AdvaMedDx
Vital Insights | Transforming Care

June 15, 2018

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

RE: Docket No. FDA-2018-D-0944; *Draft Guidance for Industry; Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination.*

Dear Sir/Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association ("AdvaMed"), we respectfully submit these comments in response to the Draft Guidance for Industry: "*Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination"* (hereinafter "Draft Guidance").

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative diagnostic technologies supporting the advancement of personalized medicine.

GENERAL COMMENTS

We appreciate the Food and Drug Administration ("FDA" or "the Agency") efforts to develop this Draft Guidance that describes an optional streamlined submission process for determining whether use of an investigational *in vitro* diagnostic ("IVD") in a clinical trial for an oncology therapeutic is considered significant risk ("SR"), nonsignificant risk ("NSR"), or exempt. FDA encourages sponsors to use the streamlined process described in this guidance when possible to reduce administrative burden on sponsors and FDA and to maintain the current level of regulatory review. We believe this proposed approach is a positive step in supporting innovators bringing new safe and effective diagnostic technologies and medicines to the United States to advance personalized medicine.

Commissioner Gottlieb highlighted the Draft Guidance in his April 12, 2018 remarks as "a step toward our goal of having a common filing for a drug and diagnostic system where the drug is co-developed with a diagnostic test." In recent comments responding to the draft guidance "*Investigational IVDs in Used in Clinical Investigations of Therapeutic Products*," AdvaMedDx

supported the option of allowing submission of all IDE components to an investigational new drug application ("IND") rather than requiring both an investigational device exemption ("IDE") and an IND. We reiterate here our belief that an approach of submitting investigational IDE information in the IND is particularly beneficial for early-phase clinical trials of the therapeutic product (Phase 1 and 2 trials).

We thank FDA for its efforts to develop this guidance and coordinate activities amongst the three Centers—the Center for Devices and Radiological Health ("CDRH"), the Center for Biologics Evaluation and Research ("CBER"), the Center for Drug Evaluation and Research ("CDER")—and the Oncology Center of Excellence. We believe smooth coordination among the Centers and ensuring the right parties are involved early in the process is critically important for innovators.

As with any guidance, we recommend that FDA cross-reference other relevant guidances in the final guidance. For instance, we would recommend that the Draft Guidance align with, and reference as appropriate, "*Investigational IVDs Used in Clinical Investigations of Therapeutic Products*" once finalized, to support consistency.

EXPANSION TO OTHER DISEASE AREAS

In the *Federal Register* notice announcing the Draft Guidance, FDA specifically requested perspectives on whether to extend the streamlined process to other disease areas in the future. FDA stated that initially it is focusing on oncology because "FDA has received the greatest number of codevelopment submissions in this disease area and has the most experience evaluating whether the *in vitro* diagnostic is significant risk."

We support the extension of the streamlined submission process to other disease areas in the future. We recommend conducting a "lessons learned" exercise with industry after FDA has received a certain number of submissions under the streamlined review process to evaluate the benefits and administrative efficiencies gained from the streamlined process. These lessons learned can then be applied to other disease areas.

AdvaMedDx appreciates the opportunity to provide our comments, which are intended to support FDA's efforts to advance personalized medicine. We identify in our specific comments a few areas within this Draft Guidance where we believe additional clarification would be helpful to achieve our shared goals. We provide in those specific comments accompanying recommendations to assist FDA.

