Guidance for Industry

Carcinogenicity Study Protocol Submissions

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

February 2002
PharmacologyToxicology/PDUFA

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. 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 and regulations.

I. INTRODUCTION

This guidance is intended to inform sponsors of the types of information the Center for Drug Evaluation and Research (CDER) relies on when evaluating protocols for animal carcinogenicity studies.

II. BACKGROUND

The Prescription Drug User Fee Act of 1992 (PDUFA) was reauthorized in the Food and Drug Administration Modernization Action of 1997. In conjunction with the reauthorization of PDUFA, FDA agreed to specific performance goals (PDUFA goals) for activities associated with the development and review of products in human drug applications.[2] The PDUFA goals are summarized in *PDUFA Reauthorization Performance Goals and Procedures*, an enclosure to a letter dated November 12, 1997, from the Secretary of Health and Human Services, Donna E. Shalala, to Senator James M. Jeffords.

The PDUFA goals related to special protocol assessment and agreement provide that, upon request, FDA will evaluate within 45 calendar days certain protocols and issues relating to the protocols to assess whether or not they are adequate to meet scientific and regulatory requirements identified by the sponsor. Protocols for animal carcinogenicity studies are eligible for this special protocol assessment.[3] This guidance is intended to facilitate the Agency's review of protocols for animal carcinogenicity studies by informing sponsors of the types of information the Agency relies on during its evaluation of such protocols.

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[1] This guidance has been prepared by the Office of Review Management in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] The term *human drug application* is defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act.

[3] The Agency published a draft guidance on *Special Protocol Assessment* in February 2000. Once finalized, that guidance will reflect the Agency's current views on submitting information to CDER for special protocol assessment.

Although protocol submissions not supplying all of the information described in this document can be evaluated by CDER, an incomplete package may make it extremely difficult for the Agency to reach agreement on a protocol or recommend alternative study designs. In situations where insufficient information is provided, the sponsor may be told that the committee was unable to concur with the proposed protocol.

Prior to designing carcinogenicity studies, sponsors should review the ICH guidances *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals* (March 1995) and *S1C(R) Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on a Limit Dose and Related Notes* (December 1997). The highest dose to be included in a carcinogenicity study should be based on one of the ICH endpoints.[4] Sponsors also should review *S1B Testing for Carcinogenicity of Pharmaceuticals* (February 1998), which provides guidance on species selection and alternative approaches to the standard 2-species/2-year testing paradigm.

III. GUIDANCE ON PROTOCOL SUBMISSIONS

In CDER, primary responsibility for the review of protocols for animal carcinogenicity studies lies with the review division. The review division consults with CDER's Carcinogenicity Assessment Committee (CAC) or CDER's Executive Carcinogenicity Assessment Committee (Exec CAC). These committees provide an oversight review of the study protocols and provide written comments on the appropriateness of the protocol from CDER's perspective on approaches to testing, including the study type, doses employed, and other design issues.

To facilitate the review process, at least 30 days prior to submission of the study protocol, sponsors should notify the Agency in writing that a carcinogenicity protocol will be arriving. The carcinogenicity protocol and questions regarding the protocol should be submitted in sufficient time prior to the anticipated initiation of the study to allow for meaningful discourse with the Agency and resolution of any issues before study initiation. Submission should be made to the appropriate review division in CDER. The submission should be clearly marked in bold black letters as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT. It also should be clearly marked as a carcinogenicity study protocol.[5]

PDUFA goals for special protocol assessment do not apply to requests for assessment of ongoing carcinogenicity studies. CDER intends to review the protocols for these ongoing studies and to provide a response to such review requests in a timely manner.

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[4] Toxicity, Dose-Limiting PD Effects, Exposures 25 times Human AUC, Saturation of Absorption, Maximum Feasible Dose (MFD), or Limit Dose.

[5] The Agency published a draft guidance on *Special Protocol Assessment* in February 2000. Once finalized, that guidance will reflect the Agency's current views on submitting information to CDER for special protocol assessment.

A. Information Important to Facilitate Protocol Review

The type of information important for evaluating carcinogenicity protocols will vary with the proposed study design and test approach (see the table at the end of this guidance). Not all of the information discussed below is essential for all study designs or dose selection endpoints. In all cases, however, the comprehensive submission of the following information will facilitate the Agency's protocol review. As explained in ICH guidance *S1C,* sponsors should include the basis for dose selection.

1. A toxicology study report should be included reflecting the same conditions as proposed for the carcinogenicity study (same mode of administration, same diet, same rodent strain). Unaudited draft reports (containing summary tables and individual animal data) can be submitted.[6] The usual duration of this type of study is 90 days if it is intended to support dose selection for a standard 2-year carcinogen bioassay.[7] Studies of shorter duration may be appropriate for alternative bioassays (see the recommendations in ICH *S1B* and *S1C*).

2. Metabolic profiles should be provided for the drug in humans and in the species employed for assessment of carcinogenic potential. In cases where in vivo data are unavailable, in vitro data can be used (see the recommendations in ICH *S1C*).[8]

3. Toxicokinetic data should be provided that are sufficient to estimate steady state $AUC_{(0\text{-}24)}$ for the parent drug and each major human metabolite at doses employed in the rangefinding study. For determining the appropriateness of using AUC/limit dose approaches, *major metabolites* are defined as metabolites that, if excluded from the analysis, significantly change the comparison ratios between species. Data (point estimates as well as individual animal values) should be reported separately for males and females from the same strain as proposed for the bioassay.[9]

4. Exposure (steady state $AUC_{(0\text{-}24)}$) data should be provided for the parent drug and for the major metabolites from clinical trials conducted at the maximum

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[6] See the guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995).

