Special Protocol Assessment
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Amalia Himaya at 301-796-3391 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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
Procedural

Revision 1

Special Protocol Assessment
Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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
Procedural

Revision 1

TABLE OF CONTENTS

Special Protocol Assessment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 sponsors[2] may request to meet with FDA to reach agreement on the design and size of certain clinical trials, clinical studies, or animal trials[3] (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.

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

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

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

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

II. BACKGROUND

A. Statutory Framework

Section 119(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amended section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)) and directed FDA to meet with sponsors who request to meet, provided certain conditions are met, to reach agreement on the design and size of the well-controlled clinical trials intended to form the primary basis for a demonstration of effectiveness in a marketing application submitted under section 505(b) of the FD&C Act or section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262).[7] These provisions subsequently were amended in section 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.

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

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

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

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

The SPA process does not apply to marketing applications for devices or to device protocols, including protocols for the development of companion diagnostic devices. Sponsors may submit 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.

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

B. User Fee Acts

1. Prescription Drug User Fee Act

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

Under the PDUFA V goals, the sponsor may submit a Request for qualifying protocols (see section III., Eligible Protocols and General Information) that should include "a limited number of specific questions about protocol design and scientific and regulatory requirements."[14] Of the Requests that FDA accepts (see section VI., FDA Assessment Process), the goal is to complete 90 percent of SPA reviews 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.

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

[11] The 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.

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.

- Animal carcinogenicity protocols.

- Drug substance and drug product stability protocols.

- Animal efficacy protocols for studies intended to provide primary evidence of effectiveness required for approval or licensure for products developed under the animal rule (*animal rule efficacy protocols*).

- Protocols for trials intended to form the primary basis of an efficacy claim.[18] Protocols that meet this criterion can be submitted for an SPA, regardless of the product development phase (e.g., for products developed under accelerated approval (i.e., subpart H (for drugs) or subpart E (for biological products)), such protocols might be phase 2 rather than phase 3). In addition, protocols for clinical or animal trials of bioequivalence or bioavailability that will form the basis of an efficacy claim are considered to meet this criterion and are eligible for an SPA.

- Any necessary trials 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).[19]

B. General Information

1. Meeting With FDA Before Submission of a Request

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

Therefore, before submitting a Request, the sponsor should meet with FDA to discuss the proposed trial and its regulatory context. 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 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*.

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

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

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

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

2. Reaching SPA Agreement With FDA

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

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

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

IV. PROCEDURES FOR SUBMISSION OF A REQUEST

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

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

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

A. Notice of Intent

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

B. Timing of a Request

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

C. Format of a Request

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

D. Where to Send a Request

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

V. CONTENT OF A REQUEST AND SUBMISSION MATERIALS

The content of a Request and accompanying submission materials should be complete and, as stated in section 505(b)(5)(B) of the FD&C Act, the sponsor must provide information necessary 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).

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

A. Animal Carcinogenicity Protocols

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

B. Drug Substance and Drug Product Stability Protocols

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

- *Q1A(R2) Stability Testing of New Drug Substances and Products*
- *Q1B Photostability Testing of New Drug Substances and Products*
- *Q1C Stability Testing for New Dosage Forms*
- *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*
- *Q1E Evaluation of Stability Data*
- *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*

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

[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.

C. Animal Rule Efficacy Protocols

Before submitting a Request, the sponsor should have FDA concurrence on the animal 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. The Request should include a detailed protocol and focused questions regarding the protocol such as study design, conduct, objectives, endpoints, data analysis, and evaluation criteria. The sponsor should include background information, separate from the protocol, that describes in detail all relevant data (including clinical data), assumptions, and information that can assist FDA in evaluating the protocol and responding to the sponsor's questions. Although most of this information should have been discussed during previous interactions with FDA, this section should provide explanations of the scientific and regulatory basis for the study design, endpoints, statistical analysis plan, and the agreed-upon animal model. In addition, the document should provide a detailed plan describing how the effective dose in animals will be translated to an appropriate dosing regimen in humans. Sponsors should consult the guidance for industry *Product Development Under the Animal Rule* when developing background documents.

D. Clinical Trial Protocols

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

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

- Draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*[28]
- Draft guidance for industry *Non-Inferiority Clinical Trials*[29]
- Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*

[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.

- Guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*

- ICH guidance for industry *E3 Structure and Content of Clinical Study Reports*

- ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*

- ICH guidance for industry *E9 Statistical Principles for Clinical Trials*

- ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*

- ICH guidance for industry *M4 Organization of the CTD*

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

- Include information about the role of the trial in the overall development of the product.

- Consider the relevance of the population to be studied to the U.S. population in which the product is intended to be used, taking into account sex and age distribution[30] and ethnic diversity reflective of the U.S. population. If the population in the proposed trial is narrow, any plans to study the product in a broader population should be described. If the trial will recruit the majority of enrollees from outside of the United States, the submission should include an explanation of why the results should be considered applicable to a U.S. population, and/or identify additional planned trials that will provide an adequate understanding of the benefits and risks of the therapy for the U.S. population, considering ethnic, genomic, standard of care, and other factors relevant to the specific therapy.

- Provide adequate information to justify the critical design features of the trial, including, but not limited to:

  – Explaining reasons for dose selection, and, if applicable, justification for not including more than one dose.

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

- Describing and explaining choice of trial endpoints, including identification of the primary and secondary endpoint(s), and plans for controlling overall type I error rate (false positive rate).

- Describing choice of trial design (e.g., dose-response, superiority, add-on, noninferiority, equivalence) and control (e.g., placebo, best supportive care, active control). If the trial is a noninferiority trial, the choice of active control and the noninferiority margin derived from the estimated treatment effect of the active control should be identified and justified. If the protocol includes adaptive features, then decision rules for adaptations while controlling overall type I error rate and operational bias should be justified. Enrichment designs, if considered, should be based on scientific rationale and the design should take prevalence of the disease into consideration.

- Describing and explaining duration of therapy.

- Describing methods of endpoint assessment.

- Describing procedures to minimize bias at all stages (e.g., randomization, blinding, endpoint assessment committee, data monitoring committee).

- Describing the statistical approach, including a well-developed statistical analysis plan and plans for minimizing and dealing with missing data. Any planned interim analyses should be described, with the level of significance allocated for the planned interim analyses.

The sponsor should also consider the following:

- Sponsors should fully document and justify complex or novel eligibility criteria, biomarker testing as an entry criterion, endpoints, and analysis plans. As noted in section III.B.1., Meeting With FDA Before Submission of a Request, FDA encourages sponsors to request a meeting before submitting the Request. A meeting is especially useful for novel or complex issues. Furthermore, novel or complex issues may necessitate expert consultation (e.g., with an advisory committee expert) to evaluate novel protocol features, which may extend review times beyond the first cycle review goal of 45 days (see section VI.E., Potential for Delay of FDA Response).

- Historically controlled trials (comparison with adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations) are usually reserved for special circumstances and can raise particular problems for adequate efficacy and safety assessment. If the sponsor submits a protocol for a single-arm trial for an SPA, the sponsor should justify why a concurrently controlled trial is not feasible or cannot be conducted ethically.[31]

[31] See ICH E10.

- 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.

VI. FDA ASSESSMENT PROCESS

A. Determining Whether a Submission Is Appropriate for an SPA

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).

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.

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.

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

- It contains a protocol for an ongoing trial, or the investigation will begin in less than 45 days.[33,34]

- It contains a protocol for which valuation and critical features are adequately described by existing guidance (e.g., conventional stability study). (See section V.B., Drug Substance and Drug Product Stability Protocols, for further explanation.)

- It does not provide sufficient content and detail as described in section V., Content of a Request and Submission Materials, including:

  – A detailed protocol

  – Specific questions for FDA to address

  – Adequate background documents to support the critical elements of the trial design, or to determine whether it can adequately address scientific and regulatory requirements for the purpose identified by the sponsor

- Prior FDA concurrence has not been obtained for the animal model to be used in the proposed animal rule efficacy study (see section V.C., Animal Rule Efficacy Protocols).[35]

- As stated in the PDUFA V and BsUFA goals, the sponsor has not had a meeting (e.g., end-of-phase 2/pre-phase 3 meeting (or end-of-phase 1 meeting, if applicable) or a BPD Type 2 or Type 3 meeting) with the review division for the clinical trial that is the subject of the SPA (where the trial is intended to support efficacy or trials to prove biosimilarity and/or interchangeability).[36]

[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.

B. Assessment of the SPA Submission

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

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

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

C. Revisions During FDA Assessment

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

D. FDA Response to Sponsor

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

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

E. Potential for Delay of FDA Response

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

1. Advisory Committee or External Consultant Review

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

2. Internal FDA Consultative Review

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

VII. SPONSOR OPTIONS AFTER RECEIPT OF NONAGREEMENT SPA LETTER

Sponsors should note that, despite additional communications in writing and/or additional Type A or BPD Type 1 meetings, sponsors and FDA may not reach agreement on all aspects of the protocol and specific questions posed. Nonagreement letters may identify areas in which FDA concurs with the sponsor's proposal, even if an SPA agreement letter cannot be issued. The 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*.

654
655 ### A. Initiate Trial Without SPA Agreement
656
657 Sponsors can initiate a trial after receipt of a nonagreement SPA Letter (assuming that all
658 relevant requirements are met for conducting the trial). FDA agreement is not required before
659 proceeding with critical trials intended to form primary evidence of effectiveness, and FDA
660 reviews marketing applications on the basis of submitted data, regardless of whether FDA
661 previously agreed with the design of the protocol in an SPA agreement. If the results from the
662 trial are submitted in a marketing application, FDA will review the results and determine
663 whether they support the approval of the application. Applications that meet the statutory
664 standards will result in approval.
665
666 ### B. Do Not Initiate Trial and Respond in Writing to Address Nonagreement
667
668 Sponsors can respond in writing to amend the protocol or provide additional supporting
669 information to address the reasons for the nonagreement expressed by FDA. This amendment
670 and response will be considered an SPA resubmission, not a new SPA submission under PDUFA
671 V and BsUFA performance goals, and FDA will make every effort to complete the review within
672 45 days. In some cases, changes to the protocol included in the SPA resubmission may not
673 require the full additional review period. In such situations, FDA will make every effort to
674 complete the review as soon as practicable.
675
676 Resubmissions should be complete and should address outstanding critical protocol issues. As
677 previously mentioned, an SPA is intended to provide feedback on critical protocol design issues
678 rather than minor protocol details that would be well managed by sponsors. SPA resubmissions
679 should address specific issues identified in the nonagreement SPA Letter and should not address
680 or introduce new issues or items for discussion. Introducing significant new material alters the
681 developmental context and may warrant a meeting to discuss the new information.
682
683 ### C. Request a Type A or BPD Type 1 Meeting to Discuss Nonagreement
684
685 Sponsors can request a Type A or BPD Type 1 meeting with the division to discuss
686 nonagreement issues. If FDA believes that meeting with a sponsor is the best way to resolve
687 outstanding issues regarding an SPA, FDA can suggest in the SPA Letter that the sponsor request
688 such a meeting. Type A and BPD Type 1 meeting requests are handled according to PDUFA V
689 or BsUFA goals for meeting management, respectively.[38] At a Type A or BPD Type 1 meeting,
690 FDA and the sponsor should discuss any remaining issues and uncertainties regarding the
691 protocol but may not necessarily come to final agreement on all remaining issues. If the issues
692 of concern are resolved, SPA agreement could be documented in the meeting minutes.
693
694

[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*.

VIII. DOCUMENTATION

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

IX. CHANGES IN OR RESCISSION OF SPECIAL PROTOCOL ASSESSMENT AGREEMENTS

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

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun."

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

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

A. Changes in an SPA Agreement

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

B. Rescinding an SPA Agreement

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

FDA recognizes that the written agreements reached as part of the SPA process are important to 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.*

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

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

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

Although the process under section 505(b)(5)(B) of the FD&C Act does not apply to devices, some alterations to a device used in a codevelopment program may affect the type or interpretation of the data collected in the drug trial.[41] For example, device alterations might change the characteristics of the enrolled patient population or could alter the threshold for a 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.

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

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

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

If, after review of any additional submitted material, consultation with internal or external experts (as appropriate), and discussions with the sponsor, the division director concludes that the SPA agreement should be rescinded, he or she will issue a Special Protocol Rescind Agreement letter that details the data and information that support that decision. As stated in section 505(b)(5)(D) of the FD&C Act, if the division director makes such a determination, the sponsor will be given an opportunity for a meeting, regardless of whether the sponsor met with FDA before receiving the Special Protocol Rescind Agreement letter, at which the division director will document the scientific issue involved. This meeting will be a Type A or BDP Type 1 meeting under the PDUFA V or BsUFA goals, respectively. This post-action meeting provides the possibility to reach agreement on a developmental path forward, even if the agreement is outside of an SPA agreement.

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

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

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

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

X. DISPUTE RESOLUTION

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

[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.

GLOSSARY

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.