Respectfully submitted,

/s/

Jamie Wolszon
Associate Vice President
Technology and Regulatory Affairs

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
1	I	21	If found to be SR, such a trial may require approval of an investigational device exemption (IDE) in addition to being conducted under an active investigational new drug application (IND).	We propose adding for clarification.
2	I	26 - 29	~~Regardless of~~ ~~whether~~ A study involving an investigational IVD determined to be ~~SR or~~ NSR~~, it~~ must follow the abbreviated IDE requirements outlined in 21 C.F.R. § 812.2(b), including generating and retaining data that demonstrate analytical validation of the investigational IVD. The Investigational IVD should have demonstrated analytical validity (e.g., adequate feasibility data for the biomarker or disease characteristic) such that it is able to give accurate measurements from subject specimens, as applied to the intended use/indications for use clinical trial population. SR studies may be applicable for abbreviated requirements or may require an IDE to be submitted and subject to full IDE requirements. Sponsors can contact CDRH directly with questions relating to analytical validation of the investigational IVD.	Use of the term "analytical validation" in this context could imply that assay verification studies had already been completed prior to initiation of IVD usage in a therapeutic trial, which might not be necessary or appropriate in all cases. If adequate feasibility data have been obtained, in most cases the needs would be served and not constrain sponsors to execute assay verification studies in advance of utilizing the IVD in the clinical study. In particular, execution of assay verification studies prior to conducting a clinical trial of the therapeutic may not be necessary or appropriate if it is not known if the particular assay would be taken forward to commercialization. In addition, the paragraph states that a SR or a NSR study would be expected to follow abbreviated requirements under 21 C.F.R. § 812.2. Pursuant to that regulation, NSR studies would follow abbreviated requirements. By contrast, SR studies are subject to full IDE requirements. We propose adding language to clarify this distinction.

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
3	II	40 - 42	The streamlined submission process described in this guidance applies only to clinical trials involving codevelopment of an investigational IVD with an oncology investigational drug. It does not apply to codevelopment programs in other disease areas at this time. FDA may develop similar streamlined submission processes for other disease areas in the future.	As discussed above, in response to the question FDA posed in the *Federal Register* announcement, AdvaMed would encourage FDA to adopt a similar streamlined process provided for disease areas in addition to oncology.
4	II	50 - 54	If an invasive biopsy that presents a potential for serious risk to the health, safety, or welfare of the subject is required for investigational IVD testing for enrollment, and the risk outweighs the benefit to the patient, the study is not eligible for the streamlined submission process. If an invasive biopsy is merely optional per the study protocol, the streamlined process would still apply. Sampling procedures which are generally not considered to provide significant risk include, for example, skin punch biopsies, shave biopsies, fine needle aspirates of superficial lymph nodes, certain guided biopsies, and lumbar puncture for the collection of cerebrospinal fluid. If a sponsor submits such a study via the streamlined process, FDA will notify the sponsor ~~to consult with CDRH for a study risk determination through the Q-submission program~~ of the study risk determination. If the investigational IVD is SR, CDER/CBER will confirm the SR determination in the May Proceed Letter responding to the IND and may ask the sponsor to submit an IDE to CDRH and to wait to initiate the trial until after the IDE is approved.	We believe that FDA should consider allowing the streamlined submissions process if the benefit of the therapeutic outweighs the risk (in situations, for example, where other oncology treatments have failed). This would help reduce the administrative burden while maintaining the required level of regulatory review. In addition, we would recommend that FDA clarify the term "invasive biopsy" by providing examples of biopsies considered invasive and non-invasive. We propose including the examples of NSR sampling procedures that FDA has previously identified. Moreover, if a sponsor submits an invasive biopsy sample investigational IVD via the streamlined process, we would recommend that CDER/CBER consult with CDRH to make the SR or NSR study risk determination, rather than asking the sponsor to submit the same information to CDRH for review. Consultation between CDER/CBER and CDRH will streamline the process by allowing the

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
				sponsor to submit the investigational IVD information once to FDA, rather than first submitting to CDER/CBER and then a second time to CDRH.
5	III	59 - 62	Instead of reviewing the SR/NSR/exempt status of an investigational IVD as part of the IND, could the Agency also consider the appropriate risk determination status as part of the Pre-IND meeting package if the sponsor chose such an option?	FDA risk consideration of risk determination status at as part of the Pre-IND meeting package could help avoid potential delay in study start in the event an assay is determined to be SR and an IDE consequently needs to be submitted. In some cases, analytical data might need to be generated and assembled for submission. Earlier SR determination could help provide the sponsor with adequate time to generate and assemble this information.
6	III	68 - 69	Add the following bullet point after line 67: • <u>In cases where multiple IVDs are utilized in the therapeutic product trial, it may be most efficient if the therapeutic product sponsor serves as the lead sponsor or the therapeutic product sponsor designates the IVD sponsor that would serve as the lead sponsor.</u>	Since the therapeutic sponsor would be the central coordination point for the multiple IVDs and their respective sponsor(s), the therapeutic sponsor presumably would already have in place any confidentiality measures necessary (or be assured that their appointed IVD lead sponsor has these measures in place).
7	III	68 - 69	Add the following bullet point after line 67: • <u>Regardless of whether individual or multiple IVDs are utilized in the therapeutic product trial, the lead sponsor should assure that the appropriate letters of authorization to FDA that authorize the lead sponsor (or the other involved</u>	The center reviewing the IVD(s) (CDRH/CBER) needs permission from the therapeutic product sponsor to rely on the data in the New Drug Application ("NDA")/Biologics License Application ("BLA") to support the Premarket Approval Application ("PMA") (or other device

