:

Trade name:

Generic name (list alphabetically):

Code name:

Chemical name:

CAS registry number:

Mole file number:

Molecular formula/molecular weight:

Structure:

Relevant INDs/NDAs/DMFs:

Drug class:

Indication:

Clinical formulation:

Route of administration:

Proposed clinical protocol:

Previous clinical experience:

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction:

Safety evaluation:

Safety issues relevant to clinical use:

Other clinically relevant issues:

Conclusions:

Communication review:

Investigator's brochure/informed consent review:

RECOMMENDATIONS:

Internal comments:

External recommendations (to sponsor):

Draft letter content for sponsor (if not same as above):

Future development issues:

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc: list:

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):

Studies reviewed within this submission:

Studies not reviewed within this submission:

Introduction and drug history:

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PHARMACOLOGY:

Primary pharmacodynamics:

Mechanism of action:

Drug activity related to proposed indication:

Secondary pharmacodynamics:

Pharmacology summary:

Pharmacology conclusions:

SAFETY PHARMACOLOGY:

Neurological effects:

Cardiovascular effects:

Pulmonary effects:

Renal effects:

Gastrointestinal effects:

Abuse liability:

Other:

Safety pharmacology summary:

Safety pharmacology conclusions:

PHARMACOKINETICS/TOXICOKINETICS:

PK parameters:

Absorption:

Distribution:

Metabolism:

Excretion:

Other studies:

PK/TK summary:

PK/TK conclusions:

TOXICOLOGY:**Study title:****Key study findings:****Study no:****Volume #, and page #:****Conducting laboratory and location:****Date of study initiation:****GLP compliance:****QA report:** yes () no ()**Drug, lot #, radiolabel, and % purity:****Formulation/vehicle:****Methods (unique aspects):****Dosing:**

Species/strain:

#/sex/group or time point (main study):

Satellite groups used for toxicokinetics or recovery:

Age:

Weight:

Doses in administered units:

Route, form, volume, and infusion rate:

Observations and times:

Clinical signs:

Body weights:

Food consumption:

Ophthalmoscopy:

EKG:

Hematology:

Clinical chemistry:

Urinalysis:

Gross pathology:

Organs weighed:

Histopathology:

Toxicokinetics:

Other:

Results:

Mortality:

Clinical signs:

Body weights:

- Food consumption:
- Ophthalmoscopy:
- Electrocardiography:
- Hematology:
- Clinical chemistry:
- Urinalysis:
- Organ weights:
- Gross pathology:
- Histopathology:
- Toxicokinetics:

Summary of individual study findings:

Toxicology summary:

Toxicology conclusions:

Histopathology Inventory for IND #

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				

Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

GENETIC TOXICOLOGY:**Study title:****Key findings:****Study no:****Study type** (if not reflected in title):**Volume #, and page #:****Conducting laboratory and location:****Date of study initiation:****GLP compliance:****QA reports:** yes () no ()**Drug, lot #, radiolabel, and % purity:****Formulation/vehicle:****Methods:**

Strains/species/cell line:

Dose selection criteria:

Basis of dose selection:

Range finding studies:

Test agent stability:

Metabolic activation system:

Controls:

Vehicle:

Negative controls:

Positive controls:

Comments:

Exposure conditions:

Incubation and sampling times:

Doses used in definitive study:

Study design:

Analysis:

No. of replicates:

Counting method:

Criteria for positive results:

Summary of individual study findings:

Study validity:

Study outcome:

Genetic toxicology summary:**Genetic toxicology conclusions:**

Labeling recommendations:

CARCINOGENICITY:**Study title:****Key study findings:****Study number:****Volume #, and page #:****Conducting laboratory and location:****Date of study initiation:****GLP compliance:****QA report: yes () no ()****Drug, lot #, and % purity:****CAC concurrence:****Study Type (2 yr bioassay, alternative model etc.):****Species/strain:****Number/sex/group; age at start of study:****Animal housing:****Formulation/vehicle:****Drug stability/homogeneity:****Methods:**

Doses:

Basis of dose selection:

Restriction paradigm for dietary restriction studies:

Route of administration:

Frequency of drug administration:

Dual controls employed:

Interim sacrifices:

Satellite PK or special study group(s):

Deviations from original study protocol:

Statistical methods:

Observations and times:

Clinical signs:

Body weights:

Food consumption:

Hematology:

Clinical chemistry:

Organ weights:

