
Guidance for Industry

Special Protocol Assessment

DRAFT GUIDANCE

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**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)
December 1999
Procedural**

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**U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research (CBER)**

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GUIDANCE FOR INDUSTRY¹

Special Protocol Assessment

(Due to the complexity of this draft document, please identify specific comments by line number.
Use the pdf version of the document whenever possible.)

1 I. INTRODUCTION

2 This document is intended to provide guidance to industry on procedures adopted by the Center for
3 Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER)
4 for evaluating issues related to the adequacy (e.g., design, conduct, analysis) of certain proposed
5 studies associated with the development of products in human drug applications as defined in section
6 735(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 379g(1)) (PDUFA
7 products). This guidance implements section 119(a) of the Food and Drug Administration
8 Modernization Act (the Modernization Act) by describing procedures for sponsors to request special
9 protocol assessment and for the Agency to act on such requests. For the purposes of this guidance
10 document, the term *sponsor* includes any sponsor or applicant interested in special protocol
11 assessment.

12 II. BACKGROUND

13 A. PDUFA Goals for Special Protocol Assessment

14 In conjunction with the reauthorization of the Prescription Drug User Fee Act of 1992 in November
15 1997 (PDUFA 2), FDA agreed to specific performance goals (PDUFA goals) for special protocol
16 assessment and agreement. The PDUFA goals are described in the *PDUFA Reauthorization*
17 *Performance Goals and Procedures*, an enclosure to a letter dated November 12, 1997, from the
18 Secretary of Health and Human Services, Donna E. Shalala, to Senator James M. Jeffords.

19 The PDUFA goals for special protocol assessment and agreement provide that, upon request, FDA
20 will evaluate within 45 days certain protocols and issues relating to the protocols to assess whether they
21 are adequate to meet scientific and regulatory requirements identified by the sponsor. Three types of
22 protocols related to PDUFA products are eligible for this special protocol assessment under the
23 PDUFA goals: (1) animal carcinogenicity protocols, (2) final product stability protocols, and (3)
24 clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim if the

¹ This guidance has been prepared by the Review Management Working Group comprising individuals in the Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on special protocol assessment and agreement. 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 statute, regulations, or both.

25 trials had been the subject of discussion at an end-of-phase 2/pre-phase 3 meeting with the review
26 division or if the division is otherwise aware of the developmental context in which the protocol is being
27 reviewed and the questions are being answered. The clinical protocols for phase 3 trials may relate to
28 efficacy claims that will be part of an original new drug application (NDA) or biologics license
29 application (BLA) or that will be part of an efficacy supplement to an approved NDA or BLA.

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

31 Section 119(a) of the Modernization Act amends section 505(b) of the Act (21 U.S.C. 355(b)). New
32 section 505(b)(4)(B) of the Act directs FDA to meet with sponsors, provided certain conditions are
33 met, for the purpose of reaching agreement on the design and size of clinical trials intended to form the
34 primary basis of an effectiveness claim in a marketing application submitted under section 505(b) of the
35 Act or section 351 of the Public Health Service Act (42 U.S.C. 262).² Such marketing applications
36 include NDAs, BLAs, and efficacy supplements to approved NDAs and BLAs.

37 Under new sections 505(b)(4)(B) and (C) of the Act, if a sponsor makes a reasonable written request
38 to meet with the Agency for the purpose of reaching agreement on the design and size of a clinical trial,
39 the Agency will meet with the sponsor and, if an agreement is reached, will reduce the agreement to
40 writing and make it part of the administrative record. An agreement may not be changed by the
41 sponsor or FDA after the trial begins, except (1) with the written agreement of the sponsor and FDA,
42 or (2) if the director of the FDA reviewing division determines that "a substantial scientific issue essential
43 to determining the safety or effectiveness of the drug" was identified after the testing began (section
44 505(b)(4)(C) of the Act). If a sponsor and the Agency meet regarding the design and size of a clinical
45 trial under section 505(b)(4)(B) of the Act and the parties cannot agree that the trial design is adequate
46 to meet the goals of the sponsor, the Agency will clearly state the reasons for the disagreement in a
47 letter to the sponsor. However, the absence of an articulated disagreement on a particular issue may
48 not be assumed to represent an agreement reached on that issue.

49 Meetings between the Agency and sponsors are generally helpful in reaching agreement on the design
50 and, in some cases, interpretation of carcinogenicity studies, stability studies, and clinical trials.³

51 **C. Focus of This Guidance**

² 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.

³ In March 1999 (64 FR 13591), FDA made available for comment a draft guidance for industry, *Formal Meetings with Sponsors and Applicants for PDUFA Products*, describing policies and procedures that will be adopted by CDER and CBER to enhance the productivity of meetings between the Agency and sponsors of PDUFA products. Once the draft guidance is finalized, the procedures described in the guidance will 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).

52 Sections 505(b)(4)(B) and (C) of the Act and the PDUFA goals describe Agency procedures for
53 evaluating certain protocols and working towards, and achieving, agreement with sponsors and
54 applicants on the design and size of studies and clinical trials that may be used for approval of a drug or
55 biological product. Unless otherwise stated, the procedures described in this guidance apply to special
56 protocol assessment of carcinogenicity protocols, stability protocols, and clinical protocols for phase 3
57 trials whose data will form the primary basis of an efficacy claim. As the PDUFA goals for special
58 protocol assessment are more comprehensive⁴ and specific (e.g., they give specific times for Agency
59 review) than the requirements of sections 505(b)(4)(B) and (C) of the Act, this guidance focuses on
60 procedures to achieve the PDUFA goals. The requirements of section 505(b)(4)(B) and (C) of the
61 Act will also be fulfilled by achieving the PDUFA goals for special protocol assessment.

62 **III. REQUESTS FOR SPECIAL PROTOCOL ASSESSMENT**

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

66 **A. Timing of Request**

67 CDER and CBER generally recommend that a sponsor submit a protocol intended for special protocol
68 assessment to the Agency at least 90 days prior to anticipated commencement of the study. The
69 protocol should be complete and sufficient time should be allowed to discuss and resolve any issues
70 before the study begins. *Special protocol assessment will not be provided after a study has begun.*

71 1. *Carcinogenicity Protocols*

72 A sponsor interested in Agency assessment and agreement on a carcinogenicity protocol should
73 notify the appropriate review division (CDER) or applications division (CBER) and discuss
74 planned carcinogenicity testing at an end-of-phase 2 meeting or should notify the director of the
75 appropriate division of an intent to request special protocol assessment by letter at least 30
76 days prior to submitting the request. With the notice of intent, the sponsor should submit
77 relevant background information so that the Agency may review (or re-review) reference
78 material related to carcinogenicity protocol design prior to receiving the carcinogenicity
79 protocol. The Agency is currently drafting guidance describing the type of information that
80 would be appropriate to submit before requesting carcinogenicity protocol assessment.

81 2. *Stability Protocols*

82 Generally, an end-of-phase 2/pre-phase 3 meeting should take place between the sponsor and

⁴ 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 effectiveness 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.

83 the Agency. Agreement on a standard stability protocol for primary stability batches may be
84 reached in such a meeting. A new stability protocol significantly different from the standard
85 stability protocol may be submitted to the Agency with a request for special protocol
86 assessment. Prior to requesting special protocol assessment for a stability study, a sponsor
87 should ensure that the product is sufficiently developed. The product should be in phase 3
88 development and product characterization should be complete. Production steps that may
89 affect product stability should be identified. The sponsor should also ensure that the
90 manufacturing process described in the request for assessment of the stability protocol will not
91 differ substantively from the process used for marketed material and that the tests described will
92 adequately qualify the product.

93 3. *Clinical Protocols*

94 As stated in the PDUFA goals, for special protocol assessment of a phase 3 protocol for a
95 clinical trial that will form the primary basis of an efficacy claim in an NDA or BLA, the sponsor
96 should have had an end-of-phase 2/pre-phase 3 meeting with the review division so that the
97 division is aware of both the developmental context in which the protocol is being reviewed and
98 the questions that are to be answered. However, if the Agency is already familiar with the
99 developmental context of a proposed clinical trial and has an understanding of the questions that
100 will be raised regarding the protocol, as ordinarily will be the case with efficacy supplements,
101 the Agency may provide a comprehensive protocol assessment without requiring an end-of-
102 phase 2/pre-phase 3 meeting.

103 **B. Format of Request**

104 A sponsor should submit each protocol for assessment under this program as a separate amendment to
105 the sponsor's IND in triplicate with Form FDA 1571 and a cover letter attached. The cover letter
106 should clearly identify the submission as a **REQUEST FOR SPECIAL PROTOCOL**
107 **ASSESSMENT** in bolded block letters at the top and should clearly state the type of protocol being
108 submitted (i.e., carcinogenicity, stability, or clinical).

109 **C. Where to Send a Request**

110 The request should be submitted to the appropriate review division in CDER or applications division in
111 CBER. A copy of the cover letter should be sent via fax as follows.

112 For carcinogenicity protocols:

- 113 • in CDER, to the project manager for the application in the appropriate review division and the
114 Associate Director for Pharmacology and Toxicology in the Office of Review Management
- 115 • in CBER to the director of the appropriate applications division

116 For stability protocols:

- 117 • in CDER, to the project manager for the application in the appropriate review division and the
118 appropriate chemistry team leader
- 119 • in CBER, to the director of the appropriate applications division

- 120 For clinical trials intended to form the primary basis of an efficacy claim:
121 • in CDER, to the project manager for the application in the appropriate review division
122 • in CBER, to the director of the appropriate applications division

123 A sponsor interested in seeking special protocol assessment before submitting an IND should contact
124 the chief of the project management staff in the appropriate review division in CDER or should submit a
125 written request to the director of the appropriate applications division for the product in CBER.

126 Sponsors who request special protocol assessment without an IND should note that the Agency will not
127 be able to provide special protocol assessment without being fully informed of the overall development
128 plan for the drug or biological product.

129 **D. Content of a Request**

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

136 To facilitate FDA's assessment of the issues raised by the sponsor, a request should discuss in
137 reasonable detail all data, assumptions, and information needed for an adequate evaluation of the
138 protocol. For example:

- 139 • The sponsor should include information needed to assess the role of the study in the overall
140 development of the drug.
- 141 • The sponsor should submit information supporting the proposed trial, including power
142 calculations, the choice of study endpoints, and other critical design features (e.g., choice of
143 control, duration, methods of assessment).
- 144 • The sponsor should clearly describe any regulatory outcomes (e.g., approval of a specific
145 claim, breaking orphan exclusivity, a comparative claim) and final labeling that the sponsor
146 believes would be supported by the results of the study.
- 147 • A sponsor interested in Agency assessment of a stability protocol should include product
148 characterization and relevant manufacturing data, information regarding the proposed market
149 packaging configuration (if known), the proposed drug product strengths, and the expected
150 shelf-life.

151 Special protocol assessment is designed to evaluate individual protocols primarily in response to
152 specific questions posed by the sponsors. While more general drug development issues, such as the
153 *number* of trials needed or adequacy of supportive evidence for a given efficacy claim, are factors in
154 assessing the overall adequacy of a proposed protocol, they are not considered part of the special
155 protocol assessment program. Questions pertaining to such general drug development issues should be

156 discussed in routine drug development meetings and correspondence with the review or applications
157 division and, as appropriate, with the review office.

158 **IV. AGENCY ASSESSMENT**

159 **A. Action on the Request**

160 After receiving a written request for special protocol assessment, the review or applications division
161 director will decide whether the submission is appropriate for such assessment. In CDER, this decision
162 will be based on recommendations from the clinical team leader, chemistry team leader, or
163 pharmacology/toxicology team leader, as appropriate. In CBER, the decision will be based on the
164 recommendations of the review team. If the division concludes that special protocol assessment is
165 appropriate, the division will proceed with the assessment (see **Assessment of the Protocol** below).
166 If special protocol assessment is not appropriate (i.e., the protocol does not meet the criteria for special
167 protocol assessment), the division should notify the sponsor of the reasons for the determination as soon
168 as possible after the Agency's receipt of the request. If the sponsor is notified by telephone or fax, a
169 hard copy of the letter documenting the determination should follow.

170 **B. Assessment of the Protocol**

171 For each special protocol assessment under this program, the centers will answer any questions that are
172 appropriate, providing comments on issues related to protocol design, study conduct and execution,
173 data analysis, and implications for labeling. The Agency's assessment will be based primarily on the
174 questions posed by the sponsor, the underlying data, assumptions, and information described by the
175 sponsor, and relevant Agency policies and guidance documents. Any change in the underlying data,
176 assumptions, and information could affect the assessment of the protocol. Comments from the review
177 team should be sent to the sponsor in a special protocol assessment letter within 45 calendar days of
178 receipt of the request for special protocol assessment. If the letter is faxed to the sponsor, a hard copy
179 should follow.