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
			sponsors) to cross-reference the premarket submissions or incorporate the relevant content by reference have been secured.	premarket submission if applicable), and the center reviewing the therapeutic product (CDER/CBER) needs permission from the IVD sponsor(s) to rely on the data in the PMA (or other device premarket submission if applicable) to support the NDA/BLA. Relevant details and guidance can be found in Appendix IV of the FDA draft guidance titled "Principles for Codevelopment of an *In Vitro* Companion Diagnostic Device with a Therapeutic Product" (July 15, 2016).
8	III	70 -71	The list below highlights how a sponsor should present information in the IND original submission or Amendment to facilitate the streamlined submission process, when applicable*:*	We would propose adding language to explicitly state that an IND Amendment would also provide an appropriate mechanism to request a study risk determination using the streamlined submission process. The timing of the IND in relation to the need for a study risk determination is often not aligned. Therefore, an IND amendment might be necessary and it would be helpful to mention the IND amendment in the guidance document.
9	III	90	In addition to the protocol, a sponsor should include information in the IND about: • Device Description • a description of the population, if not included in the protocol	The information requested in this draft guidance does not capture all information requested for study risk determinations found in FDA Guidance Document *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*. We would recommend revising this language so that the information needed to make a

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
			• the sponsor's name and contact person(s), including titles, address, phone number, fax number, and email address.	study risk determination is the same regardless of whether a sponsor uses the proposed process or the already established pre-submission process.
10	III	90	A sponsor also may wish to include information in the IND about • a Risk Determination Proposal, outlining the company's own determination of study risk, and rationale for that determination, based on the criteria outlined in the relevant section of *"Investigational IVDs Used in Clinical Investigations of Therapeutic Products."* • Drug safety profile/prevalence of toxicities, as available in pre-clinical or other studies. • Response to first-line therapy, and progression to second and third line therapies. • Evidence obtained in Phase 1 studies in the targeted population. • The results of Institutional Review Board ("IRB") reviews that might be available at the time of submission	Either as part of the protocol, in the cover letter, or elsewhere in the IND submission, the sponsor may wish to consider including its own risk determination and supporting rationale. Inclusion of adequate and complete information on the use of the investigational IVD in the study, especially including consideration of the criteria outlined in *"Investigational IVDs Used in Clinical Investigations of Therapeutic Products,"* should make CDRH's decision-making process clearer. We believe that risk/benefit analysis of diagnostic versus response to standard of care should be considered as part of the risk determination process. Diagnostic codevelopment most often selects a population that may benefit from targeted therapy, improving outcomes versus standard of care, or in combination with standard of care. Therefore, we would suggest that FDA add language to highlight this risk/benefit aspect. IRB review decisions, if available, could provide further support for the sponsor's risk proposal. Inclusion of this information would be optional.

