1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

RE: Comments Regarding the Draft Guidance on In Vitro Companion Diagnostic Devices; FDA-2011-D-0215

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to submit comments regarding the Food and Drug Administration's ("FDA's") draft guidance document entitled *In Vitro Companion Diagnostic Devices* ("the Draft Guidance").[1] BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United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 biotechnologies, thereby expanding the boundaries of science to benefit society by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. Specifically related to products that qualify as *in vitro* companion diagnostic devices (IVCDDs) under the Draft Guidance, BIO represents companies throughout the continuum of personalized medicine, including those that develop both therapeutic and companion diagnostic products. For this reason, BIO welcomes the opportunity to work with the FDA on the development of policy in this area.

[1] Draft Guidance for Industry and Food and Drug Administration Staff, In Vitro Companion Diagnostic Devices (July 14, 2011).

I. The Contemporaneous Development Requirement Set Forth in the Draft Guidance Is Not Reflective of the Typical Path for Development of IVCDDs

BIO is concerned that the approach to contemporaneous development in the Draft Guidance fails to account for the reality of the typical development pathway for IVCDDs. According to the Draft Guidance, FDA believes that sponsors will typically co-develop the therapeutic and IVCDD products, and seek approval in a synchronous, contemporaneous manner. Although BIO agrees that, in some situations, contemporaneous approval may be possible and optimal, BIO is concerned that FDA's approach will exclude the situations where contemporaneous co-development is not possible or has not occurred for other reasons, which currently may reflect the more prevalent development pathway in current practice. BIO believes the Agency should prioritize addressing the specific scenarios whereby contemporaneous co-development is not possible or has not occurred for other reasons. In the typical course of development and partnering between the therapeutic and IVCDD product, the need for an IVCDD may not arise until late in development of the therapeutic product. For example, the development of IVCDDs may not be desirable or realistic until it is understood whether the clinical safety and efficacy of the therapeutic is sufficiently demonstrated. Other situations where contemporaneous development may not be feasible include 1) identification of a biomarker late in the development of the therapeutic; 2) identification of a biomarker after approval of the therapeutic product; 3) subsequent clinical validation of the biomarker in phase 2 or phase 3 with a confirmatory study to demonstrate clinical utility post-approval using prospective-retrospective analysis; and 4) a delay in demonstration of the analytical validity of the assay.

BIO believes that FDA should revise the Draft Guidance to either 1) acknowledge that, although contemporaneous approval may be optimal in some situations, the Agency recognizes that the typical course of development may be asynchronous and the evidentiary standards for that pathway will be addressed in separate guidance; or 2) provide guidance for the data requirements in these situations where the need for the IVCDD is not recognized until a point late in the development cycle of the therapeutic that is not conducive to synchronous development and approval of an IVCDD.

Where uncertainty exists whether the *in vitro* diagnostic is needed, FDA should adopt a general policy that it will not delay approval of a therapeutic product when the *in vitro* diagnostic is not immediately ready at the same time. Additionally, FDA should allow *in vitro* diagnostic development and regulatory review to conclude after approval of the therapeutic product, pursuant to a post-market commitment of the therapeutic product sponsor, unless to do otherwise would be clearly inconsistent with ensuring public health. FDA's approach to addressing the pathway for asynchronously developed products must provide adequate flexibility to account for the practical reality of the typical course of development of these products. Specifically, in some cases it would be in the public health interest to approve the therapeutic product when the IVCDD is still investigational or not otherwise approved.

II. The Regulatory Pathway for the IVCDD Should Be Clarified to Specify When the 510(k) Pathway May Be Appropriate for the IVDCC

Throughout the Draft Guidance, FDA makes reference to either "PMA or 510(k)" submissions or approval/clearance. BIO agrees that, based on individual circumstances, IVCDDs may require either a pre-market approval application (PMA) or 510(k); however, FDA should clarify in the Final Guidance the criteria it will use to assess the risk of the IVCDD, and when it would be appropriate to submit a 510(k) notification.

BIO disagrees with the statement in the Draft Guidance that"[e]xperience indicates that most IVD companion diagnostic devices will be Class III devices, although there may be cases when a class II classification with premarket notification (510(k)) or other type of submission is appropriate." Rather, BIO believes that the IVCDD's classification is a risk-based determination, and the Agency should carefully examine each individual application to determine what regulatory pathway is most appropriate. The risk associated with the IVCDD should be evaluated based on the safety and effectiveness of the device in the context of the marketing application for the therapeutic counterpart. Instead of considering the risk of the IVCDD and the therapeutic independently where the RX/DX pair is contemporaneously developed and reviewed, FDA should examine what approach would provide adequate review and evaluation of the risk in the most efficient and least burdensome approach. It may be redundant or unnecessary to require a separate, extensive evaluation in the context of a PMA when the IVCDD and therapeutic counterpart are developed and reviewed contemporaneously. FDA should consider whether these situations are evaluated in the context of a 510(k) or *de novo* review.

III. The Definition of "In Vitro Companion Diagnostic Device" Should Be Clarified and Terminology Used Throughout the Draft Guidance Should be Harmonized

BIO is concerned that a lack of clarity in the definition of IVCDDs in the Draft Guidance and inconsistent use of terminology relating therapeutic products to diagnostics could lead to confusion in implementation. First and foremost, we believe that stakeholders and FDA have used of the term "companion diagnostics" to describe a variety of different types of test, and reliance on this term risks the insertion of pre-conceived notions into the understanding of these types of products intended to be addressed under the Draft Guidance. Accordingly, BIO recommends the use of a new, more concise term in the Draft Guidance than "*in vitro* companion diagnostic device products." For example, the Draft Guidance could refer to these products as "Rx/Dx paired products," with the individual components referred to as the "Rx paired product" or the "Dx paired product."

Regardless of the defined term used to describe these products, FDA should better clarify the definition to include only those *in vitro* diagnostic tests that have a well-supported, direct and definitive impact on a prescribing determination for a therapeutic product. The definition of IVCDD in the Draft Guidance should explicitly exclude all *in vitro* diagnostic tests not coupled with a specific therapeutic product. FDA should also clarify that tests used to measure prognostic markers, enrich clinical trials, and assess compliance are not included within the IVCDD definition.

Related to this core definition, FDA should clarify the applicability of the Draft Guidance of the IVCDD as it relates to the safety and effectiveness of the therapeutic product. The Draft Guidance uses various phrases to describe the relationship between the therapeutic product and the IVCDD, such as 'depends upon', 'is essential for', 'could be essential for', 'determining factor', etc. To prevent confusion and ambiguity, FDA should harmonize this terminology to describe the relationship between the therapeutic product and the IVCDD.

Finally, the definitions of assay validation versus device qualification for intended use are not clear in the Draft Guidance and should be clarified.

IV. FDA Should Describe in the Final Guidance a Sensible, Cohesive Framework for Review of IVCDD and Their Associated Therapeutic Products

Given the complexity associated with the co-development of IVCDDs and the associated therapeutic, BIO recommends the FDA establish appropriate internal policies and procedures across the Centers to facilitate the development and approval of therapeutic products that are intended for use with IVCDDs. To properly implement the intention of the Draft Guidance and the recommendations above, FDA should describe and implement an aligned, cohesive framework for review of an IVCDD and their associated therapeutics. This framework should use a dedicated organization or dedicated personnel to review each product in the context of the other and issue coordinated regulatory decisions. The organization or personnel should have authority to offer advice, review, and render regulatory decisions on both types of products, including with respect to cross-labeling issues. In addition, the process for resolving disputes should be clearly described, and it may be helpful to designate liaisons or coordinators who act like ombudsman to assist the Centers coordinate and address problems.

The overall regulatory framework for the development of IVCDDs would benefit from a well-defined process with clear roles and responsibilities for designated review within the division – including transparency regarding the roles for each Center and the expected timeline for its involvement. For example, FDA could provide in guidance a publicly-available process flow chart illustrating these roles and the timeline. Close collaboration between review divisions (CDER/CBER, CDRH) and the IVCDD and therapeutic sponsor is needed and should not be left to case-by-case guidance regarding review of submissions for the therapeutic product and IVCDD. A separate guidance is essential to describe the process and requirements from initial meetings to FDA submission review for regulatory staff and sponsors. It may also be helpful for FDA to prepare an internal-facing guidance in the Agency's Manual of Policies and Procedures (MAPP) or similar standard operating procedure (SOP) on this topic for consistency in review.

V. FDA Should Provide Guidance on the Appropriate Regulatory Submissions and Review Processes at Different Stages of Development of the Therapeutic Product

In line with our comment that the Agency must develop guidance for both contemporaneous co-development and for the situation of the asynchronous course of development of therapeutic products and IVCDDs, FDA should provide specific advice for developing the IVCDD at different stages of therapeutic product development. The Final Guidance should address the data requirements and evidentiary standards for the reciprocal labeling of therapeutics and IVCDDs, including the amount of evidence needed to classify the devices where the labels indicate that use

of the IVCDD is required, recommended, or for information-only. FDA should explain whether the phase of drug development will affect the evidentiary standard. The Draft Guidance should clarify instances when FDA may require a prospective clinical trial versus the acceptability of using supportive data from existing literature and/or prospective-retrospective analysis.

The Draft Guidance does not address when the therapeutic product's label must be updated to reflect approval/clearance of a new IVCDD. The Final Guidance needs to provide a description of the supporting evidence that would be required by the IVCDD.

The Draft Guidance assumes a close collaboration between the IVCDD manufacturer and the therapeutic developer, specifically with reference to relabeling of a device. A close collaboration between the IVD manufacturer and therapeutic sponsor is desirable; however, potential scenarios exist where this is not possible (*e.g.*, the holder of rights to an IVD might be either unable or unwilling to collaborate to re-label or pursue approval/clearance for development of this new therapeutic product). FDA should explain the regulatory path for such an issue.

The Final Guidance or associated guidance documents should address the appropriate regulatory submissions and review processes along the development timeline in the following circumstances:

- When the analytical and/or clinical validity of the biomarker has not been completed prior to initiation of phase 3 registrational studies;

- In clinical contexts where biomarker negative data may be unattainable due to ethical concerns (*e.g.*, exposing patients whose biomarker results are negative is inappropriate from Phase 1 studies on);

- In the context of certain clinical trial design that may not allow for the full ascertainment of an IVCDD's sensitivity and specificity, and where more information is needed regarding the nature of the analytical study package to support clinical testing of an in vitro diagnostic device and whether this varies dependent upon the intended use of the diagnostic device (efficacy, safety, dosing, etc);

- For the use of prospective-retrospective (as defined by FDA[2]) analysis study designs and appropriate use of banked samples;

- For the use of more than one investigational use only (IUO) *in vitro* diagnostic test in a pivotal trial; and

- For the use of bridging or concordance studies to link existing clinical data with older/different versions of the *in vitro* diagnostic test used in the clinical studies.

VI. FDA Should Provide a Clear Standard Concerning Whether the IVCDD Will Be Described on the Basis of Class or a Specific Product

[2] From pg. 941 of white paper: *Prospective–retrospective biomarker analysis for regulatory consideration: white paper from the industry pharmacogenomics working group* – "At the FDA Industry In vitro Diagnostic (IVD)/ Companion Diagnostic Drug Roundtable Meeting (Washington, DC; 24 March, 2009)"

Regarding the issue of class vs. specific product labeling in the label for the therapeutic product, BIO is concerned regarding the potential negative affect this may have on innovation in the diagnostics industry. In the case where the therapeutic and IVCDD products are co-developed, the data generated on the IVCDD is proprietary, and should not be opened to a general class labeling claim, absent demonstration by other class members regarding the safe and effective use of each device. The inclusion of class labeling in the absence of such a requirement is improper, and risks a substantial negative impact on innovation for novel IVCDDs.

Regardless of the approach, the labeling of the therapeutic must provide sufficient information to adequately describe the performance characteristics of the IVCDD used in the confirmatory clinical trials. BIO recommends that the therapeutic's Clinical Trial portion of the label include the specific IVCDD tradename used in the clinical trials. Assays from different manufacturers may have different performance characteristics, which could result in inappropriate selection of patients (*e.g.*, increased false positives or false negatives).

VII. FDA Should Provide for an Elective Exemption of an IVCDD from the IDE Requirements When the IVCDD and Therapeutic Product Are Being Evaluated Under an IND

It is BIO's view that, when the IVCDD is being evaluated in clinical trials involving the therapeutic counterpart under an investigational new drug application (IND) with Institutional Review Board (IRB) oversight, a requirement for a separate investigational device exemption (IDE) is redundant and unnecessary as a separate regulatory requirement. The Draft Guidance should make clear that, when a IVCDD is studied in the context of an active IND, it may be exempt from the IDE requirements for these studies, if the IVCDD information is submitted to the IND. In addition, existing IND regulations provide sufficient oversight when IVCDDs are used in an exploratory manner to evaluate biomarkers in non-pivotal studies, where the performance of the IVCDD is not being evaluated to support approval/clearance.

The only possible exception to this policy would be the rare cases in which the diagnostic test is invasive and would directly present patient risk; however, it may be sufficient for the integrated assessment of the risks and benefits by the overall trial procedures to be addressed under one regulatory procedure (*i.e.*, the IND). CDRH's expertise could be requested to assess the risks presented by an invasive device, this could occur in the context of an IND submission.

VIII. Use of the Term "Combination Products" in the Draft Guidance is Misplaced, Unnecessary and Results in Confusion

The Draft Guidance makes reference to these paired products as potentially combination products, and suggests that a single application might be used for the paired products. BIO believes that the reference to combination products should be removed, as it is both misplaced and confusing. FDA should remove any reference to combination products in the Draft Guidance.

IX. Comments on Specific Provisions of the Draft Guidance

Specific Language in Draft Guidance	Location of Specific Language in Draft Guidance	Recommendation
"The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any *generic equivalents* of the therapeutic product." (*emphasis added*)	Page 6	FDA should clarify whether the term "generic equivalents" includes biosimilars. If not, FDA should provide further clarification on the requirements for biosimilar products.
Reference is made to "…patients who are most likely to benefit…"	Page 6, 1st bullet.	FDA should expand upon this language and make reference to the identification of patients who are unlikely to benefit (the opposite of the original description) either in this bullet or a separate bullet.
In vitro diagnostic tests may "rise to an IVD companion diagnostic level" in some cases.	Page 7, Footnote 7.	BIO agrees that *in vitro* diagnostic tests are not IVCDDs where they provide "useful" information about a therapeutic product's use but are "not a determining factor" in its safe and effective use. FDA should remove this reference in footnote 7 to eliminate the ambiguity.
The Draft Guidance includes among those *in vitro* diagnostic tests essential for the safe and effective use of a corresponding therapeutic product to include in vitro diagnostic tests that "[m]onitor response to treatment for the purpose of adjusting treatment (*e.g.*, schedule, dose, discontinuation) to achieve improved safety or effectiveness"	See Pg. 7, Second Bullet.	Would therapeutic drug monitoring also fit into this category? More clarity is needed regarding the scope of this statement.

Specific Language in Draft Guidance	Location of Specific Language in Draft Guidance	Recommendation
The Draft Guidance states "…existing device that has already been approved or cleared for another purpose."	See Page 7, Paragraph 2.	Consider a well-established *in vitro* diagnostic test that has been marketed long before the therapeutic is developed, and which would be adequate "as-is" for the new therapeutic product. Would this IVCDD still need a new label and demonstration of fitness for the new use (covered specifically on page 11 and also fitting the third case listed on page 7)? FDA should clarify that the development of the therapeutic in this case does not induce a requirement for the IVCDD manufacturer to collaborate with the therapeutic manufacturer in the approval/clearance process. Additionally, FDA should add a new sentence to the end of the paragraph: "Each of these cases will require a demonstration that the IVD has performance characteristics suitable for its intended use with the new therapeutic product."
The Draft Guidance states that "[a]ll diagnostic devices used to make treatment decisions in a clinical trial of a therapeutic product..."	See Page 12.	FDA should clarify how the Agency interprets use of in vitro companion diagnostic devices "to make treatment decisions." Specifically, how does this apply with respect to using a biomarker as a selection criterion vs. as an enrichment criterion where the result of a biomarker analysis may be used in an exploratory analysis?

Specific Language in Draft Guidance	Location of Specific Language in Draft Guidance	Recommendation
The Draft Guidance states that the "…the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices. In such cases, FDA will expect the sponsor to conduct the trial under full IDE regulations."	See Page 12, Para 1.	FDA should clarify when it is appropriate to file in vitro companion diagnostic device information to an IDE versus an IND. The draft guidance would benefit from specific example of scenarios whereby an IDE is appropriate vs. an IND.

Respectfully Submitted,

Paul Sheives, JD
Director, Diagnostics and Personalized Medicine Policy