[7] Irrespective of method of dosage qualification, a rangefinding study is important to ensure that doses selected are likely to be tolerated in the carcinogen bioassay. The need for a rangefinding study may be obviated by the existence of other information, such as chronic toxicity data, depending on the design and outcome of the chronic toxicity studies.

[8] Regardless of endpoint used for dose selection, this information is used to ensure that the animal species proposed for testing is a reasonable surrogate for assessing carcinogenic potential in humans.

[9] This information is used to justify selected doses on the basis of multiple of human systemic exposure, saturation of absorption, or limit dose endpoints. Irrespective of dose-selection endpoint, this information is used in the selection of the appropriate dose spread and can be used for product labeling.

recommended human dose (MRHD) or other appropriate human reference dose if the MRHD exposure data are unavailable.[10] Where pharmacokinetics differ significantly between sexes, data from males and females should be reported separately, as a sex difference can modify the study approach and conclusions. It is our experience that sex differences occur rarely.

5. Plasma protein binding data should be provided for the parent drug and the major human metabolites (to the extent feasible) in the rodent test species over the range of concentrations encountered in the dose-rangefinding experiment and in humans at concentrations encountered in clinical trials conducted at the reference dose.

6. A summary of the investigations into the genotoxic potential of the drug and its major human metabolites should be included.[11] Positive genotoxicity results for parent or metabolites can preclude use of AUC ratios, limit dose (ICH Guidances S1C and S1C(R)), and influence the choice of alternatives assays.

B. The Resubmission of Previously Submitted Reports

When a sponsor relies on reports critical to the chosen dose-selection endpoint that were previously submitted to the Agency, CDER encourages sponsors to resubmit the actual reports or, at least, summaries of the reports. Previously submitted reports can be referenced by submission number and correspondence date (rather than being resubmitted), but submitting the actual reports or their summaries will speed the Agency's review of the carcinogenicity protocol.

C. Use of Body Weight Gain Decrements in a Rangefinding Study in Establishing the Top Dose for a Carcinogenicity Study

In a dietary administration study, when body weight gain decrements are accompanied by reductions in food consumption and such body weight effects are the only basis for dosage selection, it is important for the sponsor to document that the reduced consumption is not a consequence of a palatability problem. This documentation is important because if the drug is not palatable, higher doses might be tolerated with another mode of administration (e.g., gavage), and the proposed dietary mode of administering doses may not be appropriate.

D. The Selection of Doses for Rangefinding Experiments

The chosen doses should clearly elicit effects that can be used as endpoints as recommended in the ICH guidances. The doses selected should include a dose that is

[10] In some cases the MRHD is unknown at the time of carcinogenicity protocol initiation, and an alternative reference dose can be used to determine human exposure. An example of an acceptable alternative approach could be to determine exposure at a human dose eliciting toxicity such that higher doses would not be acceptable for the indication. The basis for the choice of the human dose used in the comparison should be provided.

[11] This information is used to determine the appropriateness of using the multiple of human systemic exposure or limit dose endpoints in accordance with ICH guidances.

without significant toxicity. It is generally unnecessary to include the maximum feasible dose in the design of the rangefinding experiments when it is known that doses lower than the maximum feasible dose, when administered by the same mode of administration in other toxicity studies, are clearly not tolerated or exceed other acceptable dose selection endpoints. In the absence of such information from other studies, it may be prudent to include the maximum feasible dose in the design of the rangefinding experiments.

E. Presentation of Data from Rangefinding or Other Toxicity Studies

Results of toxicity studies submitted in support of dose-selection should be presented in a tabular format and reported separately for males and females. Histopathology tables that provide information on both incidence and severity of findings are important to allow adequate dose selection. Clinical pathology tables should include the group mean value and standard deviation for each parameter reported. Graphical illustration of changes in body weight over the course of the study is encouraged.

F. Use of the Limit Dose

The ICH guidance *S1C(R)* supports the use of a limit dose (1500 mg/kg/day) when certain criteria are met. One of those criteria is that it can be ensured that the rodent exposure to the drug and metabolites at 1500 mg/kg/day exceeds systemic human exposure (AUC) at the MRHD by greater than an order of magnitude. For the purposes of this guidance, CDER considers this has been demonstrated if the lower 95 percent confidence limit for AUC in the rodent is at least 10 times the AUC in humans at the MRHD.

Tabular Summary of Types of Data Useful for Evaluation of Carcinogenicity Bioassay Protocols

Dose Selection Endpoint	Types of Data Useful for Evaluation of Carcinogenicity Bioassay Protocols				
	General Toxicity Information	Genotoxicity	Human and Animal Metabolism	Animal AUC [a.] (Unbound)	Human AUC [a.] (Unbound)
Toxicity (MTD)	√	A	m	---	---
Multiple of Human Exposure (25 X)	√	√	√	√	√
Saturation of Absorption of Drug Related Substances	√	A	m	√	---
MFD	√	A	m	---	---
Limit Dose	√	√	√	√	√
Pharmacodynamic Effects	√	A	m	---	---

[a.] AUC for unbound drug is crucial where unbound fraction of drug is greater in humans than animals, but can be used in other circumstances.

√ Important to support this dose selection endpoint for alternative and standard model

A Important for selection of alternative model for these dose selection endpoints

m Information used primarily to support test model (species and strain) for these endpoints

--- Not applicable to this endpoint