Biotechnology Innovation Organization

October 13, 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-1703

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product; Draft Guidance for Industry and Food and Drug Administration Staff" (Draft Guidance)."

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.

General Comments

BIO is supportive of FDA's efforts to provide a practical regulatory guide for sponsors engaged in developing a therapeutic product and an accompanying IVD companion diagnostic (i.e. codevelopment).

In general, the Draft Guidance is helpful in describing general principles to guide codevelopment for contemporaneous therapeutic product and device marketing authorizations, regulatory requirements, administrative and clinical trial planning/execution considerations. BIO notes, however, that this draft guidance seems to also refer to the concept of a "complementary" diagnostic in the text. In light of FDA's recent approval of a device that belongs to this this new category, we request that the Agency reference "complementary" devices in the current draft, clarify regulatory requirements for approval of "complementary" diagnostics by issuing guidance devoted to the topic as well as discuss appropriate regulatory principles to compare and contrast to companion diagnostics. Furthermore, the guidance should discuss the principles and criteria for making an assessment to distinguish between companion and complementary diagnostics. This will allow industry to weigh the evidentiary requirements and provide input to the Agency.

Similarly, as we look forward to the future of Precision Medicine, some 'companions' are likely to be medical devices other than in vitro diagnostics (e.g., medical mobile application, wearables, etc.) Either by footnote, as noted for future IDE guidance or in the guidance text, BIO believes that it would be beneficial for FDA to provide recommendations on similarities and differences between IVDs and other types of medical devices.

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BIO notes that the document would benefit if some sections were expanded to provide additional information. Namely, Section G, "Labeling Considerations", should provide greater clarity to and information on labeling considerations for both companion and complementary diagnostics, refer to and potentially expand on other guidance documents that are salient to the subject (e.g. "In Vitro Companion Diagnostic Devices). Although some detail is provided on adverse event reporting in the post-market setting, we think this guidance would benefit from a short discussion of these issues, including references to previous guidances that are relevant to these topics.

Similarly, it would be very helpful if the final guidance addressed some of the more challenging aspects of codevelopment such as multi-variate analyte CDx development, development and review considerations for "test system" IVDs (i.e. comprised of assay, instrument, software). For example, the document could provide, among other considerations, more in-depth validation information for multi-variate companion diagnostics and/or provide reference to other guidance documents (i.e. Next Generation Sequencing-Based In Vitro Diagnostics draft guidance) and its relevance and application in the context of these important and novel technologies.

In the same vein, BIO suggests that the final guidance include a section on how clinical trial outcomes can affect IVD codevelopment and approvals in terms of possible outcomes (e.g. when the IVD does not result in a clear predictive outcome when employed in conjunction with a therapeutic in a clinical trial).

Lastly, BIO believes that harmonization of terminology is of great importance and benefit in this and other guidance documents. Namely, the Biomarkers, Endpoints, and other Tools (BEST) Glossary, issued by FDA and NIH in January 2016, defined several types of biomarkers, including: predictive biomarkers, monitoring biomarkers, pharmacodynamic/response biomarkers, safety biomarkers as well as others. We note that some of the terminology and concepts in the present guidance are not consistent with terms and concepts outlined in the BEST Glossary and strongly recommend harmonization between the two documents.

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,

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Uros V. Djekic, PhD
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

/S/
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/S/
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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines: 131-133 and footnote 6	In lines 131-133, the draft guidance states: "This guidance is also intended to assist FDA staff participating in the review of candidate IVD companion diagnostics[6] or their associated therapeutic products." Footnote 6, refers to 'candidate IVD':" For the purposes of this document, the term *candidate IVD companion diagnostic* is used to refer to an IVD that the sponsor(s) believes is necessary to support the safe and effective use of the corresponding therapeutic product and is the version of the IVD that will be reviewed by FDA in a premarket submission." However, "version to be reviewed by FDA" does not align to later text in the document where, for example, cross-over studies may be performed and 'pre-cursor' kits may be used.	BIO recommends the following edit (underlined text in blue) to footnote 6: "For the purposes of this document, the term *candidate IVD companion diagnostic* is used to refer to an IVD that the sponsor(s) believes is necessary to support the safe and effective use of the corresponding therapeutic product and is the pre-cursor IVD or the version of the IVD that will be reviewed by FDA in a premarket submission."
II. BACKGROUND		
Lines: 162-165	The draft guidance text states: "Since that time, interest in identifying biomarkers that could be used as biological targets for therapeutic product development, prognostic indicators, or predictors of	BIO suggests the following deletion and addition to the text: "Since that time, interest in identifying biomarkers that could be used as ~~biological targets for~~ biological tools for patient enrichment in therapeutic product development as

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	patient response to specific therapeutic products has grown tremendously. There are now numerous examples of therapeutic products with an accompanying IVD companion diagnostic" The term "biological targets" for therapeutic product development does not convey the utility of biomarker based diagnostics.	well as pharmacodynamic markers for assisting dose selection, prognostic indicators, or predictors of patient response to specific therapeutic products has grown tremendously. There are now numerous examples of therapeutic products with an accompanying IVD companion diagnostic"
Lines:143-146	The draft guidance currently states: "Although this guidance focuses on IVD companion diagnostics, many of the principles discussed may also be relevant to the codevelopment of therapeutic products with IVDs that do not meet the definition of an IVD companion diagnostic but that are nonetheless beneficial for therapeutic product development or clinical decision making." This statement appears to be referring to a "complementary" diagnostic as described in other documentation. BIO suggests being consistent in naming. Therefore, we recommend that FDA specify this in this guidance document, as well as provide additional guidance where complementary and companion diagnostics differ (e.g. Assessment of Companion vs Complementary, Labeling).	BIO suggests the following edit to the text of the draft guidance: "Although this guidance focuses on IVD companion diagnostics, many of the principles discussed may also be relevant to the codevelopment of therapeutic products with IVDs that do not meet the definition of an IVD companion diagnostic but that are nonetheless beneficial for therapeutic product development or clinical decision making, (i.e., Complementary Diagnostic or other clinically informative test)." Additionally, BIO recommends that the term "complementary" diagnostic be added to the BEST glossary to facilitate consistency and harmonization.

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	In addition, for purposes of harmonization of terminology, we recommend including the "complementary" diagnostics in the Biomarkers, Endpoints, and other Tools (BEST) Glossary.	
III. PRINCIPLES OF THE CODEVELOPMENT PROCESS		
Lines: 220-223	The draft guidance indicates:" Whenever appropriate, both sponsors should be present at meetings with the review centers responsible for the therapeutic product and the IVD, so that each sponsor is clearly informed about the Agency's thinking on both products. The term 'both' refers to one medical device and one drug sponsor. There is a possibility that multiple pharmaceutical companies or multiple device companies may be engaged in the co-development.	BIO suggests the following edits: "Whenever appropriate, ~~both~~ medical device and pharmaceutical sponsors should be present at meetings with the review centers responsible for the therapeutic product and the IVD, so that each sponsor is clearly informed about the Agency's thinking on both products."
Lines: 216-223	The draft guidance states: "Because many novel or complex issues can be raised by including an investigational IVD in therapeutic product clinical trial design, FDA strongly recommends that the sponsors of both the therapeutic product and the IVD meet with the appropriate FDA review centers prior to launching a trial intended to advance the development of the therapeutic product and the IVD companion diagnostic. Whenever	BIO recommends that the Agency consider developing and implementing a process for integrating engagement with different centers within FDA to help increase efficiency of the codevelopment process.

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	appropriate, both sponsors should be present at meetings with the review centers responsible for the therapeutic product and the IVD, so that each sponsor is clearly informed about the Agency's thinking on both products."	
A. GENERAL		
Lines: 227-229	The text in the draft indicates: "Ideally, the need for an IVD companion diagnostic would be identified early in the course of therapeutic product development so that an analytically validated test can be prospectively incorporated into the design of the therapeutic product clinical trials." However, the expectations for analytical demonstration of accuracy and reliability are unclear for prototype biomarker tests (CTAs), which are distinct from the drug concentration assays described in the bioanalytical method validation guidance.	BIO suggests that FDA clarify the expectations for analytical demonstration of accuracy and reliability for prototype biomarker tests (CTAs), which are distinct from the drug concentration assays and described in the bioanalytical method validation guidance.
Lines: 249-254	The draft guidance indicates: "Although codevelopment as a process does not require simultaneous development of the IVD companion diagnostic and the therapeutic product from beginning to end, the availability of an IVD with "market-ready" analytical performance characteristics (i.e., a test that is completely specified with complete analytical validation and meets the	BIO suggests that FDA include references to later sections of the draft guidance, such as, Section 3 "IVD Bridging Strategies." A cross-reference would be helpful here.

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	therapeutic product sponsor's expectations for performance) is highly recommended at the time of initiation of clinical trial(s) intended to support approval of the therapeutic product." The guidance includes other strategies if market ready test is not available at time of clinical trial initiation. This section does not indicate other possibilities.	
Lines: 265-269	The draft guidance indicates: "Sponsors with IVD-related questions may use the Pre-Submission (Pre-Sub) program to seek feedback from CDRH or CBER at any time in the codevelopment process. Similarly, therapeutic product development questions may be directed to the appropriate therapeutic product review center (CDER or CBER). In either scenario, the review centers will typically consult one another to ensure coordinated review." It is not entirely clear what is meant by "typically". Furthermore, the word appears to imply that there are scenarios in which product centers may or may not consult with each other in the process of codevelopment.	BIO suggests that FDA expand or clarify the meaning of the word "typically" and consider developing and implementing a process for integrating engagement with different centers within FDA to help increase efficiency of the codevelopment process. Refer to similar comment to lines 216-233.
B. ***REGULATION OF INVESTIGATIONAL IVDS AND THERAPEUTIC PRODUCTS***		

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Lines: 249-254	The draft guidance indicates: "Although codevelopment as a process does not require simultaneous development of the IVD companion diagnostic and the therapeutic product from beginning to end, the availability of an IVD with "market-ready" analytical performance characteristics (i.e., a test that is completely specified with complete analytical validation and meets the therapeutic product sponsor's expectations for performance) is highly recommended at the time of initiation of clinical trial(s) intended to support approval of the therapeutic product." The guidance includes other strategies if market ready test is not available at time of clinical trial initiation. This section does not indicate other possibilities.	BIO suggests that FDA include references to later sections of the draft guidance, such as, Section 3 "IVD Bridging Strategies." A cross-reference would be helpful here.
1. RISK ASSESSMENT AND IDE REQUIREMENTS		
Lines: 307-313	The draft guidance states: "…then the abbreviated requirements described in 21 CFR 812.2(b) apply, including the requirement to provide to the reviewing institutional review board (IRB) a brief explanation of why the IVD is not significant risk. If the IRB disagrees with the sponsor and concludes that the investigation involves a significant risk device, the IRB is required to notify the	BIO suggests that FDA provide clarification of this risk level which will aid sponsors in informing the order of activities, for example, obtain a CDRH or CBER opinion on risk level/need for IDE prior to submission to IRB or go directly to IRB. Specific examples of "non-significant risk" and "significant risk" determinations would be very useful.

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	investigator and where appropriate, the sponsor. Sponsors can also seek a risk determination from CDRH or CBER through the Pre-Sub program. Note that FDA's determination will supersede that of the sponsor or IRB." Risk calculation should be defined so that sponsors understand key differences between significant and non-significant risks devices.	
Lines: 312-313	FDA draft guidance states: "Note that FDA's determination will supersede that of the sponsor or IRB."	BIO recommends clarification of the text and proposes the following addition: Note that FDA's determination of the IVD being a significant risk device or not will supersede that of the sponsor or IRB.
Lines: 349-350	The current draft guidance text reads:" "Another criterion for exemption under 21 CFR 812.2(c)(3) is that the testing must not require invasive sampling that presents significant risk to the subject." Although the draft guidance refers to 21 CFR 812.3(k) in footnote 33 (line 355) for a definition of noninvasive sampling, it would be helpful if the guidance provided specific examples e.g., PET imaging.	BIO suggests that the specific examples of invasive sampling be included in the final guidance.
2. SUBMISSION OF INVESTIGATIONAL IVD INFORMATION RELATED TO INVESTIGATIONAL DRUGS OR BIOLOGICAL PRODUCTS		

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Lines: 459-461	The current text of the draft guidance indicates that: "If the analytical validity is critical to determining whether the clinical trial can meet its stated objectives, lack of such data could be a reason to place the IND on clinical hold". The guidance would benefit from inclusion of specific examples.	BIO recommends that FDA include specific examples for clarity.
Lines: 471-474	The draft guidance states:" Note that all data related to investigational IVDs (including IDE-exempt or non-significant risk IVDs) submitted in an IND may be reviewed by the relevant IVD review center at the request of the appropriate therapeutic product review center if it determines that such review is necessary and requests an intercenter consult." Sharing information regarding inter-center consultation requests and communicating this information to drug sponsors will aid drug and IVD manufacturer communications with CDRH and will be beneficial for planning purposes. The guidance document should include provisions and procedures for communicating to the drug sponsor intercenter consultation requests and the purpose of these request.	BIO suggests that the guidance document include provisions for communicating to drug sponsors when an intercenter consultation has been requested as well as the purpose of such request.
3. IDE APPLICATIONS FOR INVESTIGATIONAL IVDS IN CODEVELOPMENT TRIALS		

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Lines: 500-501	The last bullet in the paragraph outlining the types of information typically requested in an IDE states: "The clinical trial protocol, either through direct submission or by reference to the appropriate IND". However, the CDx program may be early where acceptable early forms of the approved clinical trial protocol would be a clinical trial protocol synopsis. What appears important for the IDE is the critical protocol descriptions on how the IVD is described and used.	BIO recommends the following edit to the draft guidance text: "The clinical trial protocol, clinical trial synopsis, or descriptions how the IVD is described and used, either through direct submission or by reference to the appropriate IND"
C. PLANNING AHEAD FOR IVD VALIDATION IN POTENTIAL CODEVELOPMENT PROGRAMS		
1. EXPECTATION FOR ANALYTICAL VALIDATION PRIOR TO INVESTIGATIONAL IVD USE IN THERAPEUTIC PRODUCT TRIALS		
Lines: 507-530	Section C.1. "Expectation for Analytical Validation Prior to Investigational IVD Use in Therapeutic Product Trials", may be interpreted to mean that FDA requires a final analytical validation module to be complete before starting a trial.	BIO suggests that FDA clarifies the level of analytical validation required prior to starting a non-registrational clinical trial (e.g. using the assay to select patients for enrollment into a Phase 1 expansion cohort).
Lines: 518-521	The current draft guidance text reads: "When a significant risk investigational IVD is to be used in a clinical trial for a therapeutic product, an evaluation to demonstrate that the IVD is sufficiently analytically robust, particularly around the	BIO recommends that the subsequent version of the guidance:

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	test's clinical decision point(s),where necessary, should be conducted prior to using the IVD in the therapeutic product clinical trial." From the text, it is not clear whether the evaluation should always be done prior to use of the IVD in the therapeutic clinical trial; there may be instances where this is not possible. Additionally, the term "sufficiently robust" should be discussed in the context of whether there may be any variations in criteria across technologies.	1. Discusses whether there may be any variations in criteria between technologies to meet "sufficiently robust" 2. Clarifies whether evaluation should always be done prior to use of the IVD in the therapeutic clinical trial and discusses any instances where this may not be possible. Additionally, BIO proposes the following edit (blue, underlined text) to the current draft guidance text: "When a significant risk investigational IVD is to be used in a clinical trial for a therapeutic product, an evaluation to demonstrate that the IVD is sufficiently analytically robust, particularly around the test's clinical decision point(s), should preferably be conducted prior to using the IVD in the therapeutic product clinical trial."
3. IVD PROTOTYPES IN EARLY-PHASE THERAPEUTIC PRODUCT CLINICAL TRIALS		
Lines: 554-555	The draft guidance states: "A CTA used in the early-phase clinical trials, or a new design of the CTA, is often further developed as the candidate IVD companion diagnostic if the early-phase clinical trials of the therapeutic product yield promising results." Early-phase clinical trials include trials to determine safety, tolerability, proof of biology and proof of concept. From the	BIO recommends that FDA clarify whether "early-phase clinical trials" in the draft guidance include trials to determine safety, tolerability, proof of biology and proof of concept (barring pivotal phase III trials). Additionally, BIO recommends that the text be rephrased to: "A CTA used in the early-phase clinical trials, or a new design of the CTA, is often further developed as the candidate IVD companion diagnostic if the early-phase clinical trials of the therapeutic product ~~yield promising~~

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	current text, it is unclear whether all of the sated trials are encompassed. Additionally, the phrase "promising results" does not specify if biomarker use is necessary for clinical decision making.	~~results~~ demonstrate the utility of the biomarker test for decision-making."
Lines: 565-567	The current draft guidance reads: "To assure that results are not affected by site of testing, FDA recommends that the sponsor evaluate comparability of test results among potential sites prior to initiating trial testing at those sites. This can be achieved through a site qualification scheme or other mechanism." The draft guidance neither provides information on the parameters that should be considered by sponsors to demonstrate comparability of test results at multiple sites nor does it explain the features of a site qualification scheme.	BIO recommends that FDA expand and clarify the current draft guidance to include information on parameters that should be considered by sponsors to demonstrate comparability of test results at multiple sites as well as explain the features of a site qualification scheme (e.g. adding footnotes to list key test performance as well as essential site qualification parameters).
5. PRESCREENING FOR ELIGIBILITY FOR THERAPEUTIC PRODUCT CLINICAL TRIALS		
Lines: 625-631	The current text of the draft guidance indicates that: "Prescreening can create particular problems for sponsors attempting to evaluate a novel therapeutic product's safety and efficacy in an intended population, as well as for the IVD manufacturer attempting to provide an unbiased demonstration of performance of the IVD companion diagnostic.	BIO would appreciate FDA's clarification and further comment on: 1. Approaches that might be taken to characterize performance of a diagnostic when pre-screening is unavoidable. Local testing is standard of care in many institutions, especially NGS in the oncology field.

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	Prescreening may result in a biased clinical trial population that does not represent the population that would be selected by the IVD companion diagnostic in real-world testing. Thus, planning to enroll subjects into a trial based on confirmation of a local test result is strongly discouraged." Although mentioned later in the guidance (e.g. lines 641-644), unavoidable pre-screening and potential approaches to address issues that arise should be addressed greater depth in the document especially in instances in which local testing is the standard of care (e.g. NGS). With exception to one example to avoid potential bias from prescreening (lines 633-639), there are no other suggestions. Furthermore, the provided example is difficult to execute, particularly in low prevalence diseases where tissue availability is minimal or too valuable to spare.	2. Potential approaches to resolve situations in which a study population may be skewed (e.g. specific examples) 3. Resolving selection bias
Lines: 630-631	FDA draft guidance states: "Thus, planning to enroll subjects into a trial based on confirmation of a local test result is strongly discouraged."	BIO suggests the following revision: "Thus, planning to enroll subjects into a trial based on confirmation of a local test result is ~~strongly~~ discouraged, but may be done where there is reasonable assurance that the local test is reliable.

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	However, local testing does occur, and the revised language provides guidance when a local test is used.	
6. PREANALYTIC PROCEDURES AND TESTING PROTOCOLS		
D. THERAPEUTIC PRODUCT CLINICAL TRIAL DESIGN CONSIDERATIONS		
1. GENERAL CONSIDERATIONS FOR EARLY THERAPEUTIC PRODUCT DEVELOPMENT		
2. GENERAL CONSIDERATIONS FOR LATE THERAPEUTIC PRODUCT DEVELOPMENT		
Lines: 809-810	The draft guidance states: "FDA does not object to this approach categorically because it may be appropriate in some situations (see also Section III.D.3 of this guidance). A modification of the design, however, could stratify by assay cutoff." It is unclear which situation described in Section III.D.3 is alluded to as potentially being of value. Additionally, It would be helpful if FDA would expand on stratification by assay cutoff trial design.	BIO requests that FDA clarify/specify the situation that is referenced in this text and in Section III.D.3. as well as that an additional figure (e.g. 1C) be included in the final guidance what a stratification by assay cutoff trial design would look like.
3. PROGNOSTIC AND PREDICTIVE MARKERS		
Lines: 825-845	Although limited information is provided in lines 792-796 and in footnote 64, this section would benefit from discussion and clarity with regard to addressing scenarios where a marker is both predictive and prognostic.	BIO recommends that this section of the draft guidance be expanded and clarify scenarios where a marker is both predictive and prognostic (e.g., what would be required in terms of clinical studies to be conducted as evidence?) and reference other sections of the guidance salient to the topic (e.g. lines 792-796 and footnote 64)

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4. PROSPECTIVE-RETROSPECTIVE APPROACHES		
Lines: 825-845 and Figure 1a	Clinical trial design for prognostic and predictive markers are typically more complex and should be addressed in the guidance to provide sponsors insight into FDA's current thinking. The trial designs presented in the guidance are very basic and may not be representative of the majority of trials currently being designed.	BIO suggests that Section D.2. (General Considerations for Late Therapeutic Product Development) be amended to include more permutations of trial design to deliver predictive claims, i.e. Positive predictive, Negative Predictive, studies with Co-primary endpoints and high ranked secondary endpoints related to marker status.
Lines: 838-842	The draft guidance text reads: "In clinical trial designs depicted in Figure 1 above, for a continuous marker for which a firm cutoff has not been determined, there could be randomization at varying degrees of marker positivity, or less formally, there could be a post-hoc analysis of the treatment effect at a range of cutoff values." The use of the word "continuous" in this context is not clear.	BIO would appreciate further explanation/clarification of its use in this context (e.g. in a footnote).
Lines: 881-882	Currently, the draft guidance states that: "The statistical analysis plan should include a plan to address robustness (sensitivity) of study conclusions to missing test results." The current text should be clarified to avoid confusion between sensitivity being discussed here as opposed to clinical	BIO suggests the following edit to the draft guidance text: "The statistical analysis plan should include a plan to address robustness (sensitivity analysis) of study conclusions to missing test results."

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	sensitivity, analytical sensitivity, and relationship to robustness.	
Lines: 886-889	The draft guidance states: "The impact of missing data on clinical performance (e.g., hazard ratio in marker-defined subset) should be analyzed. To evaluate the sensitivity of clinical performance to missing data, a model 888 may be used to impute missing test results based on the variables described above." The guidance would benefit from further elaboration and clarity on the evaluation of sensitivity of clinical performance to missing data with a model to impute missing data.	BIO suggests that FDA expand and clarify on the evaluation of sensitivity of clinical performance to missing data with a model to impute missing data (e.g. provide examples).
5. CONSIDERATIONS FOR IDENTIFYING INTENDED POPULATIONS		
Lines: 979-983	Currently, the draft guidance states: "Therefore, it is very important that the cutoff be specified prior to using the test in a clinical trial. In most cases, inclusion of some subjects below the cutoff can be useful to refine the cutoff (e.g., when subjects with values below the cutoff have some likelihood of achieving the treatment effect of the therapeutic product), even if the primary analysis includes only subjects above the cutoff."	BIO would appreciate FDA's clarification and further comment on: 1. Please elaborate on cutoff determination including scenarios that involve stratification. 2. Please provide guidance on how a joint meeting could be used to establish the need for a refined cutoff through CDER and CDRH.

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	The process for specifying the cutoff is not entirely clear from the text in the draft guidance.	
Lines: 983-987	The current draft guidance states: "It is recognized that the optimal cutoff may be unknown before clinical data are available in a reasonable number of subjects. In such cases, another clinical trial confirming the results with the new cutoff, or an adaptive design that allows intra-trial cutoff alterations, would be necessary to ensure that positive results are not due to bias or chance." However, if the described approach is adopted, analytical performance validity may not be optimal, potentially requiring additional analytical validation studies post marketing.	BIO would appreciate FDA's clarification and further comment with regard adoption of the proposed approach for confirmation of results with a new cutoff on analytical performance validity (e.g. if it is not optimal, would additional analytical validation studies be needed post marketing?)
E. THERAPEUTIC PRODUCT CLINICAL TRIAL DESIGN CONSIDERATIONSCONSIDERATIONS FOR IVD DEVELOPMENT IN LATE THERAPEUTIC PRODUCT DEVELOPMENT		
Lines: 993-995	Currently, the draft guidance reads: "Therefore, it is important that the investigational IVD(s) used in these trials is completely specified and that analytical validation is complete and meets the therapeutic product sponsor's expectations for performance." 'Completely' is a subjective adjective that can be interpreted multiple ways.	BIO recommends the following edits to the draft guidance text: "Therefore, it is important that the investigational IVD(s) used in these trials is ~~completely~~ specified and that analytical validation ~~is complete and~~ meets the therapeutic product sponsor's expectations for performance."

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	Importance for this sentence is that the IVD is specified and analytically validated.	
Lines: 1022-1023	The draft guidance states: "The new IVD design may be established with a set of procured clinical samples similar to the subjects in the trial or samples from earlier investigational trials." It would be very helpful to expand and describe in the guidance a scenario which involves multiple cutoffs in the clinical trial design (e.g. line 840-842). In clinical trial designs depicted in Figure 1 (lines 775-782) above, for a continuous marker for which a firm cutoff has not been determined, there could be randomization at varying degrees of marker positivity; or less formally, there could be a post-hoc analysis of the treatment effect at a range of cutoff values.	BIO suggests that the draft guidance expand on test vs. validation sets and to include discussion on FDAs advice when multiple cutoffs are planned.
2. EFFECT OF CHANGES TO THE TEST DESIGN		
Lines: 1036-1038	Currently, the draft guidance states: "If a revised IVD is implemented, generally a bridging study (see Section III.E.3.) would be needed to demonstrate high concordance between the two IVDs." The guidance document does not appear to go into too much detail nor provide additional guiding discussion on what	BIO recommends that the guidance document provide additional information and discussion on what "high concordance" could mean in different technology, disease, and therapeutic contexts.

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	"high concordance" could mean in different technology, disease, and therapeutic contexts.	
3. IVD BRIDGING STUDIES		
Line: 1049	The draft guidance states: "…to show that results with the candidate IVD companion diagnostic are very similar to those with the CTA. " The text does not speak to the criteria for determining "similarity".	BIO recommends that the guidance document provide criteria for how "similar" is determined.
Lines: 1054-1058	The current draft guidance notes: "The ability of the candidate IVD companion diagnostic to predict the efficacy of the therapeutic product can be supported indirectly by high analytical concordance with the CTA on a large number of representative samples" It is not entirely clear what is meant by "large number" of representative samples.	BIO recommends that FDA clarify and expand on what is meant by a "large number" of representative samples as well as provide guidance on acceptable statistical approaches to define this large number.
Lines: 1057-1058, 1075-1076 and 1078-1084	In lines 1057-1058, 1075-1076 and 1078-1084 the draft guidance states: "…including samples from subjects excluded from the trial because they were marker-negative by the CTA." "FDA recognizes, however, that there are many reasons why all the samples tested with the CTA may not be available for retesting"	BIO suggests that FDA include general guidance for appropriate numbers of marker negative samples that should be re-tested in bridging studies.

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	"If only a subset of samples is retested, the sponsor should ensure that the characteristics of the subset adequately reflect the characteristics that affect test performance (e.g., tumor size, histology, melanin content, necrotic tissue, resected tissue versus core needle biopsy) and that the characteristics of the subjects that may affect therapeutic product efficacy (e.g., patient demographics, stage of disease, stratification factors) are proportionally preserved in the retest sample set when compared to the samples in the original set.", respectively. Taken together, the guidance indicates that for bridging studies, samples from subjects excluded due to marker negativity should be included in bridging. The guidance goes on to describe subset characteristics for which to ensure proportionality. However, there is no recommendation on appropriate numbers of marker negative specimens (some trials may pre-screen and reject very large percentages of individuals as marker negative).	
Lines: 1063-1065	"The ideal bridging study is one in which all samples tested with the trial test are retested with the candidate IVD companion diagnostic and valid test	BIO would appreciate FDA's clarification and further comment on which type of substitute tissues could be used for a bridging study.

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	results are obtained and used to assess comparative performance." In some older studies samples are not available or the sample stability is past or baseline sample vs. study sample may be required.	
F. PLANNING FOR CONTEMPORANEOUS MARKETING AUTHORIZATIONS		
1. COORDINATING REVIEW TIMELINES		
Lines: 1174-1175	The FDA draft guidance currently indicates: "When implemented appropriately, the modular PMA approach allows the applicant to resolve deficiencies identified by the IVD review center earlier in the review process, making the final review more likely to be completed concurrently with review of the therapeutic product." This sentence implies that the IVD sponsor will always have deficiencies needed to be resolved.	BIO suggests the following changes: "When implemented appropriately, the modular PMA approach allows for additional review time and, if needed, ~~the applicant to resolve~~ resolution of deficiencies identified by the IVD review center earlier in the review process, making the final review more likely to be completed concurrently with review of the therapeutic product."
Lines: 1207-1208	The current text reads: "There are two types of inspections that can occur in the context of a PMA submission: bioresearch monitoring (BIMO) inspections and manufacturing inspections."	BIO suggests the following edits to enhance clarity between the different types of inspections: "There are two types of inspections that can occur in the context of a PMA submission: (1) bioresearch monitoring (BIMO) inspections of IVD testing sites and (2) IVD manufacturing site inspections."

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	It would be beneficial if more clarity between the two types of inspections were more apparent in the text.	
Lines: 1217-1220	The draft reads: "Nonetheless, the IVD manufacturer should still submit information about the clinical testing sites, including clinical line data, to the PMA for BIMO review. FDA will coordinate review and inspections of clinical sites, as needed, among the appropriate review center(s)." This section of the guidance indicates IVD manufacturers should submit information about various items for BIMO review. It would be helpful to reference Section F,1.v., "Letters of Authorization" in case required information is held by the drug company.	BIO suggests that Section F.1.iii. (Bioresearch Monitoring Inspections and Manufacturing Inspections), reference Section F.1.v. (Letters of Authorization) in case required information is held by the drug company.
3. SHIPMENT AND VERIFICATION OF AN IVD COMPANION DIAGNOSTIC PRIOR TO MARKETING AUTHORIZATION		
Lines: 1331-1336	The current draft guidance text states: "In most cases, a laboratory will need time to set up and verify a new IVD before it can be used for routine clinical testing." The guidance would benefit from differentiation and clarification between laboratories that were and were not involved in the clinical studies.	BIO suggests that the next iteration of the document include differentiation of laboratories that were involved in the clinical study from those that were not and indicate similarities and differences with regard to shipment and verification between the two (e.g. What if anything is the laboratory required to do in the way of documentation if the laboratory was not originally included as one of the sites for the clinical study? Would the laboratory not included in the