180 1. *Revisions During Agency Assessment*

181 The Agency may communicate with the sponsor regarding the protocol before issuing a special
182 protocol assessment letter. In such cases, the sponsor may choose to submit a revised
183 protocol. If, for any reason, a sponsor submits a revised protocol while the Agency is
184 reviewing an earlier version of the same protocol, the Agency ordinarily will not respond to the
185 questions posed about the earlier version of the protocol and will consider the original request
186 withdrawn. The Agency will consider a request for special protocol assessment of a revised
187 protocol to be a new request and will act on the revised protocol within 45 days.

188 2. *Advisory Committee Review*

189 The Agency may, as necessary, seek advisory committee review of a clinical protocol or may
190 obtain advisory review from selected advisory committee members, special Government

191 employees, or other consultants. In either circumstance, in lieu of a special protocol assessment
192 letter, the sponsor should be notified within 45 calendar days after the Agency's receipt of the
193 request for special protocol assessment that an advisory committee or selected advisory
194 committee members will review the protocol. If known, the date of the advisory committee
195 meeting or consultation with advisory committee members should be provided to the sponsor
196 with the notification. If the clinical protocol will be presented to an advisory committee, the
197 presentation should be scheduled to take place at the next *available* advisory committee
198 meeting. A special protocol assessment letter, including comments from the review team based
199 on advice from the advisory committee or selected advisory committee members, should be
200 sent to the sponsor within 45 calendar days of the expert review of the protocol. If the
201 notification or special protocol assessment letter is faxed to the sponsor, a hard copy should
202 follow.

203 **V. MEETINGS**

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

213 **VI. DOCUMENTATION**

214 **A. Form of Documentation**

215 All agreements and disagreements between the Agency and the sponsor regarding special protocol
216 assessments, including Agency responses to questions about protocol design, primary efficacy
217 endpoints, study conduct, data analysis, and the kind of labeling statements one could expect if the data
218 are supportive and the product is approved, should be clearly documented in writing. These special
219 protocol assessments may be documented in the special protocol assessment letter and/or the minutes
220 of the Type A meeting. While a special protocol assessment may document the Agency's agreement
221 that the design and planned analysis of a study adequately address objectives in support of a regulatory
222 submission, the Agency will not necessarily agree that a specific finding (e.g., a particular p value on the
223 primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or
224 support an approval decision. Such determinations are made after review of a complete marketing
225 application and are based on the totality of data in the application.

226 **B. Changes in Documented Special Protocol Assessments**

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

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

234 Documented special protocol assessments should be considered binding on the review division and
235 should not be changed at any time, except as follows.

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

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

243 • A clinical protocol assessment will no longer be considered binding if (1) the sponsor and FDA
244 agree in writing to change the protocol or (2) the director of the review division determines that
245 a substantial scientific issue essential to determining the safety or effectiveness of the drug has
246 been identified after the testing has begun (section 505(b)(4)(C) of the Act). If the director of
247 the review division makes such a determination, (1) the determination should be documented in
248 writing for the administrative record and should be provided to the sponsor and (2) the sponsor
249 should be given an opportunity for a meeting at which the review division director will discuss
250 the scientific issue involved (section 505(b)(4)(D) of the Act). This meeting will be a Type A
251 meeting under the PDUFA goals for meeting management.

252 **C. Personnel Changes**

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

256 **VII. DISPUTE RESOLUTION**

257 A sponsor should first seek to resolve disagreements with FDA action under the special protocol
258 assessment program with the review or applications division. Any dispute regarding study design
259 should be resolved prior to initiation of the trial. If the sponsor is not satisfied with the response
260 provided by that FDA component, the sponsor may elect to pursue the Agency's procedures for formal

261 dispute resolution (21 CFR 10.75, 312.48, and 314.103).⁵ However, if an advisory committee
262 evaluates a protocol as part of special protocol assessment, further review by the advisory committee
263 need not be obtained as part of dispute resolution.

⁵ A draft guidance for industry, *Formal Dispute Resolution: Appeals Above the Division Level*, was made available to the public for comment in March 1999 (64 FR 13587) and is currently being finalized.