Biotechnology Innovation Organization

July 19, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2016-D-1174

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Special Protocol Assessment; Draft Guidance for Industry."

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO is supportive of FDA's efforts to clarify the special protocol assessment (SPA) process for sponsors through the updated draft Special Protocol Assessment guidance, which provides helpful clarification on which protocols are eligible for SPA, as well as other updates and details.

Notwithstanding that the draft guidance is helpful in describing FDA's processes, generally, BIO believes that the final guidance should place more emphasis on, and describe opportunities for, less formal modes of communication (e.g., by telephone or email to allow for timely resolution of any area(s) of disagreement) throughout the SPA process (e.g., during the initial 45-day review period, following receipt of a non-agreement letter, when an amendment may or may not warrant re-submission, during review of a re-submission). Such open and less formal interactions between sponsors and FDA would facilitate reaching agreement in an efficient and effective manner.

Similarly, BIO believes that implementation and consistent application of the final version of the guidance offers an opportunity to focus on the importance of cross-division and within-division consistency in SPA processes. Moreover, the draft guidance and process, in general, would benefit from development of assessment process tools (e.g., checklists, Manual of Policies and Procedures [MaPPs], Standard Operating Policies and Procedures [SOPPs]) which are likely to promote predictability of outcomes.

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To provide clarity to sponsors looking to determine the value of pursuing a SPA in the context of complex design questions, further description of the concepts of "substantial scientific issue" and "essential to determining the safety or efficacy" are crucial. Although some general scenarios are provided in Section IX. "Changes in Or Rescission of Special Protocol Assessment Agreements," they cover a broad range of possibilities that may be open to interpretation, potentially resulting in concerns about reliance on SPA agreements as mitigation against uncertainty in late-stage development as well as potentially dissuading sponsors from pursuing SPA discussions with the agency.

Likewise, it would be helpful for the final version of the guidance to include more procedural details, such as further description of the process for meetings on agreement and rescission of a SPA (e.g., Type A).

Lastly, we note that use of the terms "trial" and "study" is not consistent throughout the draft guidance; likewise, the term "animal trial" is not commonly used in industry. Consistency in utilization of these terms in the final version of the guidance would be helpful.

We provide additional, more specific comments on the draft guidance in the table following this text. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Uros V. Djekic, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

/S/
Cartier Esham, Ph.D.
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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines:29-31	The draft guidance currently states that "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)." The original SPA guidance (published in 2002) stated that FDA would provide comments related to protocol design and implications for labeling: "For example, the centers will provide comments on issues related to protocol design, study conduct and execution, data analysis, and implications for labeling." This aspect connecting protocol design and labeling appears absent in the current text, but represents a critical element of the process, and is a driver behind many sponsors' decision to seek input from FDA through the SPA process. Although eventually addressed later in the document, BIO suggests that this key sentence note that FDA would provide feedback regarding labeling implications of study design.	BIO suggests the following edit to the text of the draft guidance: "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, and implications for labeling).
II. BACKGROUND		

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A. STATUTORY FRAMEWORK		
Lines: 109-113 and 775-781	From line 109 to 113, the draft guidance indicates: "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 about companion diagnostic protocols and device-specific issues to the Center for Devices and Radiological Health (CDRH)." Additionally, starting with line 775, the guidance states: "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 co-development program may affect the type or interpretation of the data collected in the drug trial. 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	BIO would appreciate FDA's clarification and further comment on: 1. The applicability of the device exclusions outlined in lines 109-113 to combination products, particularly to those in which the primary mode of action (PMOA) is a drug or biologic. 2. The SPA review process for drug protocols that include co-development with a device: a. Combination drug/device product in which the drug or biologic elicits the PMOA b. Instances in which drugs rely on a device technology as a critical design element of the study. 3. Eligibility of the usability testing protocol of a combination product for a SPA. 4. CDRH's participation in the SPA process.

