
Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)**

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Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION AND BACKGROUND

The purpose of this guidance is to describe 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 from investigational device exemption (IDE) requirements.² If the IVD in the trial is determined to be SR in the streamlined process, the sponsor may need to submit an IDE to the appropriate center (Center for Devices and Radiological Health (CDRH) or Center for Biologics Evaluation and Research (CBER)) in addition to submitting an investigational new drug application (IND) to the appropriate center (Center for Drug Evaluation and Research (CDER) or CBER). 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.

A study involving an investigational IVD that is determined to be NSR must follow the abbreviated requirements outlined in 21 CFR 812.2(b).³ A study involving an investigational IVD that is determined SR requires an IDE application to be submitted and is subject to the full IDE requirements.

¹ This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health at the Food and Drug Administration.

² 21 CFR 812.2(c).

³ For more information about the abbreviated requirements for NSR devices, see the guidance for industry and FDA staff *In Vitro Diagnostic (IVD) Device Studies — Frequently Asked Questions* (June 2010). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. APPLICABILITY OF THE STREAMLINED SUBMISSION PROCESS

Sponsors should consider the following information concerning the applicability of the streamlined submission process:

- 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.
- Sponsors can continue to submit requests for risk determinations to CDRH for investigational IVDs in oncology codevelopment studies using the Q-submission program.⁴
- The streamlined submission process described in this guidance does not apply to IND-exempt studies.
- The streamlined submission process described in this guidance can only be used for new INDs and does not apply to a new protocol submitted to an existing IND or protocol amendments introducing or changing the use of an investigational IVD.
- FDA encourages sponsors to discuss their interests in using this streamlined submission process during pre-IND meetings.
- 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,⁵ the trial is not eligible for the streamlined submission process. If a sponsor submits such a trial via the streamlined process, FDA will notify the sponsor to consult with CDRH or CBER for a study risk determination through the Q-submission to allow for greater input from CDRH or CBER staff.

⁴ For more information about study risk determination through the Q-submission program in CDRH, see the guidance for industry and FDA staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (May 2019).

⁵ See 21 CFR 812.3(m).

III. DESCRIPTION OF THE STREAMLINED SUBMISSION PROCESS

The sponsor should submit to the appropriate center (CBER or CDER) all information about the oncology codevelopment program (including information about the investigational IVD) in the trial protocol for the IND. As part of the IND review, CBER or CDER will consult with CDRH or CBER, as appropriate, and determine if the investigational IVD is SR, NSR, or exempt. The sponsor should consider the following for the submission:

- One sponsor should take the lead in communicating with FDA about the IND. FDA intends to communicate all feedback (including feedback about the investigational IVD) to the same lead sponsor. Sponsors should consider the following:
 - In the case where multiple IVDs are used in the oncology therapeutic trial, the drug and IVD sponsors should determine who will serve as the lead sponsor for communications with FDA
 - The lead sponsor should ensure that FDA receives appropriate letters of authorization to cross-reference the premarket submissions or incorporate relevant content by reference
- The list below highlights how a sponsor should present information in the original IND submission to facilitate the streamlined submission process, when applicable:
 - On Form FDA 1571, Investigational New Drug Application, (in section 11 under “Other”), sponsors should include the text *Streamlined IVD SRD* to indicate the intent to utilize the streamlined submission process. A sponsor also can include this information in a cover letter if the sponsor intends to submit a cover letter with the IND and indicate which section(s) of the electronic common technical document contains relevant information.
 - In the protocol submitted to the IND,⁶ a sponsor should include information about how the IVD will be used in the trial; however, detailed information about the performance of the device is generally not required. Types of information to add to the protocol include the following:
 - Description of the device
 - How the results from the investigational IVD will be applied in the clinical trial
 - A description of the population and information regarding what is known about the prevalence of the biomarker (evaluated by the investigational IVD) in the patient population
 - The specimen type that will be collected for investigational IVD testing (including the anatomical site) and whether any biopsy conducted exclusively for

⁶ 21 CFR 312.23.

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investigational IVD testing could present a potential for serious risk to the health, safety, or welfare of the subject⁷

- By signing Form FDA 1571 (section 17) sponsors provide assurance of an institutional review board review of the complete clinical trial protocol and activities for the investigational IVD and the investigational drug.⁸ FDA recommends that informed consent documents reviewed by the IRB address any risks associated with the trial, including the consequences of an incorrect biomarker test result from the investigational IVD during the screening phase as well as risks associated with the investigational drug.
- Within the 30-day review time for the IND, CBER or CDER will consult with CDRH or CBER, as appropriate, and determine if the use of the investigational IVD in the clinical trial is SR, NSR, or exempt. If the investigational IVD is NSR, CBER or CDER will confirm the NSR determination in an appendix to the Study 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 Study May Proceed Letter and will ask the sponsor to submit an IDE application to CDRH or CBER and to wait to initiate the trial until after the IDE is approved. If the investigational IVD is exempt from IDE requirements, CBER or CDER will confirm the exempt status in the Study May Proceed Letter.

⁷ 21 CFR 812.3(m).

⁸ See 21 CFR 312.66 for investigational drugs and 21 CFR 812.62 for investigational IVDs.

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GLOSSARY

Exempt device

A device that is used in a manner consistent with the criteria for an exempt investigation as outlined in 21 CFR 812.2(c).

Investigational in vitro diagnostic (IVD)

An investigational IVD is an IVD “that is the object of an investigation” (21 CFR 812.3(g)). An investigation is defined as a “clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device” (21 CFR 812.3(h)). A subject is defined as “a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used on or as a control” and “may be in normal health or may have a medical condition or disease” (21 CFR 812.3(p)).

Investigational device exemption (21 CFR 812)

An exemption that permits a sponsor to lawfully ship a device that otherwise would be required to comply with a performance standard or to have premarket approval. The exemption is for the purpose of conducting investigations of that device.

Investigational new drug (21 CFR 312.3)

A new drug or biological product used in a clinical investigation. The term also refers to a biological product that is also an IVD used in a clinical investigation.

Noninvasive

As defined in 21 CFR 812.3(k), noninvasive, when applied to a diagnostic device or procedure, means one 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. For purposes of this part, 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.

Nonsignificant risk device

A device that does not meet the definition of a significant risk device (see below and 21 CFR 812.3(m)).¹ FDA may consider certain nonexempt investigational IVDs in a therapeutic product trial to present risks that are not considered significant. In such cases, the investigational IVD is considered to be nonsignificant risk.

Significant risk device

Under 21 CFR 812.3(m), a significant risk device means an investigational device that:

¹ For more information about nonsignificant risk studies, see the information sheet guidance for institutional review boards, clinical investigators, and sponsors *Significant Risk and Nonsignificant Risk Medical Device Studies* (January 2006). FDA has also issued the draft guidance for industry, FDA staff, sponsors, and IRBs *Investigational IVDs Used in Clinical Investigations of Therapeutic Products* (December 2017), for commenting purposes. When final, this guidance will represent the FDA’s current thinking on factors to consider in making a risk determination. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.