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

Erica Takai
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Rm. 5456
Silver Spring, MD 20993-0002
301-796-6353

BIO Comments Re: Notice to Public of Website Location of CDRH Fiscal Year 2020 Proposed Guidance Development; In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions (FDA Docket No. FDA-2012-N-1021)

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) Notice to Public of Website Location of CDRH Fiscal Year 2020 Proposed Guidance Development; In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions.

BIO is the world's largest trade association representing approximately 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place. Specifically, many of BIO's members develop, market, or are impacted by diagnostic technologies for a variety of research, investigational, and clinical uses. BIO's members also develop therapeutic products that are guided by diagnostics tests that provide the right treatment for the right patient at the right time—the essence of the modern precision medicine paradigm.

BIO appreciates FDA's effort to evaluate this guidance and ensure it remains useful and up to date. BIO has found this guidance very useful but acknowledges that certain portions should be updated to reflect current law, regulation, and FDA practice. Rather than withdrawing the guidance, BIO requests that the guidance be revised to reflect FDA's current thinking and practice. We propose that the guidance



be revised to better describe FDA’s expectations with respect to use of IVDs in drug trials and companion diagnostic co-development.

For example, the guidance could be updated to better describe when FDA expects IDEs for IVD studies that require tumor tissue or organ biopsy, particularly in oncology. BIO also proposes that FDA update the guidance with questions and answers addressing the use of IVDs in drug clinical studies, including companion diagnostic co-development. We recommend that the guidance be harmonized and cross-referenced with other FDA guidance addressing use of IVDs in drug trials. Specific suggestions are provided in the table that follows.

BIO appreciates this opportunity to comment on FDA’s In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions Guidance. We would be pleased to provide further input or clarification of our comments, as needed, and should you have any questions about the content of this letter, please contact Jeremy Isenberg, Manager for Health Policy, at jisenberg@bio.org.

Sincerely,

/S/

Jeremy Isenberg

Manager, Health Policy
Biotechnology Innovation Organization (BIO)
www.bio.org

Specific Comments

LINE # (or Page/ Paragraph)	COMMENT w/RATIONALE (Rationale for change is mandatory)	PROPOSED CHANGE
I. Background		
II. Introduction		
1. Definition of a medical device	The definition of a medical device in the Federal Food, Drug, and Cosmetic Act has been modified since the publication of this guidance.	Suggest updating to the definition as modified by the 21 st Century Cures Act.
4. FDA Divisions responsible for IVD review	CDRH has been reorganized recently, such that this guidance no longer includes accurately identifies the names of the centers and contacts.	Suggest updating to reflect CDRH reorganization.
5. Contact information	CDRH has been reorganized recently, such that this guidance no longer includes accurately identifies the names of the centers and contacts.	Suggest updating to reflect CDRH reorganization.
III. General Regulatory Issues		
2. How do I determine the applicability of the IDE regulation to my IVD study?	1. The concept of an IDE is introduced prior to risk determinations.	1. Suggest introducing the concept of risk within IVD development and co-development 2. Suggest updating with the risk determination considerations in section III.3



