
Special Protocol Assessment Guidance for Industry

DRAFT GUIDANCE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)**

**May 2016
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Revision 1

Special Protocol Assessment Guidance for Industry

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**Special Protocol Assessment
Guidance for Industry¹**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information on the procedures and general policies adopted by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for special protocol assessment (SPA).

SPA is a process in which sponsors² may request to meet with FDA to reach agreement on the design and size of certain clinical trials, clinical studies, or animal trials³ (i.e., a Request for SPA (*Request*); see section III., Eligible Protocols and General Information) to determine if they adequately address scientific and regulatory requirements. As part of this process, sponsors should submit specific questions about protocol design and scientific and regulatory requirements. After FDA completes the SPA review, FDA issues an SPA Letter including an assessment of the protocol, agreement or nonagreement with the proposed protocol, and answers to the sponsor's relevant questions.⁴

An SPA agreement indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design (e.g., entry criteria, dose selection, endpoints, and planned analyses). These elements are critical to ensuring that the trial conducted under the protocol has the potential to support a future submitted application's ability to meet regulatory requirements for approval.⁵ Feedback on these issues provides the greatest benefit to sponsors in

¹ This guidance has been prepared by the SPA Working Group in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

² For the purposes of this guidance, the term *sponsor* includes any sponsor or applicant interested in SPA.

³ For the purposes of this guidance, the term *trial* includes clinical trials, clinical studies, or animal studies or trials discussed in the context of SPA.

⁴ See the Glossary for definitions of terms.

⁵ For the purposes of this guidance, the term *approval* refers to both approval of new drug applications and licensure of biologics license applications.

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34 planning late-phase development strategy. However, an SPA agreement does not indicate FDA
35 concurrence on every protocol detail, as described further in section III.B.2, Reaching SPA
36 Agreement With FDA.

37
38 Because SPA provides for the evaluation of protocols for trials that have not been initiated,⁶ the
39 conduct and results of the subsequent trial are not part of the evaluation. Therefore, the existence
40 of an SPA agreement does not guarantee that FDA will file (accept) a new drug application
41 (NDA) or biologics license application (BLA), or that the trial results will be adequate to support
42 approval. Those issues are addressed during the review of a submitted application; however, it is
43 hoped that trial quality will be improved by the SPA process.

44
45 This draft guidance revises the guidance for industry *Special Protocol Assessment* issued in May
46 2002. After it has been finalized, this guidance will replace the May 2002 guidance. Significant
47 changes from the 2002 version include: clarifying which protocols are eligible for SPA; adding
48 animal rule efficacy protocols intended to support approval under 21 CFR part 314, subpart I,
49 and 21 CFR part 601, subpart H, for drugs and biological products, respectively; adding
50 protocols intended to support approval of a biosimilar biological product; providing greater detail
51 about the content of an SPA submission; and clarifying the process for rescinding an SPA
52 agreement.

53
54 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
55 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
56 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
57 the word *should* in Agency guidances means that something is suggested or recommended, but
58 not required.

59 60 61 **II. BACKGROUND**

62 63 **A. Statutory Framework**

64
65 Section 119(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA)
66 amended section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C.
67 355(b)) and directed FDA to meet with sponsors who request to meet, provided certain
68 conditions are met, to reach agreement on the design and size of the well-controlled clinical trials
69 intended to form the primary basis for a demonstration of effectiveness in a marketing
70 application submitted under section 505(b) of the FD&C Act or section 351 of the Public Health
71 Service (PHS) Act (42 U.S.C. 262).⁷ These provisions subsequently were amended in section
72 7002(d)(1) of the Biologics Price Competition and Innovation Act of 2009 to include any

⁶ See section VI.A., Determining Whether a Submission Is Appropriate for an SPA, for a definition of *initiation date*.

⁷ Section 119(b) of FDAMA also amended section 505(j) of the FD&C Act, and directed FDA to meet with sponsors and applicants, provided certain conditions are met, to reach agreement on the design and size of bioavailability and bioequivalence trials needed to support applications submitted under section 505(j) of the FD&C Act (i.e., abbreviated new drug applications). Adequacy of trial design to support 505(j) applications is outside the scope of this guidance.

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73 necessary trials for biosimilar biological product applications under section 351(k) of the PHS
74 Act.

75
76 In 2013, the Pandemic and All Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)
77 further amended the SPA provisions to provide for SPA agreements regarding animal and
78 associated clinical trials conducted in support of applications for products developed under
79 21 CFR part 314, subpart I, and 21 CFR part 601, subpart H (the animal rule).⁸ The amendments
80 in section 301 of PAHPRA provided for the use of the SPA process with respect to studies
81 conducted in support of product development “in the case where human efficacy studies are not
82 ethical or feasible, of animal and any associated clinical trials which, in combination, are
83 intended to form the primary basis of an effectiveness claim.” These revisions to the SPA
84 provisions are consistent with FDA’s previous approach to interpreting the SPA provisions
85 broadly; most products developed under the animal rule will be used as medical countermeasures
86 for serious events that require rapid distribution and deployment, and would be approved and
87 ready for use in advance of such an event.

88
89 As set forth in the current SPA provisions in sections 505(b)(5)(B) and (C) of the FD&C Act, if a
90 sponsor makes a reasonable written request to meet with FDA to reach agreement on the design
91 and size of a trial covered by the statute, FDA will grant the request. If FDA and the sponsor
92 reach an agreement, FDA will put the agreement in writing and make it part of the administrative
93 record (see section II.B., User Fee Acts, for a discussion of FDA’s performance goals for
94 review). Neither FDA nor the sponsor may change an agreement after the trial begins except:
95 (1) with the written consent of the sponsor; or (2) if the FDA division director determines that “a
96 substantial scientific issue essential to determining the safety or effectiveness of the drug has
97 been identified after the testing has begun.”⁹ Should it be necessary for FDA to change or
98 rescind an SPA agreement, FDA will first give the sponsor the opportunity for a meeting at
99 which the FDA division director will be present and at which the director will document the
100 scientific issue involved. This process is discussed in greater detail in section IX., Changes in or
101 Rescission of Special Protocol Assessment Agreements.

102
103 If a sponsor and FDA meet regarding the design and size of a trial under section 505(b)(5)(B) of
104 the FD&C Act and the parties cannot agree that the trial design is adequate to meet the stated
105 goals, FDA will state the reasons for the nonagreement in a letter to the sponsor. Potential paths
106 forward after receipt of a nonagreement letter are described in section VII., Sponsor Options
107 After Receipt of Nonagreement SPA Letter.