Gross pathology:

Histopathology:

Toxicokinetics:

Results:

Mortality:
Clinical signs:
Body weights:
Food consumption:
Hematology:
Clinical chemistry:
Organ weights:
Gross pathology:
Histopathology:
 Non-neoplastic:
 Neoplastic:
Toxicokinetics:

Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model:
Evaluation of tumor findings:

Carcinogenicity summary:**Carcinogenicity conclusions:**

Recommendations for further analysis:

Labeling Recommendations :**Addendum/appendix listing:**

Dose-ranging study report:
CAC report:
Alternative study protocols and CAC report:
Sponsor's incidence of histopathology findings:
List of organs and tissues examined:
Body weight changes versus dose level:
 Group body weight summary:
 Individual data listing:

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:**Study title:****Key study findings:****Study no.:****Volume #, and page #:****Conducting laboratory and location:****Date of study initiation:****GLP compliance:****QA reports:** yes () no ()**Drug, lot #, radiolabel, and % purity:****Formulation/vehicle:****Methods:**

Species/strain:

Doses employed:

Route of administration:

Study design:

Number/sex/group:

Parameters and endpoints evaluated:

Results:

Mortality:

Clinical signs:

Body weight:

Food consumption:

Toxicokinetics:

For fertility studies:

In-life observations:

Terminal and necroscopic evaluations:

*OR**For embryofetal development studies:*

In-life observations:

Terminal and necroscopic evaluations:

Dams:

Offspring:

OR

For peri-postnatal development studies:

In-life observations:

Dams:

Offspring:

Terminal and necroscopic evaluations:

Dams:

Offspring:

Summary of individual study findings:

Reproductive and developmental toxicology summary:

Reproductive and developmental toxicology conclusions:

Labeling recommendations:

SPECIAL TOXICOLOGY STUDIES:

Study title:

Key study findings:

Study no:

Volume #, and page #:

Conducting laboratory and location:

Date of study initiation:

GLP compliance:

QA reports: yes () no ():

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle:

Methods:

Dosing:

Observations and times:

Results:

Summary of individual study findings:

Conclusions:

ADDENDUM TO REVIEW:

(if necessary)

APPENDIX/ATTACHMENTS:

**ATTACHMENT B:
NDA REVIEW FORMAT
PHARMACOLOGY/TOXICOLOGY**

NDA number:

Review number:

Serial number/date/type of submission:

Information to sponsor: Yes () No ()

Sponsor and/or agent:

Manufacturer for drug substance :

Reviewer name:

Division name:

HFD #:

Review completion date:

Drug:

Trade name:

Generic name (list alphabetically):

Code name:

Chemical name:

CAS registry number:

Mole file number:

Molecular formula/molecular weight:

Structure:

Relevant INDs/NDAs/DMFs:

Drug class:

Indication:

Clinical formulation:

Route of administration:

Proposed use:

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction:

Safety evaluation:

Safety issues relevant to clinical use:

Other clinically relevant issues:

Conclusions:

Communication review:

Labeling review:

RECOMMENDATIONS:

Internal comments:

External recommendations (to sponsor):

Draft letter content for sponsor (if not same as above):

NDA issues:

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc: list:

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):

Studies reviewed within this submission:

Studies not reviewed within this submission:

Introduction and drug history:

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PHARMACOLOGY:

Primary pharmacodynamics:

Mechanism of action:

Drug activity related to proposed indication:

Secondary pharmacodynamics:

Pharmacology summary:

Pharmacology conclusions:

SAFETY PHARMACOLOGY:

Neurological effects:

Cardiovascular effects:

Pulmonary effects:

Renal effects:

Gastrointestinal effects:

Abuse liability:

Other:

Safety pharmacology summary:

Safety pharmacology conclusions:

PHARMACOKINETICS/TOXICOKINETICS:

PK parameters:

Absorption:

Distribution:

Metabolism:

Excretion:

Other studies:

PK/TK summary:

PK/TK conclusions:

TOXICOLOGY:**Study title:****Key study findings:****Study no:****Volume #, and page #:****Conducting laboratory and location:****Date of study initiation:****GLP compliance:****QA report:** yes () no ()**Drug, lot #, radiolabel, and % purity:****Formulation/vehicle:****Methods (unique aspects):****Dosing:**

Species/strain:

#/sex/group or time point (main study):

Satellite groups used for toxicokinetics or recovery:

Age:

Weight:

Doses in administered units:

Route, form, volume, and infusion rate:

Observations and times:

Clinical signs:

Body weights:

Food consumption:

Ophthalmoscopy:

EKG:

Hematology:

Clinical chemistry:

Urinalysis:

Gross pathology:

Organs weighed:

Histopathology:

Toxicokinetics:

Other:

Results:

Mortality:

Clinical signs:

Body weights:

- Food consumption:
- Ophthalmoscopy:
- Electrocardiography:
- Hematology:
- Clinical chemistry:
- Urinalysis:
- Organ weights:
- Gross pathology:
- Histopathology:
- Toxicokinetics:

Summary of individual study findings:

Toxicology summary:

Toxicology conclusions:

Histopathology Inventory for NDA #

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				

Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed

*, organ weight obtained

GENETIC TOXICOLOGY:

Study title:

Key findings:

Study no:

Study type (if not reflected in title):

Volume #, and page #:

Conducting laboratory and location:

Date of study initiation:

GLP compliance:

QA reports: yes () no ()

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle:

Methods:

Strains/species/cell line:

Dose selection criteria:

Basis of dose selection:

Range finding studies:

Test agent stability:

Metabolic activation system:

Controls:

Vehicle:

Negative controls:

Positive controls:

Comments:

Exposure conditions:

Incubation and sampling times:

Doses used in definitive study:

Study design:

Analysis:

No. of replicates:

Counting method:

Criteria for positive results:

Summary of individual study findings:

Study validity:

Study outcome:

Genetic toxicology summary:

Genetic toxicology conclusions:

Labeling recommendations:**CARCINOGENICITY:****Study title:****Key study findings:****Study number:****Volume #, and page #:****Conducting laboratory and location:****Date of study initiation:****GLP compliance:****QA report: yes () no ()****Drug, lot #, and % purity:****CAC concurrence:****Study Type (2 yr bioassay, alternative model etc.):****Species/strain:****Number/sex/group; age at start of study:****Animal housing:****Formulation/vehicle:****Drug stability/homogeneity:****Methods:**

Doses:

Basis of dose selection:

Restriction paradigm for dietary restriction studies:

Route of administration:

Frequency of drug administration:

Dual controls employed:

Interim sacrifices:

Satellite PK or special study group(s):

Deviations from original study protocol:

Statistical methods:

Observations and times:

Clinical signs:

Body weights:

Food consumption:

Hematology:

Clinical chemistry:

Organ weights:

Gross pathology:

Histopathology:

Toxicokinetics:

Results:

Mortality:

Clinical signs:

Body weights:

Food consumption:

Hematology:

Clinical chemistry:

Organ weights:

Gross pathology:

Histopathology:

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 Neoplastic:

Toxicokinetics:

Summary of individual study findings:

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Evaluation of tumor findings:

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Carcinogenicity conclusions:

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CAC report:

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Sponsor's incidence of histopathology findings:

List of organs and tissues examined:

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 Group body weight summary:

 Individual data listing:

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:**Study title:****Key study findings:****Study no.:****Volume #, and page #:****Conducting laboratory and location:****Date of study initiation:****GLP compliance:****QA reports:** yes () no ()**Drug, lot #, radiolabel, and % purity:****Formulation/vehicle:****Methods:**

Species/strain:

Doses employed:

Route of administration:

Study design:

Number/sex/group:

Parameters and endpoints evaluated:

Results:

Mortality:

Clinical signs:

Body weight:

Food consumption:

Toxicokinetics:

For fertility studies:

In-life observations:

Terminal and necroscopic evaluations:

*OR**For embryofetal development studies:*

In-life observations:

Terminal and necroscopic evaluations:

Dams:

Offspring:

OR

For peri-postnatal development studies:

In-life observations:

Dams:

Offspring:

Terminal and necroscopic evaluations:

Dams:

Offspring:

Summary of individual study findings:

Reproductive and developmental toxicology summary:

Reproductive and developmental toxicology conclusions:

Labeling recommendations:

SPECIAL TOXICOLOGY STUDIES:

Study title:

Key study findings:

Study no:

Volume #, and page #:

Conducting laboratory and location:

Date of study initiation:

GLP compliance:

QA reports: yes () no ():

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle:

Methods:

Dosing:

Observations and times:

Results:

Summary of individual study findings:

Conclusions:

ADDENDUM TO REVIEW:

(if necessary)

APPENDIX/ATTACHMENTS: