
Special Protocol Assessment Guidance for Industry

**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)**

**April 2018
Procedural**

Revision 1

**OMB Control Number 0910-0014
Current expiration date available at <https://www.reginfo.gov>
(Search ICR and enter OMB control number)
See additional PRA statement in section XI of this guidance.**

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
<https://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
<https://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)**

**April 2018
Procedural**

Revision 1

TABLE OF CONTENTS

I. INTRODUCTION..... 1

II. BACKGROUND 2

III. ELIGIBLE PROTOCOLS AND GENERAL INFORMATION..... 2

A. Eligible Protocols 2

B. General Information 3

 1. *Meeting With FDA Before Submission of a Request..... 3*

 2. *Reaching SPA Agreement With FDA..... 4*

IV. PROCEDURES FOR SUBMISSION OF A REQUEST..... 5

A. Notice of Intent..... 6

B. Timing of a Request..... 6

C. Format of a Request..... 6

D. Where to Send a Request 6

V. CONTENT OF A REQUEST AND SUBMISSION MATERIALS 7

A. Animal Carcinogenicity Protocols..... 7

B. Drug Substance and Drug Product Stability Protocols 7

C. Animal Rule Efficacy Protocols..... 7

D. Clinical Trial Protocols..... 8

VI. FDA ASSESSMENT PROCESS 10

A. Determining Whether a Submission Is Appropriate for an SPA 10

B. Assessment of the SPA Submission 12

C. Revisions During FDA Assessment 13

D. FDA Response to Sponsor 13

VII. SPONSOR OPTIONS AFTER RECEIPT OF SPECIAL PROTOCOL ASSESSMENT — NO AGREEMENT LETTER..... 13

VIII. DOCUMENTATION..... 14

IX. CHANGES IN OR RESCISSION OF SPECIAL PROTOCOL ASSESSMENT AGREEMENTS 15

A. FDA and Sponsor Agreement on Changes in an SPA Agreement 15

B. FDA Rescinding of an SPA Agreement..... 15

X. DISPUTE RESOLUTION 18

XI. PAPERWORK REDUCTION ACT OF 1995..... 18

GLOSSARY..... 20

REFERENCES..... 21

APPENDIX: LEGAL BACKGROUND 23

Special Protocol Assessment Guidance for Industry¹

This guidance represents 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 office 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 ask to meet with FDA to reach agreement on the design and size of certain clinical trials, clinical studies, or animal studies³ (i.e., a Request for SPA (hereafter *Request*); see section III., Eligible Protocols and General Information) to determine if they adequately address scientific and regulatory requirements for a study that could support marketing approval.

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) for a study intended to support a future marketing application. These elements are critical to ensuring that the trial conducted under the protocol can be considered an adequate and well-controlled study that can support marketing approval.⁴ Feedback on these issues provides the greatest benefit to sponsors in 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.

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

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

Contains Nonbinding Recommendations

The existence of an SPA agreement does not guarantee that FDA will file (accept) a new drug application (NDA) or biologics license application (BLA),⁵ or that the trial results will be adequate to support approval. Those issues are addressed during the review of a submitted application and are determined based on the adequacy of the overall submission.

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 summary of the statutory framework is provided in the Appendix.

III. ELIGIBLE PROTOCOLS AND GENERAL INFORMATION

A. Eligible Protocols

Under section 505(b)(5)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Prescription Drug User Fee Act (PDUFA) goals, and the Biosimilar User Fee Act (BsUFA) goals, the following protocols are eligible for a Request:

- 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*).

⁵ See the draft guidance for industry *Refuse to File: NDA and BLA Submissions to CDER*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. See also MAPP 6025.4 *Good Review Practice: Refuse to File* (available at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>) and SOPP 8404 *Refusal to File Procedures for Biologics License Applications, New Drug Applications and Efficacy Supplements* (available at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm>).

Contains Nonbinding Recommendations

- Protocols for trials intended to form the primary basis of an efficacy claim.⁶ 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., 21 CFR 314.500, subpart H (for drugs), or 21 CFR 601.40, 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.
- Protocols for any necessary clinical study or studies to prove biosimilarity and/or interchangeability (e.g., protocols for pharmacokinetic and pharmacodynamic studies, protocols for comparative clinical studies 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 studies intended to support a demonstration of interchangeability).⁷

B. General Information

1. Meeting With FDA Before Submission of a Request

The PDUFA 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,^{8,9} or biosimilar biological product development (BPD) Type 2 or Type 3 meeting, respectively.¹⁰ Therefore, before submitting a Request, the sponsor should meet with FDA to discuss the proposed trial and its regulatory context and to identify the particular questions of interest regarding the protocol. If the proposed trial that will be the subject of a Request was not

⁶ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. (We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.) For the purposes of this guidance, the term *efficacy claim* is defined by its use in the PDUFA goals letter; see note 8, *supra*.

⁷ FDA has published several guidances related to biosimilarity and interchangeability. See the Biosimilars guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>. In addition, see section 744G(3) and (4) of the FD&C Act and section 351(i) of the Public Health Service Act for the statutory definition of *biosimilar biological product*, *biosimilar biological product application*, and definitions of selected terms used in this guidance.

⁸ FDA first agreed to specific PDUFA goals for SPA in November 1997 in conjunction with PDUFA II, the reauthorization of PDUFA. 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

(<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm143135.htm>). The program has been reauthorized every 5 years; the most recent goals letter is available on the FDA website at

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm149212.htm>.

⁹ See the BsUFA goals letter titled “Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022” available on the FDA website at

<https://www.fda.gov/downloads/forindustry/userfees/biosimilaruserfeeactbsufa/ucm521121.pdf>. The program is considered for reauthorization every 5 years; updated goals letters are posted on the FDA website at

<https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm>.

¹⁰ See the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

Contains Nonbinding Recommendations

previously discussed at a drug development meeting, a separate meeting may be appropriate to ensure understanding of the regulatory context (see section IV., Procedures for Submission of a Request, when an SPA meeting is requested, but an investigational new drug application (IND) has not been filed). FDA strongly encourages sponsors to request such meetings to discuss such trials and the Request. As provided in section 505(b)(5) of the FD&C Act, if a sponsor makes a reasonable written request for such a meeting, FDA will grant the meeting request. In some cases (e.g., protocols to support submission of an efficacy supplement or a carcinogenicity study), FDA may already be familiar with the regulatory context, or it can be adequately described in the Request and supporting materials. In such cases, some sponsors have decided not to submit a meeting request and FDA has accepted the Request for SPA without having had a prior meeting.

Sufficient information should be provided in the meeting request to ensure that all relevant disciplines and offices that should participate are identified, to permit detailed discussion of the relevant issues, and to facilitate subsequent FDA review of an SPA submission. These detailed discussions are especially important if the development plan will include trial 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.¹¹ Discussions with FDA regarding the development of an appropriate animal model under the animal rule 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 (see section V.C., Animal Rule Efficacy Protocols).

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.B., Assessment of the SPA Submission, 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. FDA will also provide advice on other important concerns identified during review, even in the absence of a specific question. Although the goal of an SPA is to reach concurrence on the adequacy of protocol elements of a study intended to support a finding of safety and efficacy, an SPA agreement with FDA indicates concurrence with critical trial design concepts but does not imply that FDA has reviewed, or concurs with, protocol details that do not affect approvability.

¹¹ 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.

Contains Nonbinding Recommendations

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 in the cover letter, including any protocol elements intended to support a potential statement in labeling. The sponsor should identify potential labeling statements for discussion with FDA, with appropriate objectives and statistical analysis that are intended to support this claim. Claims not agreed upon at the meeting, and not supported by appropriate prespecified objectives and appropriate control for multiplicity are unlikely to support inclusion in labeling.

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 in its entirety 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 in the application as a whole 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 and the sponsor is notified of such (see section IX., Changes in or Rescission of Special Protocol Assessment Agreements), the existence of an SPA agreement does not mean that the application as a whole will meet the statutory standard for approval.

IV. PROCEDURES FOR SUBMISSION OF A REQUEST

A Request should be submitted to a sponsor's existing IND for each protocol the sponsor wants reviewed under an SPA. 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 and then submit a Request to the IND.

FDA encourages electronic submissions in electronic common technical document format.¹² Electronic submission enhances the receipt, processing, and review of an SPA submission, particularly in view of the multidisciplinary input required to complete the SPA.

¹² See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. As is further described in that guidance, electronic submission of commercial INDs in electronic common technical document format will be required after May 5, 2018.

Contains Nonbinding Recommendations

A. Notice of Intent

Informing FDA of an upcoming Request will facilitate efficient review by FDA, and may permit earlier feedback to the sponsor. Notification can be communicated during a drug development meeting or as an informal fax or email to the regulatory project manager.

B. Timing of a Request

To allow sufficient time for FDA review and comment, as well as for resolution of outstanding high-level issues before the initiation of the proposed trial,¹³ CDER and CBER generally recommend that a sponsor submit a Request and submission materials to FDA sufficiently in advance of the anticipated start of the trial, so that FDA assessment can be completed before the protocol is finalized and submitted to the investigational review board(s). The protocol, including a planned statistical analysis that includes critical statistical components, 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.¹⁴ If only minor issues remain, sponsors can proceed with protocol implementation, recognizing that a subsequent protocol amendment may be needed after study initiation. 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.¹⁵ 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.

¹³ 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.

¹⁴ See the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*.

¹⁵ See 21 CFR 312.23(d).

Contains Nonbinding Recommendations

V. CONTENT OF A REQUEST AND SUBMISSION MATERIALS

The content of a Request and accompanying submission materials should be complete and the sponsor must provide information necessary for discussion and agreement on the design and size of the trial.¹⁶ Any areas of incomplete information should be identified and adequately justified by the sponsor. Similarly, the sponsor should reference in the Request any relevant discussions and agreements with FDA on the phase 3 protocol based on previous meetings (e.g., an end-of-phase 2/pre-phase 3 meeting, end-of-phase 1 meeting, or BPD Type 2 or Type 3 meeting). Relevant guidances that may be helpful to sponsors, both for supporting the trial design and for determining whether a Request is appropriate, are cited in References. Sponsors are advised to consult the Drugs and Biologics guidance web pages for the most current lists of available guidances.¹⁷

A. Animal Carcinogenicity Protocols

A sponsor should include relevant background information in addition to the complete protocol for CDER requests.¹⁸

B. Drug Substance and Drug Product Stability Protocols

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

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.

C. Animal Rule Efficacy Protocols

Before submitting a Request, a 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

¹⁶ See section 505(b)(5)(B) of the FD&C Act.

¹⁷ See <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> and <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, respectively.

¹⁸ See the guidance for industry *Carcinogenicity Study Protocol Submissions*. Additional information may be found in MAPP 7412.1 Rev. 2 *Management of CDER Executive Carcinogenicity Assessment Committee and Communication of Committee Proceedings* at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

Contains Nonbinding Recommendations

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, evaluation criteria, and the plan for ensuring data quality and integrity. 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 document 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) a 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 rely on only one 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. Sufficiency of one trial to support approval is an appropriate topic for the end-of-phase 2 meeting held before SPA submission.

For protocols for clinical studies intended to support a demonstration of biosimilarity and/or interchangeability, a sponsor should describe in the submission how the protocol will support a demonstration of biosimilarity and/or interchangeability.¹⁹

In addition, sponsors should review relevant FDA and ICH guidances for industry (see References).

A sponsor should submit background information adequate to support critical design elements. This background information generally can be contained within the protocol, but also can be submitted as a separate document if the protocol does not provide a detailed and complete rationale, or if additional information is needed for FDA to address specific questions. Additional supporting documentation is especially important for consideration of novel endpoints to demonstrate clinical efficacy and any unusual design features. The SPA agreement

¹⁹ FDA has issued guidances related to the design of clinical studies intended to support a demonstration of biosimilarity and/or interchangeability in a BLA submitted under section 351(k) of the Public Health Service Act. These guidances are available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>.

Contains Nonbinding Recommendations

describes concurrence on critical elements of the overall protocol design, but does not imply concurrence on these supportive documents. The accompanying submission materials can:

- Include information about the role of the trial in the overall development of the product.
- Document and justify complex or novel eligibility criteria.
- 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 distribution²⁰ 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, more diverse population should be described. If the sponsor has feasibility information indicating that 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.
 - 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.
 - If a sponsor submits a protocol for a single-arm trial for an SPA, justifying why a concurrently controlled trial is not feasible or cannot be conducted ethically.
 - Describing and explaining duration of therapy.

²⁰ See the guidance for industry *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*.

Contains Nonbinding Recommendations

- Describing methods of endpoint assessment.
- Justifying the use of novel biomarkers if used to select the population, monitor drug response or safety, or as an endpoint to support a labeling claim.
- Describing procedures to minimize bias at all stages (e.g., randomization, blinding, endpoint assessment committee).
- Describing the statistical approach, including a planned statistical analysis that includes critical statistical components and plans for reducing and imputing missing data. Any planned interim analyses should be described, with the level of significance allocated for the planned interim analyses.

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 (i.e., development of a drug and a companion diagnostic device) where a sponsor requests an SPA for the drug, the sponsor 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 the Appendix under Statutory Framework. Sponsors should direct questions about companion diagnostic protocols to the Center for Devices and Radiological Health.²¹

VI. FDA ASSESSMENT PROCESS

A. Determining Whether a Submission Is Appropriate for an SPA

After receiving a Request and submission materials (*SPA submission*), the decision to accept the Request is made by the division director in consultation with the appropriate reviewers and team leaders. If the division director concludes that the submission is not appropriate for an SPA, the division will notify the sponsor as soon as practicable about the determination and the specific reasons for the decision. Generally, a rapid form of communication will be followed by a letter.

²¹ See the guidance for industry and Food and Drug Administration staff *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*. This guidance is available on the FDA Medical Devices/Cross-Center Final Guidance web page at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm>.

Contains Nonbinding Recommendations

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.
- It contains a protocol for an ongoing trial.^{22,23}
- It contains a protocol for which evaluation 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).
- As stated in the PDUFA 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 at which the regulatory context for the study or trial that is the subject of the SPA was discussed (where the trial is intended to support efficacy or trials to prove biosimilarity and/or interchangeability).²⁴

²² 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.

²³ See note 11, *supra*.

²⁴ See notes 8 and 9, *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 meeting requests, and FDA has granted the Requests without having had a prior meeting.

Contains Nonbinding Recommendations

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 proposed protocols are current, complete, and accurate, because any change in the underlying data, assumptions, and information could affect the assessment of protocols and the resulting recommendations and/or SPA agreements.

For animal carcinogenicity protocols submitted to CDER, review staff will present their assessments to the Executive Carcinogenicity Assessment Committee (ECAC). The ECAC renders a final judgment on a 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).

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 any type of SPA submission. FDA can seek advisory committee review or advice from advisory committee members, other special government employees, or other external consultants, and will consider the advice provided. Advisory committee discussion of protocols submitted for SPA generally will not be open to the public. FDA will follow standard procedures to protect confidentiality of commercial trade secret information. 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.

If such input is needed, FDA's response may be delayed. If such a delay occurs, FDA should inform the sponsor as soon as practicable, but no later than 45 calendar days of receipt of the Request, generally by fax or email followed by a mailed letter. The communication will include the reason for the delay, the anticipated date of FDA's response, and an overview of the specific issues that will be reviewed.

Contains Nonbinding Recommendations

After additional input has been obtained, 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 or external consultants, as soon as practicable, but no later than 45 calendar days of the advisory committee meeting or consultant review of the protocol.

C. Revisions During FDA Assessment

FDA should communicate with the sponsor regarding deficiencies or problems with the protocol to allow for potential resolution as soon as possible and before issuing a Special Protocol Assessment — No Agreement 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. If FDA considers the SPA withdrawn, the division will notify the sponsor, followed by a letter that includes the rationale for the action. 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 and BsUFA goals, FDA committed to sending an SPA letter (see sections VIII., Documentation, and VI.B., Assessment of the SPA Submission) 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.²⁵ The division will mail the letter to the sponsor, even if the letter was first sent by fax or email.

VII. SPONSOR OPTIONS AFTER RECEIPT OF SPECIAL PROTOCOL ASSESSMENT — NO AGREEMENT 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 protocols and specific questions posed. A Special Protocol Assessment — No Agreement letter may identify areas in which FDA concurs with the sponsor's proposal, even if a Special Protocol Agreement letter cannot be issued. The following options are available to sponsors after receiving Special Protocol Assessment — No Agreement letters:

- **Initiate Trial Without SPA Agreement** — Sponsors can initiate trials after receipt of Special Protocol Assessment — No Agreement letters. FDA agreement is not required before proceeding with trials intended to form primary evidence of effectiveness, and

²⁵ See the 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) and the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

Contains Nonbinding Recommendations

FDA reviews marketing applications on the basis of submitted data, regardless of whether FDA previously agreed with protocol designs in SPA agreements. If the results from a 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.

- **Do Not Initiate Trial and Respond in Writing to Address Nonagreement** — Sponsors can respond in writing to amend protocols 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 and BsUFA performance goals, and FDA will make every effort to complete the subsequent review within 45 days. In some cases, changes to the protocol included in the SPA resubmission may not require the full additional review period, and 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 Special Protocol Assessment — No Agreement letters 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.

- **Request a Type A or BPD Type 1 Meeting to Discuss Nonagreement** — Sponsors can request Type A or BPD Type 1 meetings with the divisions 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 Special Protocol Assessment — No Agreement letter that the sponsor request such a meeting. Type A and BPD Type 1 meeting requests are handled according to PDUFA or BsUFA goals for meeting management, respectively.²⁶ At a Type A or BPD Type 1 meeting, FDA and the sponsor should discuss 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 in advance of FDA issuing a Special Protocol Agreement letter.

VIII. DOCUMENTATION

All agreements between FDA and the sponsor regarding an 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

²⁶ See notes 8 and 9, *supra*. See the 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) and the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

Contains Nonbinding Recommendations

should consist of an 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 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.”²⁷

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

A. FDA and Sponsor Agreement on 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.²⁸ In general, requests to modify an SPA agreement will be reviewed as soon as practicable and will include discussion with the sponsor as appropriate. FDA will make every effort to complete its review and amend the agreement within 45 days of receipt. More substantial or complex changes may require additional input (see section VI.B., Assessment of the SPA Submission) or longer review times.

B. FDA Rescinding of an SPA Agreement

In rare cases, FDA may rescind an SPA agreement. Since the Food and Drug Administration Modernization Act of 1997 was enacted through 2016, CDER has issued more than 1,000 SPA agreements; less than 1 percent of those SPAs 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

²⁷ See notes 8 and 9, *supra*.

²⁸ Because of CBER’s organizational structure, SPAs are binding on the product office rather than the *division*.

Contains Nonbinding Recommendations

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 or senior management 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 are affected

Note that if the sponsor fails to follow the protocol that was agreed upon with FDA consistent with the SPA agreement, or makes substantive changes in the protocol without agreement with FDA (e.g., change in endpoint or population), then FDA will consider the results from the study as a review issue; FDA will not, however, be bound by the SPA agreement because the study conducted was not within the agreed terms of the SPA. Note that minor changes to protocols (e.g., changes in noncritical conduct of the trial or editorial changes) typically would not affect the SPA agreement. Although 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.²⁹ 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 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.

²⁹ 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.

Contains Nonbinding Recommendations

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 ability to interpret 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 BPD Type 1 meeting under the PDUFA 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. Standard FDA procedures to protect confidentiality will be followed.

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 discuss the scientific issue involved. This meeting will be a Type A or BPD Type 1 meeting under the PDUFA 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 depend on 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.

Contains Nonbinding Recommendations

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 a related, 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, sponsors are responsible for continued product development and they should review the results of published scientific investigations and other sources of data and information and ascertain whether these 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 agreements.

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), the PDUFA goals letter,³⁰ the BsUFA goals letter,³¹ and the guidance for industry and review staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level*. 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, irrespective of whether FDA obtained input from an advisory committee before entering into the SPA agreement.

XI. PAPERWORK REDUCTION ACT OF 1995

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

The time required to complete this information collection is estimated to average 8 hours to prepare a notice of intent to request SPA of a carcinogenicity protocol and 15 hours to prepare a request for SPA, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to: Office of Regulatory Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

³⁰ See note 8, *supra*.

³¹ See note 9, *supra*.

Contains Nonbinding Recommendations

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information for FDA Form 1571 have been approved under OMB control number 0910-0014.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0014. The current expiration date is available at <https://www.reginfo.gov> (search ICR and enter OMB control number).

Contains Nonbinding Recommendations

GLOSSARY

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

Request for SPA (Request): The letter from a sponsor to FDA asking for a special protocol assessment (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 an SPA submission. Indicates agreement or nonagreement with specific critical elements of design and analysis of the proposed protocol and provides responses to a sponsor's questions, as appropriate.

SPA Review: FDA's review of all material submitted by a 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 a sponsor asks 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 designs 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 FDA 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.

Contains Nonbinding Recommendations

REFERENCES

The following guidances provide additional information for section V., Content of a Request and Submission Materials, of the guidance.

Drug Substance and Drug Product Stability Protocols

ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*

ICH guidance for industry *Q1B Photostability Testing of New Drug Substances and Products*

ICH guidance for industry *Q1C Stability Testing for New Dosage Forms*

ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*

ICH guidance for industry *Q1E Evaluation of Stability Data*

ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*

Clinical Trial Protocols

Draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*³²

Draft guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product*³³

Guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*

Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*

Guidance for industry *Non-Inferiority Clinical Trials*

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*

³² When final, this guidance will represent the FDA's current thinking on this topic.

³³ When final, this guidance will represent the FDA's current thinking on this topic.

Contains Nonbinding Recommendations

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

ICH guidance for industry *M4 Organization of the CTD*

Contains Nonbinding Recommendations

APPENDIX: LEGAL BACKGROUND

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 Act (PHS Act) (42 U.S.C. 262).³⁴ These provisions subsequently were amended in section 7002(d)(1) of the Biologics Price Competition and Innovation Act of 2009 to include any necessary clinical study or studies 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 special protocol assessment (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*).³⁵ 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 section 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 the User Fee Acts section in this Appendix 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

³⁴ 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.

³⁵ 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.

Contains Nonbinding Recommendations

of the drug has been identified after the testing has begun.”³⁶ 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, of the guidance.

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 of the trial, FDA will state the reasons for the nonagreement in a Special Protocol Assessment — No Agreement letter to the sponsor. Potential paths forward after receipt of this letter are described in section VII., Sponsor Options After Receipt of Special Protocol Assessment — No Agreement Letter, of the guidance.

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 can submit a Request for a protocol for the drug or biological product, but sponsors should direct questions about companion diagnostic protocols to the Center for Devices and Radiological Health. Questions about the device portion of a combination product are managed through the lead center using standard processes, but are not included in the SPA.³⁷

User Fee Acts

Prescription Drug User Fee Act

In conjunction with the reauthorization of the prescription drug user fee program in FDAMA (Prescription Drug User Fee Act (PDUFA) II), FDA agreed to specific performance goals (PDUFA goals) for SPA.³⁸ According to the PDUFA 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.”³⁹ 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

³⁶ See section 505(b)(5)(C)(ii) of the FD&C Act.

³⁷ See Staff Manual Guide 4101

(<https://www.fda.gov/aboutfda/reportsmanualsforms/staffmanualguides/default.htm>) and Rappel MJ, Hunter NL, Alexandrow AL, et al., 2017, Case Study for Lean Management in the Public Section: Improving Combination Product Review at the Food and Drug Administration, Clin Transl Sci., epub ahead of print January 12, 2017, doi: 10.1111/cts.12441.

³⁸ 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 (<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm143135.htm>). The program has been reauthorized every 5 years; the most recent goals letter is available on the FDA website at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm149212.htm>.

³⁹ Ibid.

Contains Nonbinding Recommendations

development in which they happen to be conducted.”⁴⁰ The PDUFA 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 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 goals also apply to animal carcinogenicity protocols and final product stability protocols, whereas the statutory section does not.

Under the PDUFA goals, the sponsor may submit a Request for qualifying protocols (see section III., Eligible Protocols and General Information, in the guidance) that should include “a limited number of specific questions about protocol design and scientific and regulatory requirements.”⁴¹ As set out in the PDUFA goals letter, for a protocol to qualify for SPA, the sponsor must have had a “. . . meeting with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.”⁴² For the Requests that FDA accepts (see section VI., FDA Assessment Process, in the guidance), 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.B., Assessment of the SPA Submission, of the guidance.

Biosimilar User Fee Act

In conjunction with the Biosimilar User Fee Act of 2012 (BsUFA), enacted as part of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA),⁴³ FDA agreed to specific performance goals for SPA.^{44,45} These goals were later updated, in conjunction with the Biosimilar User Fee Amendments of 2017. The updated 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 pharmacokinetic and pharmacodynamic studies, protocols for comparative clinical studies that will form the primary basis for demonstrating that there are no clinically meaningful differences between the

⁴⁰ For the purposes of this Appendix, the term *efficacy claim* is defined by its use in the PDUFA goals letter; see note 38, supra. *Subpart E or Subpart H* refers to applications submitted in accordance with 21 CFR 601.40 and 314.500, respectively.

⁴¹ See note 38, supra.

⁴² Ibid.

⁴³ See sections 401–408 of FDASIA, adding sections 744G, 744H, and 744I to the FD&C Act.

⁴⁴ See the BsUFA goals letter titled “Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022” available on the FDA Web site at <https://www.fda.gov/downloads/forindustry/userfees/biosimilaruserfeeactbsufa/ucm521121.pdf>. The program is considered for reauthorization every 5 years; updated goals letters are posted on the FDA website at <https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm>.

⁴⁵ For the statutory definition of *biosimilar biological product*, *biosimilar biological product application*, and definitions of selected terms used in this Appendix, see section 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 <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

proposed biosimilar biological product and the reference product, and protocols for clinical studies 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, in the guidance) 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 Type 2 or Type 3 meeting. Of the Requests that FDA accepts, 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.B., Assessment of the SPA Submission, of the guidance.