108
109 The SPA process does not apply to marketing applications for devices or to device protocols,
110 including protocols for the development of companion diagnostic devices. Sponsors may submit
111 a Request for a protocol for the drug or biological product, but sponsors should direct questions

⁸ In 2002, FDA amended its regulations in the final rule “New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible” (67 FR 37995, May 31, 2002). These regulations address approval of certain new products for ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances based on evidence of effectiveness from animal studies when human efficacy trials are not ethical or feasible.

⁹ See section 505(b)(5)(C)(ii) of the FD&C Act.

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112 about companion diagnostic protocols and device-specific issues to the Center for Devices and
113 Radiological Health (CDRH).

114

B. User Fee Acts

116

1. Prescription Drug User Fee Act

118

119 In conjunction with the Prescription Drug User Fee Amendments of 2012 (PDUFA V), enacted
120 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA),¹⁰ FDA
121 agreed to specific performance goals (PDUFA V goals) for SPA.¹¹ According to the PDUFA V
122 goals letter, protocols that qualify for the SPA program include “carcinogenicity protocols,
123 stability protocols, and Phase 3 protocols for clinical trials that will form the primary basis of an
124 efficacy claim.”¹² The goals letter further states, “For products that will be using Subpart E or
125 Subpart H development schemes [for accelerated approval], the Phase 3 protocols . . . should be
126 construed to mean those protocols for trials that will form the primary basis of an efficacy claim
127 no matter what phase of drug development in which they happen to be conducted.”¹³ The
128 PDUFA V goals regarding clinical protocol review and assessment are wider in scope than
129 section 505(b)(5)(B) of the FD&C Act. Both the noted statutory requirements and the PDUFA V
130 goals apply to protocols for clinical trials intended to form the primary basis of an efficacy claim
131 in original and supplemental applications. However, the PDUFA V goals also apply to animal
132 carcinogenicity protocols and final product stability protocols, whereas the statutory section does
133 not.

134

135 Under the PDUFA V goals, the sponsor may submit a Request for qualifying protocols (see
136 section III., Eligible Protocols and General Information) that should include “a limited number of
137 specific questions about protocol design and scientific and regulatory requirements.”¹⁴ Of the
138 Requests that FDA accepts (see section VI., FDA Assessment Process), the goal is to complete
139 90 percent of SPA reviews within 45 days. SPA reviews may not always be completed within 45
140 days, as further described in section VI.E., Potential for Delay of FDA Response.

141

¹⁰ See sections 101–107 of FDASIA, amending sections 735, 736, and 736B of the FD&C Act.

¹¹The PDUFA V goals letter titled “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017” is available on the FDA Web site at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>. FDA first agreed to specific PDUFA goals for SPA in November 1997 in conjunction with PDUFA II, the reauthorization of the Prescription Drug User Fee Act of 1992. The PDUFA II goals are described 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 (<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm143135.htm>).

¹² Ibid.

¹³ “Subpart E or Subpart H” refers to applications submitted in accordance with 21 CFR 601.40 and 314.500, respectively.

¹⁴ See note 11, *supra*.

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2. *Biosimilar User Fee Act*

In conjunction with the Biosimilar User Fee Act of 2012 (BsUFA), enacted as part of FDASIA,¹⁵ FDA agreed to specific performance goals for SPA.^{16,17} The BsUFA goals letter states that “[u]pon specific request by a sponsor (including specific questions that the sponsor desires to be answered), the Agency will evaluate certain protocols and related issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor,” and further specifies which protocols qualify for an SPA. They include “any necessary clinical study or studies to prove biosimilarity and/or interchangeability (e.g., protocols for comparative clinical trials that will form the primary basis for demonstrating that there are no clinically meaningful differences between the proposed biosimilar biological product and the reference product, and protocols for clinical trials intended to support a demonstration of interchangeability).”

In accordance with the BsUFA goals letter, a sponsor may submit a Request for qualifying protocols (see section III., Eligible Protocols and General Information) and should include “a limited number of specific questions about protocol design and scientific and regulatory requirements.” As set out in the BsUFA goals letter, for a protocol to qualify for SPA, the sponsor must have had a biosimilar biological product development (BPD) Type 2 or Type 3 meeting. Of the Requests that FDA accepts, the goal is to complete 80 to 90 percent of SPA reviews (increasing from fiscal year 2015 to fiscal year 2017) within 45 days. SPA reviews may not always be completed within 45 days, as further described in section VI.E., Potential for Delay of FDA Response.

III. ELIGIBLE PROTOCOLS AND GENERAL INFORMATION

A. Eligible Protocols

Per section 505(b)(5)(B) of the FD&C Act, the PDUFA V goals, and the BsUFA goals, the following protocols are eligible for a Request:

¹⁵ See sections 401–408 of FDASIA, adding sections 744G, 744H, and 744I to the FD&C Act.

¹⁶ See the BsUFA goals letter titled “Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 Through 2017” available on the FDA Web site at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf>.

¹⁷ For the statutory definition of *biosimilar biological product*, *biosimilar biological product application*, and definitions of selected terms used in this guidance, see sections 744G(3) and (4) of the FD&C Act, section 351(i) of the PHS Act, and the glossary in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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- 174 • Animal carcinogenicity protocols.
175
176 • Drug substance and drug product stability protocols.
177
178 • Animal efficacy protocols for studies intended to provide primary evidence of
179 effectiveness required for approval or licensure for products developed under the animal
180 rule (*animal rule efficacy protocols*).
181
182 • Protocols for trials intended to form the primary basis of an efficacy claim.¹⁸ Protocols
183 that meet this criterion can be submitted for an SPA, regardless of the product
184 development phase (e.g., for products developed under accelerated approval (i.e., subpart
185 H (for drugs) or subpart E (for biological products)), such protocols might be phase 2
186 rather than phase 3). In addition, protocols for clinical or animal trials of bioequivalence
187 or bioavailability that will form the basis of an efficacy claim are considered to meet this
188 criterion and are eligible for an SPA.
189
190 • Any necessary trials to prove biosimilarity and/or interchangeability (e.g., protocols for
191 comparative clinical trials that will form the primary basis for demonstrating that there
192 are no clinically meaningful differences between the proposed biosimilar biological
193 product and the reference product, and protocols for clinical trials intended to support a
194 demonstration of interchangeability).¹⁹
195

B. General Information

1. Meeting With FDA Before Submission of a Request

200 The PDUFA V and BsUFA goals letters state that protocols will qualify for the SPA program
201 only if the sponsor has had an end-of-phase 2/pre-phase 3 meeting or end-of-phase 1 meeting, as
202 appropriate,²⁰ or BPD Type 2 or Type 3 meeting, respectively.²¹
203

204 Therefore, before submitting a Request, the sponsor should meet with FDA to discuss the
205 proposed trial and its regulatory context. In some cases (e.g., protocols to support submission of
206 an efficacy supplement), FDA may already be familiar with the regulatory context, or it can be
207 adequately described in the Request and supporting materials. In such settings, some sponsors
208 have decided not to submit a meeting request, and FDA has accepted the Request without having

¹⁸ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

¹⁹ See the guidances for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*, and *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

²⁰ See notes 11 and 16, *supra*.

²¹ See the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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209 had a prior meeting. However, the efficiency of FDA’s review of the SPA submission, the
210 completeness of FDA’s answers to sponsor questions, and the quality of the future marketing
211 application may be improved by holding a meeting before submission even in the setting of a
212 well-understood development plan. FDA strongly encourages sponsors to request such
213 meetings.

214
215 As provided in section 505(b)(5) of the FD&C Act, FDA will meet with sponsors if they make a
216 reasonable written request for a meeting, and provide information necessary for discussion and
217 agreement, for the purpose of reaching agreement on the design and size of a proposed trial
218 covered by that provision. FDA will prepare written minutes of the meeting and provide them to
219 the sponsor.

220
221 Sufficient information should be provided in the meeting request to ensure that all relevant
222 disciplines and offices can participate, permit detailed discussion of the relevant issues, and
223 facilitate subsequent FDA review of an SPA submission. These detailed discussions are
224 especially important if the trial has elements with which there is little past experience (e.g., novel
225 eligibility criteria or efficacy endpoints) or has complex design or analytic features (e.g.,
226 noninferiority, bioequivalence, adaptive designs, multiplicity considerations). These discussions
227 are also critically important for reaching consensus on the use of an appropriate animal model to
228 support approval under the animal rule.²² Discussions with FDA regarding the development of
229 an appropriate animal model should begin early in the product development process so that the
230 meeting before submission of a Request focuses on final consensus on the animal model, not an
231 introduction of this topic.²³

232
233 The need for consultation during an SPA review (e.g., by special government employees or by a
234 different FDA office or center), described in section VI.E., Potential for Delay of FDA
235 Response, also should be considered and discussed at the meeting.

236 237 *2. Reaching SPA Agreement With FDA*

238
239 As noted, FDA will review the protocol for the adequacy and acceptability of critical elements of
240 overall protocol design and analysis and will respond to relevant questions posed by the sponsor.
241 Although the goal of an SPA is to reach concurrence on the adequacy of protocol elements
242 intended to support a statutory finding of safety and efficacy, an SPA agreement with FDA does
243 not imply that FDA has reviewed or concurs with each detail of the protocol. For example, an
244 SPA agreement for a protocol might communicate to the sponsor that FDA agrees with the
245 proposed primary endpoint or the sample size estimate, but might not include a detailed review
246 of the case report form; it might address the adequacy of and final timing of a radiographic
247 procedure used to measure the primary endpoint, but might not comment on the use of three
248 versus four interim radiographs.

²² See note 8, *supra*.

²³ Before submitting a Request, the sponsor should have FDA concurrence on the model proposed for use in the efficacy study (including, but not limited to, the species, the details of the challenge agent, and the conditions of exposure) and the method that will be used to extrapolate from the animal data to select an effective dose and regimen in humans.

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249
250 Sponsors should make every effort to identify unusual or potentially problematic aspects of the
251 protocol and submit specific questions in their Request (see section V, Content of a Request and
252 Submission Materials). FDA’s review of the Request is facilitated by a description from the
253 sponsor of its desired indication and development plan, including any protocol elements intended
254 to support a potential labeling claim. Absence of an FDA comment on a particular aspect of the
255 trial does not necessarily indicate agreement on that aspect if the sponsor did not specifically ask
256 about it, especially if the context of a certain protocol element has not been highlighted or
257 explained. For example, if the sponsor lists multiple secondary endpoints in the protocol but
258 does not include a corresponding question to FDA, lack of FDA comment on those endpoints
259 does not imply FDA agreement that beneficial outcomes measured by the secondary endpoints
260 can form the basis of a labeling claim. Labeling discussions would be conducted if a submitted
261 application met standards for approval.

262
263 The presence of an SPA agreement does not guarantee that a marketing application will be filed
264 or approved, even if the trial is conducted in accordance with the protocol. When an application
265 is submitted, FDA reviews the application to make a threshold determination that the application
266 is sufficiently complete to permit a substantive review; the fact that a trial conducted pursuant to
267 an SPA agreement forms the basis of an efficacy claim in the application does not mean that the
268 application meets the criteria in 21 CFR 314.101 (for NDAs) or in 21 CFR 601.2 (for BLAs)
269 with respect to filing the application. After an application has been filed, FDA reviews it to
270 evaluate whether the submitted evidence meets the statutory standard for approval. Although, as
271 set forth in the SPA provisions in the FD&C Act, FDA will not change its position regarding the
272 critical design elements agreed to as part of an SPA agreement unless a substantial scientific
273 issue essential to determining the safety or effectiveness of the product has been identified after
274 the trial begins (see section IX., Changes in or Rescission of Special Protocol Assessment
275 Agreements), this does not mean that the application as a whole meets the statutory standard for
276 approval.

277
278

IV. PROCEDURES FOR SUBMISSION OF A REQUEST

280
281 A Request should be submitted to the sponsor’s existing investigational new drug application
282 (IND) for each protocol the sponsor wants reviewed. A Request should not include more than
283 one protocol. If there is no IND for the product, FDA will assign a pre-IND number so that a
284 meeting to fully inform FDA of the overall development plan for the product can be scheduled
285 (see section III.B.1., Meeting With FDA Before Submission of a Request). The sponsor can
286 subsequently open an IND after the meeting, then submit a Request to the IND.

287
288 FDA encourages electronic submissions in electronic common technical document format.²⁴
289 Electronic submission enhances the receipt, processing, and review of an SPA submission,
290 particularly in view of the multidisciplinary input required to complete the SPA.
291

²⁴ See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

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292 **A. Notice of Intent**

293
294 To facilitate review management, sponsors should notify FDA of their intent to submit a
295 Request. The notification can be communicated during the developmental meeting, or as an
296 informal fax or email to the regulatory project manager in the review division.

297 298 **B. Timing of a Request**

299
300 To allow for sufficient time for FDA review and comment, as well as for resolution of
301 outstanding high-level issues before the initiation of the proposed trial,²⁵ CDER and CBER
302 generally recommend that a sponsor submit a Request and submission materials to FDA at least
303 90 days before the anticipated start of the trial. The protocol, including the statistical analysis
304 plan, should be complete (see section V., Content of a Request and Submission Materials). An
305 interactive process to reach concurrence on major protocol design features during the 45-day
306 review period is desirable to avoid the need for resubmission; minor issues can be resolved
307 through additional correspondence and protocol amendments after the trial begins. Protocols for
308 trials that have already begun do not qualify for an SPA (see section VI.A., Determining
309 Whether a Submission Is Appropriate for an SPA).

310 311 **C. Format of a Request**

312
313 When submitting to an IND, a sponsor should submit each protocol for an SPA as a separate
314 amendment with Form FDA 1571 and a cover letter attached. Paper submissions must be
315 submitted in triplicate.²⁶ The cover letter should identify the submission as a **REQUEST FOR**
316 **SPECIAL PROTOCOL ASSESSMENT** in bolded block letters at the top and should state the
317 type of protocol being submitted. If a sponsor does not designate a submission as a Request,
318 FDA may not immediately recognize it as such, resulting in a delay in the start and subsequent
319 timeline of the review.

320 321 **D. Where to Send a Request**

322
323 The Request should be submitted to the appropriate CDER or CBER division, using standard
324 submission processes. A copy of the cover letter should be sent via fax or secure email to the
325 regulatory project manager for the application in the appropriate division.

326 327 328 **V. CONTENT OF A REQUEST AND SUBMISSION MATERIALS**

329
330 The content of a Request and accompanying submission materials should be complete and, as
331 stated in section 505(b)(5)(B) of the FD&C Act, the sponsor must provide information necessary
332 for discussion and agreement on the design and size of the trial. Any areas of incomplete

²⁵ For example, when developing a timeline for an animal rule efficacy protocol SPA, the sponsor should consider the limited availability of laboratories capable of conducting studies employing chemical, biological, radiological, or nuclear agents.

²⁶ See 21 CFR 312.23(d).

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333 information should be identified and adequately justified by the sponsor. Relevant guidances
334 that may be helpful to the sponsor, both for supporting the trial design and for determining
335 whether a Request is appropriate, are cited in the following sections. Sponsors are advised to
336 consult the Drugs and Biologics guidance Web pages for the most current lists of available
337 guidances.

338

A. Animal Carcinogenicity Protocols

340

341 The sponsor should include the background information detailed in the guidance for industry
342 *Carcinogenicity Study Protocol Submissions* in addition to the complete protocol.²⁷

343

B. Drug Substance and Drug Product Stability Protocols

345

346 Generally, standard stability protocols should be based on the principles described in the
347 following FDA and International Council for Harmonisation (ICH) guidances and do not need an
348 SPA:

349

350 • *Q1A(R2) Stability Testing of New Drug Substances and Products*

351

352 • *Q1B Photostability Testing of New Drug Substances and Products*

353

354 • *Q1C Stability Testing for New Dosage Forms*

355

356 • *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances
357 and Products*

358

359 • *Q1E Evaluation of Stability Data*

360

361 • *Q5C Quality of Biotechnological Products: Stability Testing of
362 Biotechnological/Biological Products*

363

364 A Request can be submitted for a stability protocol that differs significantly from a standard
365 stability protocol or that raises specific questions not addressed in existing guidance. Before
366 submitting a Request for a stability protocol, a sponsor should ensure that the product is in
367 advanced clinical development and product characterization should be complete. Manufacturing
368 steps that can affect product stability should be identified. The sponsor also should ensure that
369 the manufacturing process, formulation, and container closure for the product described in the
370 Request do not differ substantively from those for the product to be marketed and that the tests
371 described will adequately qualify the product for use in the proposed protocol.

372

²⁷ Additional information may be found in MAPP 7412.1 Rev. 2 *Management of CDER Executive Carcinogenicity Assessment Committee and Communication of Committee Proceedings* at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

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373 **C. Animal Rule Efficacy Protocols**

374
375 Before submitting a Request, the sponsor should have FDA concurrence on the animal model
376 proposed for use in the efficacy study (including, but not limited to, the species, the details of the
377 challenge agent, and the conditions of exposure) and the method that will be used to extrapolate
378 from the animal data to select an effective dose and regimen in humans. The Request should
379 include a detailed protocol and focused questions regarding the protocol such as study design,
380 conduct, objectives, endpoints, data analysis, and evaluation criteria. The sponsor should include
381 background information, separate from the protocol, that describes in detail all relevant data
382 (including clinical data), assumptions, and information that can assist FDA in evaluating the
383 protocol and responding to the sponsor's questions. Although most of this information should
384 have been discussed during previous interactions with FDA, this section should provide
385 explanations of the scientific and regulatory basis for the study design, endpoints, statistical
386 analysis plan, and the agreed-upon animal model. In addition, the document should provide a
387 detailed plan describing how the effective dose in animals will be translated to an appropriate
388 dosing regimen in humans. Sponsors should consult the guidance for industry *Product*
389 *Development Under the Animal Rule* when developing background documents.

390 391 **D. Clinical Trial Protocols**

392
393 For protocols for clinical trials intended to form the basis for an efficacy claim (either under
394 traditional or accelerated approval) or intended to demonstrate biosimilarity and/or
395 interchangeability, the sponsor should describe in the submission how the protocol will fulfill the
396 required essential data elements for an adequate and well-controlled trial (21 CFR 314.126). If
397 the sponsor intends to submit data from only one clinical trial as part of its demonstration of
398 substantial evidence of effectiveness, the sponsor should refer to the guidance for industry
399 *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, and the
400 protocol design should address the recommendations in the guidance. However, the SPA review
401 by FDA will focus on the submitted protocol; an SPA agreement should not be interpreted as
402 concurrence on the sufficiency of one trial to support approval of a marketing application.

403
404 In addition, sponsors should review FDA guidances for industry on trial design, including
405 available disease- and drug class-specific guidances, and more general ICH guidances such as:

- 406 • Draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*²⁸
- 407 • Draft guidance for industry *Non-Inferiority Clinical Trials*²⁹
- 408 • Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis,*
409 *and Regulatory Applications*
- 410
- 411
- 412
- 413

²⁸ When final, this guidance will represent the FDA's current thinking on this topic.

²⁹ When final, this guidance will represent the FDA's current thinking on this topic.

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- 414 • Guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a*
415 *Reference Product*
- 416
- 417 • ICH guidance for industry *E3 Structure and Content of Clinical Study Reports*
418
- 419 • ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*
420
- 421 • ICH guidance for industry *E9 Statistical Principles for Clinical Trials*
422
- 423 • ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical*
424 *Trials*
- 425
- 426 • ICH guidance for industry *M4 Organization of the CTD*
427

428 The sponsor should submit additional background information, separate from the protocol, that
429 includes all relevant data, assumptions, and information. Such background information can
430 assist FDA in assessing the protocol and addressing the specific questions raised by the sponsor.
431 Sponsors should include adequate supporting documents with explanations of the scientific basis
432 for their specific trial design and analysis plan in the context of the disease or condition. This is
433 especially important for consideration of novel endpoints to demonstrate clinical efficacy and
434 any unusual design features. At a minimum, the accompanying submission materials should:
435

- 436 • Include information about the role of the trial in the overall development of the product.
437
- 438 • Consider the relevance of the population to be studied to the U.S. population in which the
439 product is intended to be used, taking into account sex and age distribution³⁰ and ethnic
440 diversity reflective of the U.S. population. If the population in the proposed trial is
441 narrow, any plans to study the product in a broader population should be described. If the
442 trial will recruit the majority of enrollees from outside of the United States, the
443 submission should include an explanation of why the results should be considered
444 applicable to a U.S. population, and/or identify additional planned trials that will provide
445 an adequate understanding of the benefits and risks of the therapy for the U.S. population,
446 considering ethnic, genomic, standard of care, and other factors relevant to the specific
447 therapy.
448
- 449 • Provide adequate information to justify the critical design features of the trial, including,
450 but not limited to:
 - 451 – Explaining reasons for dose selection, and, if applicable, justification for not
452 including more than one dose.
453
- 454

³⁰ See the guidance for industry *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*.

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- 455 – Describing and explaining choice of trial endpoints, including identification of the
456 primary and secondary endpoint(s), and plans for controlling overall type I error rate
457 (false positive rate).
458
- 459 – Describing choice of trial design (e.g., dose-response, superiority, add-on,
460 noninferiority, equivalence) and control (e.g., placebo, best supportive care, active
461 control). If the trial is a noninferiority trial, the choice of active control and the
462 noninferiority margin derived from the estimated treatment effect of the active control
463 should be identified and justified. If the protocol includes adaptive features, then
464 decision rules for adaptations while controlling overall type I error rate and
465 operational bias should be justified. Enrichment designs, if considered, should be
466 based on scientific rationale and the design should take prevalence of the disease into
467 consideration.
468
- 469 – Describing and explaining duration of therapy.
470
- 471 – Describing methods of endpoint assessment.
472
- 473 – Describing procedures to minimize bias at all stages (e.g., randomization, blinding,
474 endpoint assessment committee, data monitoring committee).
475
- 476 – Describing the statistical approach, including a well-developed statistical analysis
477 plan and plans for minimizing and dealing with missing data. Any planned interim
478 analyses should be described, with the level of significance allocated for the planned
479 interim analyses.
480

481 The sponsor should also consider the following:
482

- 483 • Sponsors should fully document and justify complex or novel eligibility criteria,
484 biomarker testing as an entry criterion, endpoints, and analysis plans. As noted in section
485 III.B.1., Meeting With FDA Before Submission of a Request, FDA encourages sponsors
486 to request a meeting before submitting the Request. A meeting is especially useful for
487 novel or complex issues. Furthermore, novel or complex issues may necessitate expert
488 consultation (e.g., with an advisory committee expert) to evaluate novel protocol features,
489 which may extend review times beyond the first cycle review goal of 45 days (see section
490 VI.E., Potential for Delay of FDA Response).
491
- 492 • Historically controlled trials (comparison with adequately documented natural history of
493 the disease or condition, or from the results of active treatment, in comparable patients or
494 populations) are usually reserved for special circumstances and can raise particular
495 problems for adequate efficacy and safety assessment. If the sponsor submits a protocol
496 for a single-arm trial for an SPA, the sponsor should justify why a concurrently
497 controlled trial is not feasible or cannot be conducted ethically.³¹
498

³¹ See ICH E10.

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- If accelerated approval is being considered, sponsors should provide support for the choice of the surrogate endpoint or intermediate clinical endpoint and why the selected endpoint is considered reasonably likely to predict clinical benefit, how the proposed accelerated approval meets subpart H (for drugs) or subpart E (for biological products) criteria, and how the confirmation of clinical benefit would be performed with due diligence.³²
 - Sponsors should submit specific questions for FDA response regarding critical protocol features such as expected accrual populations, primary efficacy and safety endpoints, dose range, analysis plans, and potential limitations of the proposed trial to achieve its regulatory goals.
 - In codevelopment programs where the sponsor requests an SPA for the drug, sponsors should include as part of an SPA agreement drug-related questions and responses, including a device's effect on interpretation of drug data. Device questions and responses directed toward aspects of the device's performance (i.e., device data collection that is independent of the drug) are inappropriate for inclusion in an SPA agreement, as noted in section II.A., Statutory Framework. Sponsors should direct questions about companion diagnostic protocols and device-specific issues to CDRH.
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VI. FDA ASSESSMENT PROCESS

A. Determining Whether a Submission Is Appropriate for an SPA

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After receiving a Request and submission materials (*SPA submission*), the division director consults with the review team and makes an initial determination on whether or not the submission is appropriate for such assessment. If the division director concludes that the submission is appropriate for an SPA, the division proceeds with the assessment (see section VI.B., Assessment of the SPA Submission).

530

531

532

533

If the division director concludes that the submission is not appropriate for an SPA, the division will notify the sponsor of the reasons for the determination by telephone, email, or fax followed by a letter.

534

535

An SPA submission may not be appropriate for such assessment if:

- It contains a request to evaluate more than one protocol. In such a case, FDA will ask the sponsor to submit separate requests for each protocol. This process may delay the initiation of the SPA reviews.
- 536
- 537
- 538
- 539

³² See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

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- 540 • It contains a protocol for an ongoing trial, or the investigation will begin in less than 45
541 days.^{33,34}
542
- 543 • It contains a protocol for which valuation and critical features are adequately described
544 by existing guidance (e.g., conventional stability study). (See section V.B., Drug
545 Substance and Drug Product Stability Protocols, for further explanation.)
546
- 547 • It does not provide sufficient content and detail as described in section V., Content of a
548 Request and Submission Materials, including:
549
- 550 – A detailed protocol
 - 551
 - 552 – Specific questions for FDA to address
 - 553
 - 554 – Adequate background documents to support the critical elements of the trial design,
555 or to determine whether it can adequately address scientific and regulatory
556 requirements for the purpose identified by the sponsor
557
- 558 • Prior FDA concurrence has not been obtained for the animal model to be used in the
559 proposed animal rule efficacy study (see section V.C., Animal Rule Efficacy Protocols).³⁵
560
- 561 • As stated in the PDUFA V and BsUFA goals, the sponsor has not had a meeting (e.g.,
562 end-of-phase 2/pre-phase 3 meeting (or end-of-phase 1 meeting, if applicable) or a BPD
563 Type 2 or Type 3 meeting) with the review division for the clinical trial that is the subject
564 of the SPA (where the trial is intended to support efficacy or trials to prove biosimilarity
565 and/or interchangeability).³⁶
566

³³ For the purposes of this guidance, the study initiation date for an animal rule efficacy study is defined as the first date on which an animal is assigned to the study protocol. For a clinical trial, it begins when subject screening or enrollment begins. For carcinogenicity studies, it is the first day of dosing. For stability studies, FDA recommends that, where possible, an SPA be submitted before the study begins or the first measurement point is reached. FDA accepts stability study SPAs after study initiation, because most are submitted when ICH recommendations prove to be infeasible and FDA advice is needed.

³⁴ See note 9, *supra*.

³⁵ Before submitting a Request, the sponsor should have FDA concurrence on the model proposed for use in the efficacy study (including, but not limited to, the species, the details of the challenge agent, and the conditions of exposure) and the method that will be used to extrapolate from the animal data to select an effective dose and regimen in humans.

³⁶ See notes 11 and 16, *supra*. As discussed in section III.B.1., Meeting With FDA Before Submission of a Request, in some cases (e.g., protocols to support submission of an efficacy supplement), FDA may already be familiar with the regulatory context, or it can be adequately described in the Request and supporting materials. In such settings, some sponsors have decided not to submit a meeting request, and FDA has granted the Request without having had a prior meeting.

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B. Assessment of the SPA Submission

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568
569 For each SPA submission accepted for assessment, FDA will respond to the sponsor's questions
570 focusing on protocol design, trial conduct and execution, data analysis, and labeling implications.
571 FDA's review is intended to focus on critical protocol design features, rather than a line-by-line
572 assessment of the protocol. FDA's responses are based primarily on the information provided by
573 the sponsor and relevant FDA policies and guidances; FDA also considers publicly available
574 information as appropriate. Sponsors should ensure that the data submitted in support of the
575 proposed protocol are current, complete, and accurate, because any change in the underlying
576 data, assumptions, and information could affect the assessment of the protocol and the resulting
577 recommendations and/or SPA agreement.

578
579 For animal carcinogenicity protocols, review staff will present their assessment to the Executive
580 Carcinogenicity Assessment Committee (ECAC). The ECAC renders a final judgment on the
581 protocol's acceptability. Concurrence with the general protocol design, documented in writing
582 as described below, constitutes an SPA agreement. If the ECAC does not agree with the
583 sponsor's proposed protocol design but the SPA submission contains adequate supporting data,
584 FDA may propose specific protocol recommendations (e.g., dose, trial design) that, if followed
585 by the sponsor, are considered by FDA to constitute an SPA agreement. For cases in which the
586 ECAC does not agree with the proposed protocol design and the SPA submission does not
587 provide adequate data to support recommendations for protocol design changes, the ECAC will
588 consider the SPA status to be nonagreement. The sponsor can resubmit the Request after
589 deficiencies in the supporting information are resolved, or continue without formal FDA
590 agreement.

591
592 Comments from the ECAC regarding carcinogenicity protocols, including recommendations and
593 conclusions (i.e., agreement or nonagreement), will be sent as minutes of the ECAC meeting,
594 attached to the FDA Response to the Sponsor (see section VI.D., FDA Response to Sponsor).

C. Revisions During FDA Assessment

595
596
597
598 FDA may communicate with the sponsor regarding deficiencies or problems with the protocol
599 before issuing an SPA Letter. FDA will make every effort to incorporate timely responses
600 addressing easily correctable deficiencies into the 45-day review timeline. If a sponsor submits
601 additional questions, unsolicited revisions to the protocol, or a lengthy or complex response to an
602 FDA question, or amends original submission materials with new information for any reason,
603 FDA ordinarily will not respond to the original questions and will consider the original SPA
604 submission withdrawn. FDA will consider submission of a revised protocol, or revised or
605 additional supporting materials, to be a new SPA submission with a new 45-day timeline for
606 response.

D. FDA Response to Sponsor

607
608
609
610 Under PDUFA V (90 percent of SPAs) and BsUFA (80 to 90 percent of SPAs) goals, FDA
611 committed to sending an SPA Letter (see sections VIII., Documentation, and VI.E., Potential for
612 Delay of FDA Response) to the sponsor within 45 calendar days of receipt of the SPA

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613 submission. This letter includes agreements, nonagreements, ECAC minutes (where applicable),
614 and comments from the review team. If FDA believes that meeting with a sponsor could
615 facilitate resolution of outstanding issues, the letter may include a recommendation to request a
616 Type A or BPD Type 1 meeting.³⁷ The division will mail the letter to the sponsor, even if the
617 letter was first sent by fax or email.

E. Potential for Delay of FDA Response

621 Occasionally, FDA divisions determine that input obtained from advisory committee review or
622 consultants (internal, including internal regulatory meetings, or external) is critical to the review
623 of an SPA submission. If such input is needed, FDA's response may be delayed. If such a delay
624 occurs, FDA should inform the sponsor within 45 calendar days of the receipt of the Request that
625 an advisory committee or one or more consultants will review the SPA submission. FDA should
626 advise the sponsor of: (1) FDA's reasons for the delay; and (2) an anticipated date of FDA's
627 response. The division will mail the letter to the sponsor, even if the letter was first sent by fax
628 or email.

1. Advisory Committee or External Consultant Review

631
632 FDA can seek advisory committee review or can seek advice from advisory committee members,
633 other special government employees, or other external consultants and will consider the advice
634 provided. FDA intends to send an SPA Letter to the sponsor within 45 calendar days of the
635 advisory committee meeting or consultant review of the protocol.

2. Internal FDA Consultative Review

638
639 For some animal rule efficacy protocols and certain novel clinical trial protocols, complex issues
640 may arise requiring one or more internal consultant reviews and one or more internal meetings
641 among multiple centers and/or multiple offices within FDA. In such instances, FDA intends to
642 send an SPA Letter to the sponsor, which will include comments from the review team that result
643 from consideration of advice from internal consultants, within 45 calendar days of the last
644 internal meeting.

VII. SPONSOR OPTIONS AFTER RECEIPT OF NONAGREEMENT SPA LETTER

648
649 Sponsors should note that, despite additional communications in writing and/or additional Type
650 A or BPD Type 1 meetings, sponsors and FDA may not reach agreement on all aspects of the
651 protocol and specific questions posed. Nonagreement letters may identify areas in which FDA
652 concurs with the sponsor's proposal, even if an SPA agreement letter cannot be issued. The
653 following options are available to sponsors after receiving a nonagreement SPA Letter.

³⁷ See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants* issued in May 2009. In March 2015, FDA issued the revised draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, this guidance will represent FDA's current thinking on this topic. See also the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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A. Initiate Trial Without SPA Agreement

Sponsors can initiate a trial after receipt of a nonagreement SPA Letter (assuming that all relevant requirements are met for conducting the trial). FDA agreement is not required before proceeding with critical trials intended to form primary evidence of effectiveness, and FDA reviews marketing applications on the basis of submitted data, regardless of whether FDA previously agreed with the design of the protocol in an SPA agreement. If the results from the trial are submitted in a marketing application, FDA will review the results and determine whether they support the approval of the application. Applications that meet the statutory standards will result in approval.