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		clinical study be subject to a FDA inspection if the site conducted verification of the IUO prior to marketing?)
G. LABELING CONSIDERATIONS		
Lines:1364-1415	The current FDA draft guidance offers few details regarding labeling of a therapeutic product/IVD companion diagnostic pair in Section G ("Labeling Considerations", and refers to the labeling included in the "In Vitro Companion Diagnostic Devices" guidance for more information. While this guidance does specify that the CDx label will include the drug name in the intended use statement, it provides little guidance on specific labeling for the therapeutic product. Furthermore, it does not provide information on labeling for complementary diagnostics, biosimilars, and generics. Finally, it provides no information on any specific promotional considerations for drug and CDx, and does not point to the location of that information if in another guidance document.	BIO requests from FDA to provide additional language in Section G, Labeling Considerations, that would clarify and expand on: 1. Information on therapeutic product label with regard to companion diagnostic versus complementary diagnostics 2. Labeling of biosimilar and generic products in instances in which the innovator has a CDx. 3. Specific promotional considerations for drug and CDx
4. CLAIMS FOR IVD COMPANION DIAGNOSTICS BASED ON USE IN TRIAL		
Lines: 1373-1415	In this section, the current draft guidance introduces the concept of labeling for a "selection" claim, as opposed to a "predictive" claim; while the Biomarkers, Endpoints, and other Tools (BEST) Glossary, released by FDA in 2016,	BIO recommends that the wording in the present guidance be harmonized with the recommended BEST wording (and vice versa, acknowledging that this may require concurrent revision of the BEST Glossary as well).

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	defines predictive biomarkers, there is no mention of the concept of a selection biomarker that is not a predictive biomarker. Furthermore, the document also seems to define "monitoring" claims that differ from the BEST definition of a monitoring biomarker (the guidance seems to use "monitoring" to encompass what BEST defines as three (3) separate categories of biomarkers: monitoring/response, pharmacodynamic, and safety biomarkers). BIO recommends harmonization terminology between the BEST Glossary and this draft guidance.	
APPENDIX 1: CRITICAL POINTS OF THE CODEVELOPMENT PROCESS		
Lines: 1438-1439 (Figure A1)	Figure A1 in Appendix 1: Critical Points of the Codevelopment Process is very useful. However, it would be very beneficial if it were amended to also show the early submission of the preferred Modular PMA that then extends to the expected co-approval. If possible, the BIMO and Manufacturing site inspections should be added to the timeline occurring in the early part of the PMA review.	BIO suggests including the following information into a revised version of Figure A1: 1. Submission of the preferred modular PMA 2. BIMO and manufacturing site inspections

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Lines: 1457-1459	The draft guidance indicates: "If the IVD sponsor has not initiated interaction with the appropriate IVD review center by the time the therapeutic product sponsor holds key milestone meetings, FDA strongly recommends that the IVD sponsor do so at that time." This statement is not clear.	BIO recommends that FDA clarify and/or expand.
APPENDIX 2: SUBJECT SPECIMEN HANDLING CONSIDERATIONS		
Lines: 1560-1573	The draft guidance indicates that: "When specimens are stored for later use, the sponsor should consider the stability of the analyte(s) of interest. Some analytes are labile and require special handling or storage conditions, while others are more stable and can withstand a variety of handling and storage conditions. To the degree that the stability of the analyte in the matrix of choice is not well-defined, the sponsor should perform a thorough assessment of the anticipated handling and storage conditions to ensure that conditions are selected that will allow later informative use of the samples. The draft guidance, however, does not describe or provide information with regard to scenarios in which stability of stored samples could become an issue and	BIO suggests that this section include a discussion and information with regard to scenarios in which stability of stored samples could be expected to become an issue, potential solutions for resolution, including examples of successful bridging studies.

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	potential solutions for resolution, including examples of successful bridging studies.	
Lines: 1592	The draft guidance bullet point: "IRB information" would benefit from expansion and clarification in the text.	BIO suggests that additional information be provided with regard to IRB information, including addressing: 1. What are the expectations of IRBs for testing sites? (e.g. Does FDA expect the CDx sponsor to consult an independent IRB prior to initiating testing of clinical trial samples? Or are the individual clinical site IRBs that review the clinical trial protocol, which describes the intent to test the samples, sufficient?) 2. Does FDA expect that there be a central IRB? Additionally, information should be provided with regard to expectations for each term that is commonly used for both drug and diagnostic such as analytical studies, ICD, investigational plan, investigator role, protocol, etc.
Line: 1594	Currently the bullet-point reads: "Line Listings (stratified by site and then subject)." Suggest clarification that these line listings refer to the IVD.	BIO recommends the following change to the text: "Line Listings for the device (stratified by site and then subject)."