<p>2. How do I determine the applicability of the IDE regulation to my IVD study?</p>	<ol style="list-style-type: none"> 1. The examples of an investigational IVD in FDA’s recent guidance document “Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination” (Oct. 2019) seem to broaden the definition of an IVD beyond simply “the object of a clinical investigation,” as noted in 21 CFR 809.3. Therefore, more clarity is needed in a revised version of this guidance on how 21 CFR Part 812 applies in the context of companion diagnostic co-development. 2. Additionally, the guidance includes a decision tree, which is difficult to apply to use of IVDs in drug trials or companion diagnostic co-development, because in many instances invasive biopsy is part of the standard of care and no other method for confirming a result exists. 3. FDA’s 2016 guidance, Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product, notes that “planning to enroll subjects into a trial based on confirmation of a local test result is strongly discouraged.” However, often in early stage studies, an investigational diagnostic is still in development and may not be ready to support selection of subjects. In all cases the LDT has met Clinical 	<ol style="list-style-type: none"> 1. BIO suggests that FDA clarify in this guidance how 21 CFR Part 812 applies in the context of companion diagnostic co-development. For example, does Part 812 apply only when the prototype CTA (clinical trial assay) is used for specific purposes (e.g. screening, enrollment) without the use of another legally marketed test to confirm the clinical decision? It would be helpful for FDA to clarify whether FDA would consider those prototype CTAs used for monitoring response to treatment for the purpose of adjusting treatment to achieve improved safety or effectiveness, or used to determine the concentration of a drug in a patient’s plasma to inform their treatment, to be investigational IVDs. More examples of what constitutes an investigational IVD would be helpful if FDA intends to include more than just those for screening and enrollment. 2. Suggest that FDA revise Appendix 1 to provide examples for each scenario (see later comments on Appendix 1). 3. Suggest FDA please clarify how and when an LDT (e.g. local test) would be considered an investigational IVD. If the LDT is legally marketed for that specific intended use and has received CLIA accreditation, it would seem that it is by definition not investigational. However, the FDA guidance “Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination” (Oct. 2019) and “Investigational IVDs Used in Clinical Investigations of Therapeutic Products” guidance (December 2017) imply that unless the LDT has been cleared or approved through FDA’s premarket review processes, the LDT would be considered investigational. This seems inconsistent with FDA’s current enforcement discretion approach to LDTs. Given that these local tests are legally marketed, FDA should note in these guidance documents that even if the agency discourages the practice, no additional investigational IVD requirements would apply to the use of these tests in a drug
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	<p>Laboratory Improvement Amendments (CLIA) accreditation to be offered as a test which the lab has validated.</p>	<p>trial when used in accordance with their legally marketed intended use.</p>
<p>3. How do I determine if the study is a significant or non-significant risk study under 21 CFR 812.2(b)?</p>	<p>Per this guidance, nearly every use of a CTA or companion diagnostic in a drug trial would be considered a significant risk study, unless a previously cleared or approved test exists that would be used to confirm the selection or assignment of subjects. Rarely does such a test exist, and in some cases, it may not be feasible or ethical to design studies with a placebo or standard of care treatment arm, such that the patient population must be prospectively selected using a CTA.</p> <p>Clarity is particularly needed on what sampling procedures could trigger a significant risk study in oncology, where the patient population has a high unmet need with limited treatment options.</p>	<p>We suggest that FDA revise the description of how it interprets “potential for serious risk”. Specifically, FDA may reference the guidance “Investigational IVDs Used in Clinical Investigations of Therapeutic Products” (December 2017) describes the criteria used for risk assessment, which includes considerations about availability of alternative effective therapies and safety profile of drug, among others.</p> <p>In addition, we recommended the following change in the response to Question III.3: “If the potential risk does not rise to the level described above, the study is not considered to pose a significant risk. Risk analysis of the diagnostic result as compared to the response to SOC should be considered. These decisions could be made by the clinical site IRB accounting for the patient population and currently available treatment options, recognizing that IRBs may always suggest the risk determination be triaged to FDA instead.”</p>
<p>4. How do I determine if an invasive sampling technique presents a significant risk under 21 CFR 812.2(c)(3)?</p>	<p>It has been difficult to ascertain FDA’s current thinking on when invasive sampling in a drug trial renders it a significant risk study requiring an IDE. Guidance documents, such as this one, make it seem as if every tissue biopsy in an oncology study is considered significant risk and requires an IDE, which may not be consistent with current FDA practice. The Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a</p>	<p>Since many samples in oncology trials involve invasive sampling of tumor tissue or major organ biopsy, it would be helpful to understand what FDA’s position is on these sampling methods, when they are required per standard of care or other legitimate purposes in the protocol. FDA’s December 2017 guidance, “Investigational IVDs Used in Clinical Investigations of Therapeutic Products” implied that if collected as part of the standard of care, further analysis of these samples by an investigational IVD would not be considered significant risk studies.</p> <p>Core biopsy is the most commonly used sample type in oncology trials. BIO suggests the guidance clearly describe, based on organ</p>



	<p>Therapeutic Product draft guidance issued July 2016 all make reference to “standard of care,” but do not clarify when tissue biopsy in oncology trials is considered standard of care, such that an IDE is not required. It is also unclear whether certain standard of care procedures do not present significant risk and are “Non-significant risk (NSR) procedures.” Additionally, BIO suggests that FDA clarify that invasive sampling as part of standard of care and using standard of care procedures should not be considered significant risk (SR).</p>	<p>systems, whether a core biopsy is SR or NSR, or else state that the Agency does not regulate the practice of medicine and thus the IRB may be in the best position to review risk determinations on this point. Having this clarity in the guidance would prevent sponsors from submitting an IDE to CDRH for every add on indication for which a therapy is being investigated.</p> <p>Additionally, BIO suggests that FDA clarify that invasive sampling as part of standard of care and using standard of care procedures will not be considered significant risk.</p> <p>Recommended change to the response to Question III. 4: “... For example, FDA considers sampling techniques that require biopsy of a major organ outside of the standard of care or standard of care procedures, use of general anesthesia, or placement of a blood access line into an artery or large vein (subclavian, femoral, or iliac) to present a significant risk.</p> <p>FDA does not regulate the practice of medicine. The agency defers to clinical judgment on what may be considered standard of care in oncology with respect to biopsy tumor tissue within a major organ. FDA recognizes that biopsies of this type using standard of care procedures may not present significant risk requiring approval of an IDE prior to the study. Rather, these studies could be considered NSR or IDE-Exempt, depending on the study design with the risk determination confirmed by the IRB, recognizing that IRBs may always suggest the risk determination be triaged to FDA instead.”</p>
<p>7. What if no medically established means for diagnosing the disease or condition exists?</p>	<p>FDA states in this guidance that if no medically established means exists for diagnosing the disease or condition, the study would automatically require an IDE “if the results are used in diagnosis without confirmation (e.g., to assist in determining treatment) (21 CFR 812.1, 812.2) and if a significant risk device is</p>	<p>BIO proposes that FDA revise this section to describe when, in FDA’s current thinking, a local test result may be deemed a medically established means for identifying a patient for a drug trial, such that no IDE is required.</p> <p>We also suggest FDA revise this section to note that, even when used for patient selection or treatment assignment, the study could be deemed NSR by submission of a risk determination to FDA or an IRB</p>



