Guidance for Industry

Special Protocol Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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TABLE OF CONTENTS

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I. INTRODUCTION

This document is intended to provide guidance to industry on procedures adopted by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for evaluating issues related to the adequacy (e.g., design, conduct, analysis) of certain proposed studies associated with the development of products in human drug applications as defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 379g(1)) (PDUFA products). This guidance implements section 119(a) of the Food and Drug Administration Modernization Act (the Modernization Act) by describing procedures sponsors should use to request special protocol assessment and the Agency should use to act on such requests. For the purposes of this guidance document, the term *sponsor* includes any sponsor or applicant interested in special protocol assessment.

II. BACKGROUND

A. PDUFA Goals for Special Protocol Assessment

In conjunction with the reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA) in November 1997, FDA agreed to specific performance goals (PDUFA goals) for special protocol assessment and agreement. The PDUFA goals are described in the *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 for special protocol assessment and agreement provide that, upon request, FDA will evaluate within 45 days certain protocols and issues relating to the protocols to assess whether they are adequate to meet scientific and regulatory

[1] This guidance has been prepared by the Review Management Working Group in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

requirements identified by the sponsor. Three types of protocols related to PDUFA products are eligible for this special protocol assessment under the PDUFA goals: (1) animal carcinogenicity protocols, (2) final product stability protocols, and (3) clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim if the trials had been the subject of discussion at an end-of-phase 2/pre-phase 3 meeting with the review division, or in some cases, if the division agrees to such a review because the division is aware of the developmental context[2] in which the protocol is being reviewed and the questions are being answered. The clinical protocols for phase 3 trials can relate to efficacy claims that will be part of an original new drug application (NDA) or biologics license application (BLA) or that will be part of an efficacy supplement to an approved NDA or BLA.

B. Modernization Act Provisions for Meetings and Agreements on Clinical Trials

Section 119(a) of the Modernization Act amends section 505(b) of the Act (21 U.S.C. 355(b)). New section 505(b)(4)(B) of the Act directs FDA to meet with sponsors, provided certain conditions are met, for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an efficacy claim in a marketing application submitted under section 505(b) of the Act or section 351 of the Public Health Service Act (42 U.S.C. 262).[3] Such marketing applications include NDAs, BLAs, and efficacy supplements to approved NDAs and BLAs.

Under new sections 505(b)(4)(B) and (C) of the Act, if a sponsor makes a reasonable written request to meet with the Agency for the purpose of reaching agreement on the design and size of a clinical trial, the Agency will meet with the sponsor. If an agreement is reached, the Agency will reduce the agreement to writing and make it part of the administrative record. An agreement may not be changed by the sponsor or FDA after the trial begins, except (1) with the written agreement of the sponsor and FDA, or (2) if the director of the FDA reviewing division determines that "a substantial scientific issue essential to determining the safety or effectiveness of the drug" was identified after the testing began (section 505(b)(4)(C) of the Act). If a sponsor and the Agency meet regarding the design and size of a clinical trial under section 505(b)(4)(B) of the Act and the parties cannot agree that the trial design is adequate to meet the goals of the sponsor, the Agency will clearly state the reasons for the disagreement in a letter to the sponsor

[2] For the purposes of special protocol assessment, developmental context refers to the history of the product's development that will support the proposed phase 3 clinical studies. To adequately assess the proposed protocol in relation to the sponsor's goal (e.g., indication), FDA should be aware of the product development. Product development includes, but is not limited to, nonclinical toxicology studies, dose selection, phase 2 studies, and the development of adequate manufacturing controls to ensure product quality.

[3] Section 119(b) of the Modernization Act directs FDA to meet with sponsors and applicants, provided certain conditions are met, to reach agreement on the design and size of bioavailability and bioequivalence studies needed to support applications submitted under section 505(j) of the Act (i.e., abbreviated new drug applications). FDA intends to issue a separate guidance document that will address the implementation of section 119(b) of the Modernization Act.

(PDUFA goals at VI.A.2). However, the absence of an articulated disagreement on a particular issue should not be assumed to represent an agreement reached on that issue.

Meetings between the Agency and sponsors are generally helpful in reaching agreement on the design and, in some cases, interpretation of studies submitted in support of marketing applications.[4]

C. Focus of This Guidance

Sections 505(b)(4)(B) and (C) of the Act and the PDUFA goals describe the Agency's plan for evaluating certain protocols and working towards, and achieving, agreement with sponsors and applicants on the design and size of studies and clinical trials that can be used for approval of a drug or biological product. The procedures described in this guidance apply to special protocol assessment of carcinogenicity protocols, stability protocols, and clinical protocols for trials whose data will form the primary basis of an efficacy claim. As the PDUFA goals for special protocol assessment are more comprehensive[5] and specific (e.g., they give specific times for Agency review) than the requirements of sections 505(b)(4)(B) and (C) of the Act, this guidance focuses on procedures to achieve the PDUFA goals. The requirements of section 505(b)(4)(B) and (C) of the Act will also be fulfilled by achieving the PDUFA goals for special protocol assessment.

III. PROCEDURES FOR REQUESTING SPECIAL PROTOCOL ASSESSMENT

Under the PDUFA goals, FDA will evaluate certain protocols when the sponsor requests evaluation. A separate request should be submitted for each specific protocol the sponsor would like reviewed. The procedures for requesting special protocol assessment are described below.

[4] In February 2000 (65 FR 12020), FDA made available a guidance for industry, *Formal Meetings with Sponsors and Applicants for PDUFA Products*, describing policies and procedures adopted by CDER and CBER to enhance the productivity of meetings between the Agency and sponsors of PDUFA products. The procedures described in the guidance promote the PDUFA performance goals for meeting management and section 505(b)(4)(B) of the Act. FDA intends to issue additional guidance describing CDER's and CBER's general procedures for formal meetings with sponsors of non-PDUFA products (including generic drug products).

[5] The PDUFA goals regarding clinical protocol review and assessment are wider in scope than section 505(b)(4)(B) of the Act. Both the noted statutory requirements and the PDUFA performance goals apply to protocols for clinical trials intended to form the primary basis of an efficacy claim in original and supplemental applications. The PDUFA performance goals, however, *also* apply to animal carcinogenicity protocols and final product stability protocols, whereas the statutory section does not.

A. Timing of Request

CDER and CBER generally recommend that a sponsor submit a protocol intended for special protocol assessment to the Agency at least 90 days prior to the anticipated start of the study. The protocol should be complete, and enough time should be allowed to discuss and resolve any issues before the study begins. ***Special protocol assessment will not be provided after a study has begun***.[6] Protocols for studies that have already begun can be evaluated by CDER and CBER, but they do not qualify for the 45-day time frame described in the PDUFA goals.

1. Carcinogenicity Protocols

A sponsor interested in Agency assessment and agreement on a carcinogenicity protocol should notify the appropriate review division (CDER) or applications division (CBER) and discuss planned carcinogenicity testing at an end-of-phase-2 meeting, or should notify the director of the appropriate division of an intent to request special protocol assessment by letter at least 30 days prior to submitting the request. With the notice of intent, the sponsor should submit relevant background information so that the Agency can review (or re-review) reference material related to carcinogenicity protocol design prior to receiving the carcinogenicity protocol.[7]

2. Stability Protocols

Generally, a standard stability protocol will be based on the principles described in the following guidance documents issued by the Agency and the International Conference on Harmonisation (ICH): (1) *Q1A Stability Testing of New Drug Substances and Products* (May 1997),[8] (2) *Q1C Stability Testing of New Dosage Forms* (May 1997), and (3) *Q5C Stability Testing of Biotechnological/Biological Products* (July 1997). A stability protocol significantly different from the standard stability protocol can be submitted to the Agency with a request for special protocol assessment. Prior to requesting special protocol assessment for a stability study, a sponsor should ensure that the product is sufficiently developed. The product should be in advanced clinical development, and product characterization should be complete. Manufacturing steps that can affect product stability should be identified. The sponsor should also ensure that the manufacturing process, formulation, and container closure for the drug product described in the request for assessment of the stability protocol do not differ substantively from those for the

[6] For the purposes of special protocol assessment, a study begins when patient screening or enrollment begins.

[7] In November 2000 (65 FR 66757), the Agency made available a draft guidance document for industry, *Carcinogenicity Study Protocol Submissions*. When finalized, that guidance will describe the type of information that would be appropriate to submit before requesting carcinogenicity protocol assessment and will represent the Agency's current thinking on this topic.

[8] The draft guidance, *Q1A Stability Testing of New Drug Substances and Products*, will be superseded by FDA's guidance for industry, *Q1AR Stability Testing of New Drug Substances and Products*, once it is issued in final form.

product to be marketed and that the tests described will adequately qualify the drug product.

3. Clinical Protocols

As stated in the PDUFA goals, for special protocol assessment of a protocol for a clinical trial that will form the primary basis of an efficacy claim in an NDA or BLA, the sponsor should have had a meeting with the review division so that the division is aware of both the developmental context in which the protocol is being reviewed and the questions that are to be answered. However, if the Agency is already familiar with the developmental context of a proposed clinical trial and has an understanding of the questions that will be raised regarding the protocol, as ordinarily will be the case with efficacy supplements, the Agency can provide a special protocol assessment without requiring a meeting.

B. Format of Request

A sponsor should submit each protocol for assessment under this program as a *separate* amendment to the sponsor's IND in triplicate with Form FDA 1571 and a cover letter attached. The cover letter should clearly identify the submission as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** in bolded block letters at the top and should clearly state the type of protocol being submitted (i.e., carcinogenicity, stability, or clinical). If a sponsor does not designate a submission as a request for special protocol assessment, the Agency will not be able to recognize it as such and may not review the submission under the procedures described in this guidance document.

C. Where to Send a Request

The request should be submitted to the appropriate review division in CDER or applications division in CBER. A copy of the cover letter should be sent via fax to the individuals listed below.

Carcinogenicity protocols:
- CDER - the project manager for the application in the appropriate review division and the Associate Director for Pharmacology and Toxicology in the Office of Review Management
- CBER - the director of the appropriate applications division

Stability protocols:
- CDER - the project manager for the application in the appropriate review division and the appropriate chemistry team leader
- CBER - the director of the appropriate applications division

Clinical trials intended to form the primary basis of an efficacy claim:
- CDER - the project manager for the application in the appropriate review division
- CBER - the director of the appropriate applications division

A sponsor interested in seeking special protocol assessment before submitting an IND should contact the chief of the project management staff in the appropriate review division in CDER or should submit a written request to the director of the appropriate applications division for the product in CBER. Sponsors who request special protocol assessment without an IND should note that the Agency will not be able to provide special protocol assessment without being fully informed of the overall development plan for the drug or biological product.

D. Content of a Request

In the request for special protocol assessment, the sponsor should pose focused questions concerning specific issues regarding the protocol, protocol design (including proposed size), study conduct, study goals, and/or data analysis for the proposed investigation. Although the questions should be specific to the protocol and should not address overall development strategies, the role of the study in the overall development plan should be clear to the Agency for it to answer the protocol-specific questions.

To facilitate FDA's assessment of the issues raised by the sponsor, a request in the form of a document separate from the protocol should discuss in reasonable detail all data, assumptions, and information that should be included for an adequate evaluation of the protocol. For example:

- The sponsor should include information to assess the role of the study in the overall development of the drug.

- The sponsor should submit information supporting the proposed trial, including power calculations, the choice of study endpoints, and other critical design features (e.g., choice of control, duration, methods of assessment).

- The sponsor should clearly describe any anticipated regulatory outcomes (e.g., approval of a specific claim, breaking orphan exclusivity, a comparative claim) and proposed labeling that the sponsor believes would be supported by the results of the study.

- A sponsor interested in Agency assessment of a stability protocol should include product characterization and relevant manufacturing data, specifications, information regarding the market formulation and strengths, container closure, and the retest period or shelf life that is expected to be proposed at the time of filing. If this information is contained in the IND, it can be cross-referenced by specific submission date and page number.

Special protocol assessment is designed to evaluate individual protocols primarily in response to specific questions posed by the sponsors. While more general drug development issues (e.g., the *number* of trials needed or adequacy of supportive evidence for a given efficacy claim) are factors in assessing the overall adequacy of a proposed

protocol, they are not considered part of the special protocol assessment program. Questions pertaining to such general drug development issues should be discussed in routine drug development meetings and correspondence with the review or applications division. Such drug development issues should also be discussed with the review office, as appropriate.

IV. AGENCY ASSESSMENT

A. Action on the Request

After receiving a written request for special protocol assessment, the review or applications division director will decide whether the submission is appropriate for such assessment. In CDER, this decision will be based on recommendations from the clinical team leader, chemistry team leader, statistical team leader, or pharmacology/toxicology team leader, as appropriate. In CBER, the decision will be based on the recommendations of the review team. If the division concludes that special protocol assessment is appropriate, the division will proceed with the assessment (see Assessment of the Protocol below). If the recommendations for special protocol assessment, as outlined in this guidance, are not met, the division should notify the sponsor of the reasons for the determination as soon as possible after the Agency receives the request. A submission does not meet the recommendations for special protocol assessment if, for example, the protocol is for an ongoing trial or the request for special protocol assessment does not include specific questions about the protocol design and scientific or regulatory requirements to which the Agency can respond. If the division notifies the sponsor by telephone or fax that special protocol assessment is not appropriate, the division should also send a follow-up hard copy of the letter documenting the determination.

B. Assessment of the Protocol

For each special protocol assessment under this program, the centers will answer any questions that are appropriate. For example, the centers will provide comments on issues related to protocol design, study conduct and execution, data analysis, and implications for labeling. The Agency's assessment will be based primarily on the questions posed by the sponsor, the underlying data, assumptions, information described by the sponsor, and relevant Agency policies and guidance documents. Any change in the underlying data, assumptions, and information could affect the assessment of the protocol. As stated in the PDUFA goals, comments from the review team should be sent to the sponsor in a special protocol assessment letter within 45 calendar days of receipt of the request for special protocol assessment. If the division faxes the letter to the sponsor, the division should also send a follow-up hard copy of the letter.

1. Revisions During Agency Assessment

The Agency can communicate with the sponsor regarding the protocol before issuing a special protocol assessment letter. In such cases, the sponsor can choose to submit a

revised protocol. If a sponsor submits a revised protocol, for any reason, while the Agency is reviewing an earlier version of the same protocol, the Agency ordinarily will not respond to the questions posed about the earlier version of the protocol and will consider the original request withdrawn. The Agency will consider a request for special protocol assessment of a revised protocol to be a new request and will act on the revised protocol within 45 days.

2. Advisory Committee Review

The Agency can seek advisory committee review of a clinical protocol or can obtain advisory review from selected advisory committee members, special government employees, or other consultants. In either circumstance, in lieu of a special protocol assessment letter, the sponsor should be notified within 45 calendar days after the Agency receives the request for special protocol assessment that an advisory committee or selected advisory committee members will review the protocol. FDA should advise the sponsor of (1) an expected date of the advisory committee meeting or consultation with advisory committee members, and (2) the Agency's reasons for seeking outside review of the protocol.

If the clinical protocol will be presented to an advisory committee, the presentation should be scheduled to take place at the next *available* advisory committee meeting. Advisory committee discussion of protocols submitted for special protocol assessment generally will not be open to the public. A special protocol assessment letter, including comments from the review team based on advice from the advisory committee or selected advisory committee members, should be sent to the sponsor within 45 calendar days of the advisory committee member review of the protocol. If the division faxes the notification or special protocol assessment letter to the sponsor, the division should also send a follow-up hard copy of the letter.

V. MEETINGS

If a sponsor requests a meeting with CDER or CBER after receipt of a special protocol assessment letter, the request will be handled as a request for a Type A meeting under the PDUFA goals for meeting management. This meeting will be scheduled to take place within 30 calendar days after receipt of the written request for the meeting. At the Type A meeting, the Agency representatives and the sponsor should discuss any remaining issues and uncertainties regarding the protocol. If CDER or CBER believes that meeting with a sponsor would be the best way to resolve outstanding issues regarding a special protocol assessment, the Agency can suggest that the sponsor request such a meeting. Any meeting with the sponsor should be scheduled and conducted under the policies and procedures established by CDER and CBER.[9]

VI. DOCUMENTATION

[9] In February 2000 (65 FR 12020), FDA made available a guidance for industry, *Formal Meetings with Sponsors and Applicants for PDUFA Products*, describing policies and procedures adopted by CDER and CBER to enhance the productivity of meetings between the Agency and sponsors of PDUFA products.