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	it negatively affects the ability to interpret the trial results." It is not clear how the device exclusion from SPA (outlined in lines 109-113) applies to combination products. Furthermore, taken together, the text from the two quoted sections of the draft guidance are potentially contradictory. Namely, the draft guidance implies that CDRH participation in the review of a protocol seeking an SPA agreement is limited (lines 109-113); however, the guidance suggests that device alteration could affect critical elements of the trial design, thus, lead to a scenario in which FDA may rescind an SPA agreement (lines 775-781).	
B. USER FEE ACTS		
Lines: 121-127	The draft guidance states: "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.' 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	BIO recommends that the guidance be edited by inserting the following text (identified in blue, underlined): "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.' The SPA also applies for products in which the primary basis of an efficacy claim is based on earlier trials (e.g. oncological phase IIB, rare disease trials). The goals letter further states, 'For products that will be using Subpart E or Subpart H development schemes [for

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	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.'" The wording of the current text does not appear to account for situations (e.g. in oncology, rare disease trials) where there is agreement for registration based on earlier trials e.g., phase IIB.	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.'"
Lines: 139-140, 161-164	The outlined performance goals, "90 percent of SPA reviews within 45 days", appear to apply to both standard and expedited program applications.	BIO suggests that FDA consider a shorter review clock (e.g., 30 days) or, alternatively, prioritize applications that are subject to expedited programs (*e.g.*, breakthrough designation) to ensure review in no more than 45 days
III. ELIGIBLE PROTOCOLS AND GENERAL INFORMATION		
B. GENERAL INFORMATION		
Lines:200-205	The draft guidance states: "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, or BPD Type 2 or Type 3 meeting, respectively. Therefore, before submitting a Request, the sponsor should meet with FDA to discuss the proposed trial and its regulatory context." There are instances in which SPA eligible protocols (e.g. carcinogenicity and stability protocol review) need to be started prior	BIO suggests the following edit/addition to the draft guidance (refer to blue, underlined text): 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, or BPD Type 2 or Type 3 meeting, respectively. However, there may be exceptions to this requirement (e.g. carcinogenicity and stability protocols) which may start prior to an IND submission, end-of phase 1 (EOP1) or EOP2/pre-phase 3 meeting. Therefore, before submitting a Request, the sponsor should meet with FDA to discuss the proposed trial and its regulatory context."

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	to an EOP-2/pre-phase 3 due to the long duration of the studies.	
Lines:239-261	In lines 239-243 the draft guidance states that: "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." Although this is reasonable (and sponsors are responsible to ask relevant protocol related questions), there should be clarification/acknowledgement that FDA will provide feedback on anything that is deemed critical or relevant to a critical design element that may have a regulatory implication. Alternatively, the language could be interpreted to mean that any aspect of a SPA could essentially invalidate the SPA agreement in its entirety, unless it is explicitly agreed to by the division in response to a specific comment or question on that point from the sponsor; this raises concerns about a sponsor's reliance on SPA agreements as	BIO requests from FDA to provide additional language in this section that would clarify and acknowledge that FDA will provide feedback on anything that is deemed critical or relevant to a critical design element that may have a regulatory implication, even if the sponsor did not specifically ask about it.

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	mitigation against uncertainty in late-stage development. For instance, if the primary endpoint is a radiographic one (as in the example provided in the guidance) and in FDA's view the number of radiographs (or some related parameter) is important to assess the primary endpoint for regulatory approval, FDA should comment on such an aspect. This should also be addressed in lines 400-403.	
IV. PROCEDURES FOR SUBMISSION OF A REQUEST		
B. TIMING OF A REQUEST		
Lines:303-304	The draft FDA guidance states: "The protocol, including the statistical analysis plan, should be complete (see section V., Content of a Request and Submission Materials)." Given that FDA's SPA review is intended to focus on critical protocol design features, it is likely that a complete statistical analysis plan may not be required for review and assessment of critical design features of the protocol. In many cases, the high-level description regarding the planned statistical analysis provided in the protocol should be sufficient; FDA should consider this possibility. Statistical analysis plans are separate from the protocol, generally	BIO recommends that FDA consider a draft statistical analysis plan be submitted with the protocol, as it would be difficult to have a final SAP until a final protocol is agreed to by FDA. A final SAP can be submitted after SPA agreement. We recommend the following edit to text of the draft guidance: "The protocol, including ~~the statistical analysis plan~~ a planned statistical analysis, should be complete (see section V., content of a request and submission materials)."

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	provide much greater detail beyond critical protocol design features, and are routinely completed after the protocol is finalized; requiring a completed statistical analysis plan at the time a protocol is submitted for SPA review may cause unnecessary delays to the sponsor.	
V. CONTENT OF A REQUEST AND SUBMISSION MATERIALS		
Lines: 330-337	In Lines 204-213, FDA strongly encourages that Sponsors take part in a pre-SPA Request meeting, while Section V describes the content of a SPA Request and submission materials. Additionally, lines 157-159 of the draft guidance state that the SPA Request "should include a limited number of specific questions about protocol design and scientific and regulatory requirements." The draft guidance also states in lines 330-337: "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 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	To clarify the relationship between the questions asked and advice received at the end-of-phase 2/pre-Phase 3, end-of-phase 1, or BPD Type 2 or Type 3 meeting with FDA and the questions asked and advice received through the SPA process, BIO recommends that FDA consider the following addition to Section V paragraph (lines 330-337) at line 333: "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 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 derived from previous meetings with the agency (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 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

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	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." Taken together, the relationship between the questions asked/advice received at the EOP2/pre-Phase 3, end-of-phase 1, or BPD Type 2 or Type 3 meeting with FDA and the questions asked/advice received through the SPA process do not appear to be clear. In some cases, the division may have already agreed with key concepts of a pivotal study protocol during one of these meetings that was specifically intended for discussing a proposed pivotal study design. Prior discussions and agreements should be referenced in the Request for completeness and facilitation of review.	Drugs and Biologics guidance Web pages for the most current lists of available guidances."
D. CLINICAL TRIAL PROTOCOLS		
Lines: 428-497	Lines 428-434 state: "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	BIO suggests the following edits to address the issue: "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

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	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:" Examples of accompanying submission requirements outlined in bullet points following this paragraph appear to be too prescriptive. If interpreted narrowly, or if read as an exhaustive list, this could lead to a reduction in the possibility for innovative trial designs and unconventional study approaches. Furthermore, some of the listed materials/information requested (e.g. how the trial fits into the overall development of the product, the relevance of the population to be studied to the US population) may have already been known to and discussed with FDA in the course of previous meetings (EOP2, pre-phase 3, etc.). These types of issues should be kept for discussion at a higher level, providing suggestions and guidance, and potentially referring to other technical guidances for details (e.g. ICH E10).	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~~ The accompanying submission materials ~~should~~ may include:"

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Lines: 438-447	The draft guidance states: "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." During initial planning of the study, the sponsor has no certain predictability, neither with regard to the percentage of trial participants which will be enrolled from non-US countries, nor the distribution of trial enrollees with regard to race, sex, duration of disease, concomitant medications, demographic, baseline and other characteristics. These are the types of information needed to justify	Since it is not possible to provide the type of justification outlined in lines 438-447 at the SPA stage, BIO suggests that the draft guidance be edited either by removing and replacing with reference to ICH E5 or by deleting the following text: ~~"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."~~

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	applicability of non-US study results for the US population. Because it is not possible to provide justification at the time the protocol is being reviewed, this request appears to be premature and not a relevant or appropriate consideration at the SPA stage.	
Lines:476-479	The draft guidance states: "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". Refer to issue/rationale provided for lines 303-304.	BIO suggests the following edit to the text in lines 476-479: "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"
Lines: 483–484	The draft guidance states: "Sponsors should fully document and justify complex or novel eligibility criteria, biomarker testing as an entry criterion, endpoints, and analysis plans." Use of the term "fully" in this instance reduces clarity and is open to interpretation. BIO recommends removing the word from the sentence.	BIO suggests the following edit to the text in lines 483–484: "Sponsors should ~~fully~~ document and justify complex or novel eligibility criteria, biomarker testing as an entry criterion, endpoints, and analysis plans."
Lines:511-517	Use of the term "co-development programs" in the text of the draft guidance appears to reference combination products rather than co-development with another	BIO requests that FDA clarify the meaning of term "co-development program" in the text of the guidance as well as include the definition in the glossary.

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	sponsor. It would be helpful to have this term clarified in the document, to avoid confusion.	
VI. FDA ASSESSMENT PROCESS		
A. DETERMINING WHETHER A SUBMISSION IS APPROPRIATE FOR AN SPA		
Lines: 530-532	The draft guidance indicates: "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." Clarifying in the draft guidance that the division will notify the sponsor, in instances in which a submission is inappropriate for a SPA, including the rationale for ineligibility, is a welcome change. This type of communication is of critical importance to the sponsor and should be made as soon as possible after submission of the SPA.	BIO recommends that FDA provide detailed reasons and rationale in cases a SPA is rejected, e.g., citing the reasons listed from line 536-566. 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.~~as soon as practicable, about the determination and the specific reasons for the action (*e.g.*, citing criteria outlined in the guidance). The communication should be made by telephone, email, or fax followed by a letter documenting the communication.
B. ASSESSMENT OF THE SPA SUBMISSION		
Lines: 569-570	Line 428 of the draft guidance states: "The sponsor should submit additional background information, separate from the protocol, that includes all relevant data, assumptions, and information."	Considering that the SPA review will focus on the submitted protocol (Lines 401-402) with the goal to reach concurrence on the adequacy of protocol elements intended to support a statutory finding of safety and efficacy (Lines 241-242), BIO is requesting from FDA additional clarity around the supportive nature of the background information, separate

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	Lines 569-570 of the draft guidance state "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." Taken together, these statements intimate a particular broadness to the scope of a SPA package that should be clarified in the guidance. In many cases, when FDA requests supportive documents (CEC Charters, ICFs, CRFs, etc.) as part of a SPA package, the information within these documents that is necessary for discussion, can be provided without providing final documents. Language in the guidance should not lead to an interpretation that final supportive documents are required to allow for detailed discussion of relevant issues for the protocol or that these documents could be part of the actual SPA agreement. Requiring agreement between FDA and sponsor on supportive documents could prove unfavorable to receiving timely feedback within the process and to initiation of global pivotal studies.	from the protocol. For example, in some cases, documents beyond the protocol have been requested (CEC Charter, ICFs, CRFs, etc.); however, many of these documents are not readily available when the initial protocol is finalized. BIO proposes that the guidance clarify: 1. The acceptability of these documents to be submitted as draft or early versions. 2. That these documents are not formally part of the SPA agreement (i.e. if these documents change during the conduct of the study, a new agreement with FDA is not required, and that if agreement is not secured, changes to these supportive documents do not negate the SPA agreement).
C. REVISIONS DURING FDA ASSESSMENT		
Lines:598-599	FDA draft guidance states: "FDA may communicate with the sponsor regarding	Whenever possible, FDA should communicate to sponsors identified deficiencies/issues prior to issuance of a non-

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	deficiencies or problems with the protocol before issuing an SPA Letter." An interactive review process may be very beneficial and lead to resolution of deficiencies, reducing the number of submission cycles.	agreement letter, so that the sponsor has the opportunity to address the issue as quickly as possible. Therefore, BIO suggests the following edit to the guidance document text: FDA ~~may~~ should communicate with the sponsor regarding deficiencies or problems with the protocol to allow for potential resolution as soon as possible and before issuing an SPA non-agreement Letter.
Lines:600-604	The draft guidance states, "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." A response to an FDA question may require some detail to appropriately and adequately address the question asked; "lengthy or complex response" seems arbitrary and subject to interpretation. Suggest removal of "Lengthy or complex response" from this sentence. Additionally, it is critical that both FDA and sponsor have the same understanding of the SPA Status.	BIO suggests the following edit to FDA for consideration: "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 by telephone, email, or fax followed by a letter and provide the rationale for the action."
C. FDA RESPONSE TO SPONSOR		
Lines:610-625	In lines 610-617, the draft guidance states:	BIO recommends that FDA that the following text be added following line 617:

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	"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. The division will mail the letter to the sponsor, even if the letter was first sent by fax or email." There is a metric where FDA is supposed to grant a meeting or initial feedback within 45 days of the request, but there is no timeline for a determination and/or reaching agreement once initial FDA feedback occurs.	"In most cases, FDA and sponsors should reach agreement on the SPA within 90 days of the initial SPA submission."
E. POTENTIAL DELAY OF FDA RESPONSE		
Lines:623-644	From line 623 to 628, the draft guidance states: "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	BIO has the following recommendations and suggested edits in cases in which external input is critical to FDA's review of a SPA submission: 1. Inform sponsors of a potential advisory committee meeting or consultation as soon as a determination

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	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." BIO is supportive of use of expert consultants, so long as appropriate measures to safeguard confidentiality continue to be in place. It is critical that FDA inform sponsors of a potential advisory committee meeting or consultation, as soon as practicable after determined determination is made, so the sponsor can assess whether to withdraw or move forward with the SPA request. Additionally, FDA should clarify and communicate whether any advisory committee meeting they anticipate convening would be public or closed. In addition, FDA should provide the sponsor with information as to the specific concerns raised or issues prompting FDA to seek outside assistance.	is made, so the sponsor can assess whether to withdraw or move forward with the SPA request. 2. Specify which issue(s) and for which reason(s) are the cause for seeking external expertise. 3. Indicate whether the advisory committee meeting under consideration is public or closed 4. Inform sponsors of anticipated dates for completion of external review/advisory committee meeting. 5. Clarify the process and timelines under "Internal FDA Consultative Review", particularly regarding the number of internal meetings and the overall length of the process. Suggested edits to lines 634-635: "FDA intends to send an SPA Letter to the sponsor ~~within~~ as soon as possible, but no later than, 45 calendar days of the advisory committee meeting or consultant review of the protocol. FDA also will provide an overview of specific issues triggering the perceived need for review by outside experts." Suggested edits to text in lines 641-644: "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~~ as soon as possible, but no later than, 45 calendar days of the last internal meeting."
VII. SPONSOR OPTIONS AFTER RECEIPT OF NONAGREEMENT SPA LETTER		
B. DO NOT INITIATE TRIAL AND RESPOND IN WRITING TO ADDRESS NONAGREEMENT		
Lines: 668-681	The draft guidance states:	BIO suggests the following edit:

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	"Sponsors can respond in writing to amend the protocol or provide additional supporting information to address the reasons for the nonagreement expressed by FDA. This amendment and response will be considered an SPA resubmission, not a new SPA submission under PDUFA V and BsUFA performance goals, and FDA will make every effort to complete the review within 45 days. In some cases, changes to the protocol included in the SPA resubmission may not require the full additional review period. In such situations, FDA will make every effort to complete the review as soon as practicable. Resubmissions should be complete and should address outstanding critical protocol issues. As previously mentioned, an SPA is intended to provide feedback on critical protocol design issues rather than minor protocol details that would be well managed by sponsors. SPA resubmissions should address specific issues identified in the nonagreement SPA Letter and should not address or introduce new issues or items for discussion. Introducing significant new material alters the developmental context and may warrant a meeting to discuss the new information."	In some cases, changes to the protocol included in the SPA resubmission may not require the full additional review period. In such situations, FDA will make every effort to complete the review ~~as soon as practicable~~ in 30 days or less, and will notify the sponsor of the target response date.

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	The 45-day timeline for FDA to review a SPA amendment that has been resubmitted to address receipt of a non-agreement letter seems unreasonably long; In those cases where a SPA resubmission does not require extensive changes and/or supporting information, a review period of 30 days could be reasonable, since this review would focus only on revisions to address previously identified issues and not on the full protocol and on all other supplemental documents. See similar comments below regarding section IX.A.	
C. REQUEST A TYPE A OR BPD TYPE 1 MEETING TO DISCUSS NONAGREEMENT		
Lines: 691-692	The draft guidance states: "If the issues of concern are resolved, SPA agreement could be documented in the meeting minutes." If agreement is finally reached, it would be helpful for sponsors to receive a formal SPA Agreement letter, in addition to the meeting minutes.	For clarity, BIO recommends that a formal SPA Agreement letter be sent from FDA to the sponsor based on the documented agreement in the meeting minutes: "If the issues of concern are resolved, SPA agreement could be documented in the meeting minutes and a formal SPA Agreement letter will be sent subsequently."
IX. CHANGES IN OR RESCISSION OF SPECIAL PROTOCOL ASSESSMENT AGREEMENTS		
A. CHANGES IN AN SPA AGREEMENT		
Lines: 726-729	The draft FDA guidance states: "Under section 505(b)(5)(C) of the FD&C Act, a documented SPA agreement can be modified after testing begins if FDA and	BIO recommends that FDA clarify and expand on: 1. Timeline and process for review of a modified SPA and that FDA consider establishing a 30-calendar day timeline for

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	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." While the guidance allows changes to a SPA Agreement, the specifics surrounding the change process, including but not limited to, timelines for action on an application, type of amendments required, minor versus major changes, potential meetings and communication with FDA, appear to be lacking.	review of modified SPA protocols and issuance of a SPA Modification Agreement Letter. 2. The types of amendments that require formal agreement, including provision of examples, since some amendments can be non-substantial/minor or administrative and not impact key elements of the study design. As stated above, many protocols submitted for SPA are executed globally, and the operational aspects of running an international study can be substantially affected by holding the execution of non-substantial/minor or administrative protocol amendments while awaiting FDA written agreement when the amendments do not impact critical protocol design features. 3. That FDA consider establishing a 30-day review timeline for amended SPA protocols. This is consistent with the comment (Lines 668-681) regarding the proposed 30-day timeline for review of a SPA re-submission following receipt of a non-agreement letter. While the 45-day timeline to review new SPA submissions, including those described in section VI.C resulting from the submission of additional questions or unsolicited revisions to the protocol, seems reasonable, SPA re-submissions following receipt of a nonagreement letter or amendments to a protocol already approved under a SPA

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		should in most cases require less time for review given the specific focus on the revisions only. 4. The types of meetings (e.g., Type A) that are associated with modifications to or changes with a SPA agreement.
B. RESCINDING AN SPA AGREEMENT		
Lines: 769-773	The FDA draft guidance states: "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." While the draft outlines general examples of which changes critical to design parameters may form the basis for rescission, it does not provide clear examples of minor changes that would not require a reassessment of the SPA agreement which should be included in the guidance to help sponsors understand when to seek FDA review prior to making protocol changes.	BIO recommends that FDA outline clear examples of minor changes that would not require a reassessment of the SPA agreement be included in the guidance to help sponsors understand when to seek FDA review prior to making protocol changes. Furthermore, BIO suggests the following edit to the draft guidance (identified in blue, underlined text): 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. Minor changes to protocols (e.g. changes in non-critical conduct of the trial, editorial changes, correction of errors) would not typically impact the SPA agreement. 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.