B. Do Not Initiate Trial and Respond in Writing to Address Nonagreement

Sponsors can respond in writing to amend the protocol or provide additional supporting information to address the reasons for the nonagreement expressed by FDA. This amendment and response will be considered an SPA resubmission, not a new SPA submission under PDUFA V and BsUFA performance goals, and FDA will make every effort to complete the review within 45 days. In some cases, changes to the protocol included in the SPA resubmission may not require the full additional review period. In such situations, FDA will make every effort to complete the review as soon as practicable.

Resubmissions should be complete and should address outstanding critical protocol issues. As previously mentioned, an SPA is intended to provide feedback on critical protocol design issues rather than minor protocol details that would be well managed by sponsors. SPA resubmissions should address specific issues identified in the nonagreement SPA Letter and should not address or introduce new issues or items for discussion. Introducing significant new material alters the developmental context and may warrant a meeting to discuss the new information.

C. Request a Type A or BPD Type 1 Meeting to Discuss Nonagreement

Sponsors can request a Type A or BPD Type 1 meeting with the division to discuss nonagreement issues. If FDA believes that meeting with a sponsor is the best way to resolve outstanding issues regarding an SPA, FDA can suggest in the SPA Letter that the sponsor request such a meeting. Type A and BPD Type 1 meeting requests are handled according to PDUFA V or BsUFA goals for meeting management, respectively.³⁸ At a Type A or BPD Type 1 meeting, FDA and the sponsor should discuss any remaining issues and uncertainties regarding the protocol but may not necessarily come to final agreement on all remaining issues. If the issues of concern are resolved, SPA agreement could be documented in the meeting minutes.

³⁸ See notes 11 and 16, *supra*. See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants* issued in May 2009. In March 2015, FDA issued the revised draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, this guidance will represent FDA's current thinking on this topic. See also the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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695 **VIII. DOCUMENTATION**

696
697 All agreements between FDA and the sponsor regarding SPA must be documented in writing
698 (section 505(b)(5)(C) of the FD&C Act). FDA will also document nonagreements and FDA
699 responses to the sponsor’s questions and issues identified by FDA. The primary documentation
700 should consist of the SPA Letter that includes agreement, nonagreement, comments or questions
701 to the sponsor, and ECAC minutes (if applicable).
702

703 704 **IX. CHANGES IN OR RESCISSION OF SPECIAL PROTOCOL ASSESSMENT** 705 **AGREEMENTS**

706
707 Section 505(b)(5)(C) of the FD&C Act states that any SPA agreement “shall not be changed
708 after the testing begins, except —
709

- 710 (i) with the written agreement of the sponsor or applicant; or
- 711
- 712 (ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the
713 reviewing division that a substantial scientific issue essential to determining the safety or
714 effectiveness of the drug has been identified after the testing has begun.”
715

716 The PDUFA V and BsUFA goals letters further describe changes in SPA agreements: “. . .
717 having agreed to the design, execution, and analyses proposed in protocols reviewed under this
718 process, the Agency will not later alter its perspective on the issues of design, execution, or
719 analyses unless public health concerns unrecognized at the time of protocol assessment under
720 this process are evident.”³⁹
721

722 Therefore, SPA agreements will not be changed at any time except as described below.
723

724 **A. Changes in an SPA Agreement**

725
726 Under section 505(b)(5)(C) of the FD&C Act, a documented SPA agreement can be modified
727 after testing begins if FDA and the sponsor agree in writing to modify the agreement. Generally,
728 such a modification is intended to improve the trial. An SPA agreement modified in this manner
729 is binding on the division in the same manner as the original SPA agreement.⁴⁰
730

731 **B. Rescinding an SPA Agreement**

732
733 In rare cases, FDA may rescind an SPA agreement. Since FDAMA was enacted in 1997, CDER
734 has issued more than 1,000 SPA agreements; less than 1 percent have been rescinded.
735

736 FDA recognizes that the written agreements reached as part of the SPA process are important to
737 the product development process. Written agreements on the design and size of a trial described

³⁹ See notes 11 and 16, *supra*.

⁴⁰ Because of CBER’s organizational structure, SPAs are binding upon the product office rather than the *division*.

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738 in section 505(b)(5)(B) of the FD&C Act are based on the best scientific information available at
739 the time of the agreement. However, newly available scientific knowledge in the form of data or
740 other information, or a reevaluation or improved understanding of relevant scientific knowledge,
741 may challenge or cause the scientific community and FDA to question or reject previously held
742 assumptions or beliefs supporting an earlier decision and agreement on an SPA.

743
744 FDA may rescind an SPA agreement when the division director determines that a substantial
745 scientific issue essential to determining the safety or efficacy of the product has been identified
746 after the trial has begun (section 505(b)(5)(C)(ii) of the FD&C Act). A substantial scientific
747 issue essential to determining the safety or efficacy of the product may include, but is not limited
748 to:

- 749
750 • Identification of data that would call into question the clinical relevance of previously
751 agreed-upon efficacy endpoints.
- 752
753 • Identification of safety concerns related to the product or its pharmacological class.
- 754
755 • Paradigm shifts in disease diagnosis or management recognized by the scientific
756 community and FDA.
- 757
758 • The relevant data, assumptions, or information provided by the sponsor in the SPA
759 submission are found to be false statements or misstatements, or are found to omit
760 relevant facts, such that the clinical relevance of critical components of trial design is
761 called into question, or appropriate safety monitoring and human subject protection is
762 affected.
- 763
764 • Failure of a sponsor to follow the protocol that was agreed upon with FDA (e.g., change
765 in endpoint or population). The primary endpoint is chosen to ensure that efficacy is
766 appropriately measured, and that the results of the trial will be clinically meaningful and
767 interpretable. Identification of the patient population reflects consideration of who may
768 potentially benefit from the product in the context of the proposed drug dose and
769 schedule. Changes in these or other critical design parameters may adversely affect the
770 ability to interpret the results of the trial and affect appropriate safety monitoring and
771 human subject protection. While failure of the sponsor to follow the protocol may not
772 preclude approval of the product based on review of the submitted data, it can form the
773 basis for rescission of the SPA agreement.

774
775 Although the process under section 505(b)(5)(B) of the FD&C Act does not apply to devices,
776 some alterations to a device used in a codevelopment program may affect the type or
777 interpretation of the data collected in the drug trial.⁴¹ For example, device alterations might
778 change the characteristics of the enrolled patient population or could alter the threshold for a
779 positive outcome used as a primary endpoint. If a device is altered or replaced with a different

⁴¹ Such alterations might include, for example, changed cut-off values, an altered scoring system, or addition of analytes. Changes in the performance characteristics of the device could affect sensitivity or specificity.