A. Form of Documentation

All agreements and disagreements between the Agency and the sponsor regarding special protocol assessments, including Agency responses to questions about protocol design, primary efficacy endpoints, study conduct, data analysis, and the kind of labeling statements one could expect if the data are supportive and the product is approved, should be clearly documented in writing (section 505(b)(4)(C) of the Act). These special protocol assessments can be documented in the special protocol assessment letter and/or the minutes of the Type A meeting. A special protocol assessment can document the Agency's agreement that the design and planned analysis of a study adequately address objectives in support of a regulatory submission. A special protocol assessment can also identify questions raised by the sponsor to which the Agency is unable to respond. In limited circumstances, the Agency may agree that a specific finding (e.g., a particular p value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.

B. Changes in Documented Special Protocol Assessments

As stated in the PDUFA goals for special protocol assessment and agreement,

> having agreed to the design, execution, and analyses proposed in protocols reviewed under this process [i.e., carcinogenicity protocols, stability protocols, and phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim], the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

Thus, documented special protocol assessments should be considered binding on the review division and should not be changed at any time, except as follows:

- Failure of a sponsor to follow a protocol that was agreed upon with the Agency will be interpreted as the sponsor's understanding that the protocol assessment is no longer binding on the review division.

- If the relevant data, assumptions, or information provided by the sponsor in a request for special protocol assessment change are found to be false statements or misstatements or are found to omit relevant facts, the review division will not be bound by any assessment that relied on such data, assumptions, or information.

- A documented special protocol assessment can be modified if (1) FDA and the sponsor agree in writing to modify the protocol (section 505(b)(4)(C) of the Act) and (2) such modification is intended to improve the study. A special protocol

assessment modified in this manner will be considered binding on the review division, except under the circumstances described below.

- A clinical protocol assessment will no longer be considered binding if the director of the review division determines that a substantial scientific issue essential to determining the safety or efficacy of the drug has been identified after the testing has begun (section 505(b)(4)(C) of the Act). If the director of the review division makes such a determination, (1) the determination should be documented in writing for the administrative record and should be provided to the sponsor, and (2) the sponsor should be given an opportunity for a meeting at which the review division director will discuss the scientific issue involved (section 505(b)(4)(D) of the Act). This meeting will be a Type A meeting under the PDUFA goals for meeting management.[10]

C. Personnel Changes

Changes in personnel on both the Agency's review team and the sponsor's development team are common during drug development. Personal preferences of new individuals on either team should not affect any documented special protocol assessment.

VII. DISPUTE RESOLUTION

A sponsor should first try to resolve disagreements with FDA action under the special protocol assessment program with the review or applications division. Any dispute regarding study design should be resolved before starting the trial. If the sponsor is not satisfied with the response provided by FDA, the sponsor can decide to pursue the Agency's procedures for formal dispute resolution as described in regulations (21 CFR 10.75, 312.48, and 314.103) and the guidance for industry, *Formal Dispute Resolution: Appeals Above the Division Level* (March 2000, 65 FR 12019). However, if an advisory committee evaluates a protocol as part of special protocol assessment, further review by the advisory committee need not be obtained as part of dispute resolution.

VIII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 8 hours to prepare a notice of intent to request special protocol assessment of a carcinogenicity protocol and 15 hours to prepare a request for special protocol assessment, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the

[10] In February 2000 (65 FR 12020), FDA made available a guidance for industry, *Formal Meetings with Sponsors and Applicants for PDUFA Products*, describing policies and procedures adopted by CDER and CBER to enhance the productivity of meetings between the Agency and sponsors of PDUFA products.

information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to: Office of Regulatory Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information for FDA Form 1571 have been approved under OMB Control No. 0910-0014.