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
11	III	90	We would propose that FDA suggest the location within the electronic Common Technical Document for the IND, and level of detail for description of the IVD to be submitted to the IND.	We believe clarification would be helpful to explain what FDA would like to see in the description and the expected level of detail (e.g., extent of analytical validation) of the IVD used in the oncology trial.
12	III	86 - 89	Sampling procedures which are generally not considered to provide significant risk include, for example, skin punch biopsies, shave biopsies, fine needle aspirates of superficial lymph nodes, certain guided biopsies, and lumbar puncture for the collection of cerebrospinal fluid.	This section refers to 21 C.F.R. § 812.3(m), which defines a significant risk device. Illustrative examples would be helpful to clarify the types of biopsy that FDA believes would not pose such a risk.
13	III	98 - 106	Within the 30-day review time for the IND, CBER or CDER will consult with CDRH and determine if the use of the investigational IVD in the study is SR, NSR or exempt. If the investigational IVD is NSR, CBER or CDER will confirm the NSR determination in the May Proceed Letter, which may also include a statement such as "You should ensure that NSR procedures are used in obtaining any biopsies taken for testing with the investigational IVD and submit unanticipated adverse device effect reports to the IND." If the investigational IVD is SR, CBER or CDER will confirm the SR determination in the May Proceed Letter and may ask the sponsor to submit an IDE to CDRH and to wait to initiate the trial until after the IDE is approved. CBER or CDER will consult with CDRH and determine if the use of the investigational IVD in the study is SR, NSR or exempt. If the investigational IVD is NSR, CBER or CDER will confirm the NSR determination in the May Proceed Letter, which may also include a statement such as	We would propose clarifying that the time to render a determination under the streamlined process would still be the 30 days applied to an IND. Moreover, the guidance describes how SR and NSR status would be communicated to the sponsor, but does not address how exempt status would be communicated to the sponsor. We believe it would be helpful for the guidance to correspondingly describe how the exempt status is communicated to the sponsor.

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
			"You should ensure that NSR procedures are used in obtaining any biopsies taken for testing with the investigational IVD and submit unanticipated adverse device effect reports to the IND." If the investigational IVD is SR, CBER or CDER will confirm the SR determination in the May Proceed Letter and may ask the sponsor to submit an IDE to CDRH and to wait to initiate the trial until after the IDE is approved. <u>If the investigational IVD is exempt from IDE requirements, CBER or CDER can confirm the exempt status in the May Proceed Letter.</u>	
14	III	98 - 106	We would propose that the Guidance add language outlining how FDA would communicate the SR/NSR decision outside of the May Proceed Letter.	This section describes that the NSR/SR determination will be communicated in the Study May Proceed Letter. However, the use of investigational IVD may not always be in the first study performed under the IND, for instance in the case of additional studies, or addition of use of IVD due to a protocol amendment. Therefore, it would be helpful to describe the FDA's communication process outside of the study May Proceed Letter for such situations.
15	GLOSSARY	110 - 116	We would propose replacing the language here with the extended discussion surrounding the definition of Investigational IVD on lines 86-109 of the Draft Guidance "*Investigational IVDs Used in Clinical Investigations of Therapeutic Products*."	See comment above about aligning with "*Investigational IVDs Used in Clinical Investigations."*

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
16	GLOSSARY	129 (footnote)	For more information about nonsignificant risk studies, see the information sheet guidance for IRBs, clinical investigators, and sponsors Significant Risk and Nonsignificant Risk Medical Device Studies. This guidance is available on the FDA Medical Devices and Radiation-Emitting Products guidance web page at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm. For factors to consider in making a risk determination, please refer to the relevant section of the guidance "*Investigational IVDs Used in Clinical Investigations.*"	See comment above about cross-referencing "*Investigational IVDs Used in Clinical Investigations*," if and when that guidance is finalized.
17	GLOSSARY	146	**Exempt device** Under 21 C.F.R. § 812.2(c), exempt device means one of the following: (1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time. (2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.	We believe that adding the definition of "exempt device" would promote clarity and consistency.

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
			(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing: (i) Is noninvasive, (ii) Does not require an invasive sampling procedure that presents significant risk, (iii) Does not by design or intention introduce energy into a subject, and (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. (4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk. (5) A device intended solely for veterinary use. (6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c). (7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution. In addition to the line-edit above, please describe further the reasons (with examples) why FDA might consider studies to be SR, NSR or exempt.	

Comment Number	Section	Line No	Proposed Change	Comment/Rationale
18	GLOSSARY	146	**Non-Invasive** Under 21 C.F.R. § 812.3(k), non-invasive means a diagnostic device or procedure that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive.	We believe adding the definition of "non-invasive" will provide helpful clarity.