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780 technology after the trial has begun, such a change may be considered a substantial scientific
781 issue if it negatively affects the ability to interpret the trial results.

782
783 Given that each SPA agreement is unique to the product, product development plan, patient
784 population, and/or proposed indication, decisions concerning whether to rescind an SPA
785 agreement are made on a case-by-case basis after review of the substantial scientific issue that
786 has been identified after a trial has begun, and the evaluation of its effect on the safety or
787 effectiveness of the product. The rare occurrence of rescission reflects the diligence with which
788 FDA performs an SPA review, and FDA's appreciation of the significance of a rescission
789 decision. Such an action is taken only after consideration and input from appropriate staff. FDA
790 views rescission as part of its mandate to protect the public health by ensuring that human
791 subjects are not enrolled in clinical trials that cannot meet their regulatory objectives and to
792 ensure that FDA advice to sponsors developing products for approval is based on the most
793 current scientific knowledge.

794
795 If a decision to rescind an SPA agreement is being considered, the division director will notify
796 the sponsor in writing. The notice will include the rationale for the potential action and offer an
797 opportunity for a Type A or BDP Type I meeting under the PDUFA V or BsUFA goals,
798 respectively. The purpose of the meeting will be to allow the sponsor to submit relevant data,
799 analyses, or information to address the scientific concerns and discuss their potential effects on
800 the protocol. In some cases, FDA may seek advice from external experts, which may include
801 discussing the SPA submission and the substantial scientific issue at an FDA advisory committee
802 meeting, before the review division decides whether to rescind the agreement.

803
804 If, after review of any additional submitted material, consultation with internal or external
805 experts (as appropriate), and discussions with the sponsor, the division director concludes that
806 the SPA agreement should be rescinded, he or she will issue a Special Protocol Rescind
807 Agreement letter that details the data and information that support that decision. As stated in
808 section 505(b)(5)(D) of the FD&C Act, if the division director makes such a determination, the
809 sponsor will be given an opportunity for a meeting, regardless of whether the sponsor met with
810 FDA before receiving the Special Protocol Rescind Agreement letter, at which the division
811 director will document the scientific issue involved. This meeting will be a Type A or BDP
812 Type I meeting under the PDUFA V or BsUFA goals, respectively. This post-action meeting
813 provides the possibility to reach agreement on a developmental path forward, even if the
814 agreement is outside of an SPA agreement.

815
816 If after receiving the Special Protocol Rescind Agreement letter, the sponsor disagrees, it can
817 follow the formal dispute resolution procedures (see section X., Dispute Resolution). Generally,
818 a sponsor should have had a post-action meeting before initiating the formal dispute resolution
819 procedures.

820
821 FDA should convey its decision to rescind an SPA agreement as early as possible during the
822 product development and/or application review process, recognizing that the timing of the
823 decision will be affected by when FDA receives information about or becomes aware of the
824 substantial scientific issue. FDA will also strive to identify other SPAs that could be affected by
825 the information or substantial scientific issue and notify the relevant sponsors (if any) as soon as

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826 possible. FDA anticipates that these cases will continue to be rare, prompted by significant
827 changes in medical science that undermine the basis for the prior agreements.

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829 FDA is committed to keeping current with scientific and medical innovation, and will, to the best
830 of its ability, communicate important changes in science that affect regulatory aspects of product
831 development to sponsors in the course of formal meetings and responses to submissions as soon
832 as practicable. Such changes could include evolving understanding of protocol design,
833 knowledge of ongoing clinical trials, or the accrual of data regarding other product development
834 programs in the same, or similar, pharmacological class. FDA makes every effort throughout the
835 product development process to communicate to sponsors any concerns regarding relevant new
836 information that may affect FDA's thinking regarding an SPA agreement as soon as it is
837 appropriate and feasible to do so. However, continued product development is the responsibility
838 of the sponsor, and sponsors should review the results of published scientific investigations and
839 other sources of data and information and ascertain whether they affect ongoing investigations,
840 including trials conducted under SPAs. Sponsors should notify the appropriate review division
841 as soon as they are aware of a scientific finding that might affect their SPA agreement.

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844 **X. DISPUTE RESOLUTION**

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846 If, after being notified of the FDA action (e.g., nonagreement or rescission) by the division, the
847 sponsor disagrees with the FDA action, the sponsor should first try to resolve the matter with the
848 division. If the sponsor is not satisfied with FDA's response, the sponsor can follow FDA
849 procedures for formal dispute resolution, as described in regulations (21 CFR 10.75, 312.48, and
850 314.103), in section V of the PDUFA V goals letter,⁴² in section IV of the BsUFA goals letter,⁴³
851 and the guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*.⁴⁴
852 As part of the formal dispute resolution process, FDA may decide, either on its own initiative or
853 at the request of the sponsor, to seek input from an advisory committee, even if FDA obtained
854 input from an advisory committee before entering into the SPA agreement.

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⁴² See note 11, *supra*.

⁴³ See note 16, *supra*.

⁴⁴ In September 2015, FDA issued the revised draft guidance for industry and review staff *Formal Dispute Resolution: Appeals Above the Division Level*. When final, this guidance will represent FDA's current thinking on this topic.

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GLOSSARY

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Notice of Intent: An informal notice that the sponsor plans to submit a Request.

Request for SPA (Request): The letter from the sponsor to FDA asking for an SPA.

SPA Agreement: Concurrence with the adequacy and acceptability of specific critical elements of protocol design and analysis.

SPA Letter: FDA’s action letter in response to the SPA submission. Indicates agreement or nonagreement with the proposed protocol and provides responses to the sponsor’s questions, as appropriate.

SPA Review: FDA’s review of all material submitted by the sponsor pertaining to a Request (i.e., FDA’s review of the SPA submission).

SPA Submission: A Request plus accompanying supportive materials and protocol.

Special Protocol Assessment (SPA): A process by which sponsors ask FDA to evaluate a protocol to determine whether it adequately addresses scientific and regulatory requirements for the purpose identified by the sponsor. As part of the process, sponsors generally submit specific questions about protocol design and scientific and regulatory requirements. FDA completes the review of the SPA submission and any internal and/or external consultations. FDA then sends an SPA Letter to the sponsor to close out the process. The term *special protocol assessment*, for the purposes of this guidance, refers to the processes and procedures that begin when a sponsor notifies FDA of its intent to submit a Request or its submission of a Request, and end with issuing an SPA Letter.

Special Protocol Rescind Agreement Letter: FDA’s action letter when it has determined that it will rescind an existing SPA agreement based on the fact that a substantial scientific issue essential to determining the safety or effectiveness of the product has been identified after testing began.