	<p>involved.” In many early oncology trials, no established means exists for identifying the biomarker for patient selection other than local laboratory developed tests. Additionally, in cases of rare diseases with high unmet need, where currently available therapies are lacking or not tolerable, and the investigational drug has an acceptable safety profile based on nonclinical or early clinical studies, it is conceivable that use of an investigational IVD to select patients for the trial may not pose more risk to the patient than the alternative options.</p> <p>Additionally, on page 10 of the FDA guidance on “Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product” (July 2016),¹ FDA does not identify the preferred pathway for obtaining risk determinations when IVDs are used in drug studies. As the FDA guidance on “Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination” (Oct. 2019) came out after 2010 and the guidance on Codevelopment, it is not clear whether FDA prefers that the Agency, or the IRB, review these risk</p>	<p>if the level of risk to the patient is in question. It would also be helpful to provide examples of cases where such a study might be considered NSR. For example, we believe it should be considered NSR in cases of rare diseases with high unmet need, where currently available therapies are lacking or not tolerable, and the investigational drug has an acceptable safety profile based on nonclinical or early clinical studies. FDA’s December 2017 guidance, Investigational IVDs Used in Clinical Investigations of Therapeutic Products, may also be a helpful reference.</p> <p>Recommended changes to the response to Question III.7 include: “If there is no medically established diagnostic product or procedure (which could include an academic institution, hospital-based lab developed test, existing laboratory-developed test, or in rarer cases a local hospital-based lab developed test) and clinical investigators use the results from the investigational study to decide on treatment, FDA would not consider the study exempt from IDE requirements under 21 CFR 812.2. The sponsor would need to obtain FDA approval of an IDE, or a risk determination from an IRB or FDA confirming the study is NSR, if the results are used in diagnosis without confirmation (e.g., to assist in determining treatment) (21 CFR 812.1, 812.2) and if a significant risk device is involved.”</p>
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¹ Food and Drug Administration Guidance Document: “Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product”. July 2016. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-codevelopment-vitro-companion-diagnostic-device-therapeutic-product>.



	determinations for IVDs used in drug trials.	
15. What regulations describe the content requirements for IVD premarket submissions?	This 2010 guidance was released prior to the agency’s direct de novo regulations and process, so the de novo guidance is not reflected in this section.	Suggest revising this section to include 21 CFR 860.134 and the October 2017 “De Novo Classification Process (Evaluation of Automatic Class III Designation)” guidance relating to de novo submissions.
16. Can published literature be used to support an IVD premarket submission?	This 2010 guidance was released prior to the agency’s direct de novo regulations and process, so the de novo guidance is not reflected in this section.	Suggest including “de novo” in the list of premarket submissions. Recommended changes to the response to Question III.16: CDRH and CBER believe that the principles outlined in this guidance are applicable to other submissions, specifically those for a de novo, 510(k), PMA and HDE.
IV. Investigational Studies		
4. Is FDA willing to review and discuss a study protocol even if the study is exempt from most of the 21 CFR Part 812 requirements?	This section was written before the 2019 guidance, “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program.” Therefore, the pre-submission process is not covered in this section. Similarly, the recent Breakthrough Device Designation process ² allows for additional agency interaction on IVD clinical study planning.	Suggest updating to reflect the pre-submission process. Also suggest updating this section to discuss the option for breakthrough device designation and how that can result in additional agency interactions.
4. Should I review the ICH or draft ISO 14155 when developing studies for devices that fall within the exemption at 21 CFR 812.2(c)?	This section refers to draft ISO 14155. The document was published in 2011, so the section should be updated accordingly.	

² Food and Drug Administration Guidance Document: “Breakthrough Devices Program”. December 2018. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program>.



<p>6. Under 21 CFR Part 812, what are the sponsor’s and investigator’s responsibilities for studies of a non-significant risk device conducted under the abbreviated requirements in 21 CFR Part 812?</p>	<p>When investigational IVDs are used in a drug clinical trial, some of the sponsor responsibilities may already be met by the drug study sponsor. This section does not describe how those responsibilities may be met by the drug study sponsor.</p>	<p>Suggest revising this section to note how, when IVDs are used in a drug trial or in a companion diagnostic co-development situation, some of these requirements may already be met by the drug sponsor’s responsibilities (e.g. informed consent).</p> <p>Recommended change to the response to Question IV.6: Suggest adding an asterisk after the following responsibilities, and a footnote indicating these are satisfied by the drug sponsor in the drug trial:</p> <p>“b. Obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintain such approval. *</p> <p>c. Ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care informed consent under part 50 and documents it, unless documentation is waived by an IRB under 21 CFR 56.109(c).*</p> <p>d. Comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations;*</p> <p>e. Maintain the records required under 21 CFR 812.140(b)(4) and (5) and make the reports required under 21 CFR 812.150 (b)(1) through (3) and (5) through (10);*</p> <p>f. Ensure that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a)(1), (2), (5), and (7);*</p> <p>*21 CFR Part 50 and 56, as well as 21 CFR Part 312, outline the sponsor’s responsibilities in drug studies. For drug studies involving an investigational IVD, these responsibilities may be satisfied by the drug sponsor’s corresponding responsibilities under 21 CFR Part 312, Part 50, and Part 56.”</p>
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		It would also be helpful for FDA to provide clarification on circumstances where drug studies involving an investigational IVD may be satisfied by the drug sponsor’s corresponding responsibilities.
V. Human Subject Protection		
VI. Data Considerations		
5. How much leeway is there in deciding on the populations from which human specimens are collected and under what conditions are data on simulated specimens (see the Glossary for definition) acceptable?	When an IVD is used in a clinical study of a drug, and that study will be used to support the clinical validation and marketing application of the IVD, it is unclear when commercial or contrived samples, as opposed to native samples, can be used. This can be particularly challenging when the study involves patients with a rare disease, such that it is difficult to obtain the requisite number of negative samples from the clinical study population.	Suggest updating this section to describe when these practices are appropriate in companion diagnostic co-development studies (i.e., use of an IVD in a drug study). Specifically, it would be helpful to expand on the use of commercial samples when negative samples are difficult to obtain (e.g. cases of rare disease, study designs where it is unethical to randomize negative subjects to another treatment arm).
VII. Glossary		
VIII. References		
Appendix 1: Regulatory Decision Tree (21 CFR Part 812) for IVD Investigational Studies		



	<p>The current guidance recognizes—by the inclusion of the “Significant Risk?” question—that even when invasive sampling is required, not all invasive sampling renders the study a SR study. Similarly, the guidance recognizes that not every use of an IVD without confirmation by another medically established product or procedure renders a study SR. What is unclear is FDA’s current thinking on which situations amount to a SR study and which do not.</p>	<p>BIO requests that FDA update or annotate the decision tree to better explain what constitutes “Significant Risk” in the “invasive sampling” and “use without a medically established product” portions of the decision tree.</p> <p>Also suggest adding another appendix, after the decision tree, with examples from FDA’s experience to date. We recommend that some of these examples come from the companion diagnostic co-development context. These should indicate in which situations or therapeutic areas tumor sampling or use of an investigational IVD to assign or select subjects would not be considered a SR study.</p>
<p>Appendix 2: Regulatory Framework for IVD Products</p>		
<p>Regulated as Class I, II, or III Devices</p>		
<p>Appendix 3: Sponsor’s Responsibilities for Significant Risk Device Investigations</p>		
<p>Appendix 4: Investigator’s Responsibilities for Significant Risk Device Investigations</p>		
<p>Appendix 5: Suggested Format for IDE Final Report</p>		
<p>Additional Comments or Questions</p>		
<p>Can investigational IVD studies receive expedited review (see Glossary for definition) under the Breakthrough Device Designation process?</p>		<p>Suggest updating the guidance to discuss the option for Breakthrough Device Designation and how that can result in additional agency interactions. It would also be helpful to discuss how a breakthrough therapy designation could be obtained for an IVD used in a study of a drug that has received breakthrough therapy designation or is proceeding through an expedited review program. For example, the drug study sponsor could submit a dual request for breakthrough therapy and breakthrough device designation at the same time, as in the streamlined risk determination process.</p>



		Also suggest updating to indicate what data would be appropriate to support a breakthrough device designation for a potential companion diagnostic and when, in a co-development situation, it would be appropriate to submit a breakthrough device designation request.
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