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Investigational IVDs Used in Clinical Investigations of Therapeutic Products

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Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards

DRAFT GUIDANCE

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Preface

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff or Office responsible for this guidance as listed on the title page.

I. Introduction

Personalized medicine (also referred to as "precision medicine") relies on the use of *in vitro* diagnostic (IVD) devices[1] to detect and measure biomarkers and other individual characteristics of disease or other conditions with the goal of better directing patient treatment. With the continued growth of personalized medicine, an increasing number of clinical investigations of therapeutic products (also referred to here as therapeutic product trials or studies) are using investigational IVDs to guide the management of subjects in such investigations.[2] In some cases this has led to the development of an *in vitro* companion diagnostic device that is essential to the safe and effective use of the therapeutic product, once approved.[3] The information generated by the use of investigational IVDs in therapeutic product trials may affect important aspects of treatment for the enrolled subjects and, by doing so, directly influence the types of therapeutic products or therapeutic management strategies the subjects may be exposed to during the study. Therefore, use of an investigational IVD in a therapeutic product trial may pose significant risk to subjects. FDA is concerned that sponsors (including sponsor-

[1] See 21 CFR 809.3(a) for the complete definition of *in vitro* diagnostic products.

[2] For purposes of this guidance, the terms investigation, study, and trial are used interchangeably and have the same meaning.

[3] See the guidance entitled "In Vitro Companion Diagnostic Devices" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf) which provides information about FDA's policies regarding such devices.

investigators) and IRBs may not understand that many IVDs used as a critical part of therapeutic product trials are investigational. This guidance document is intended to inform stakeholders, including institutional review boards or institutional review committees (referred to hereafter as IRBs) reviewing clinical investigations, and sponsors that therapeutic product[4] trials that include investigational IVDs are subject to FDA's Investigational Device Exemption (IDE) regulation (21 CFR Part 812), regardless of the source or manufacturer of the device, in addition to the Investigational New Drug (IND) regulation (21 CFR Part 312).

In addition, this guidance is intended to aid sponsors and IRBs in making determinations about the nature of risks of investigational IVDs used in therapeutic product studies to streamline the decision-making process, and provides information about: (i) definitions and concepts that are important in assessing investigational IVD risks (see sections III.A - III.C), (ii) the roles and responsibilities of sponsors and IRBs in complying with IDE requirements (sections III.D - III.G), and (iii) FDA's recommendations and requirements for submitting significant risk investigational IVD information in an IDE application (Appendix). The information presented in this document is consistent with FDA regulation of investigational use of IVDs in general.

FDA's guidance documents, including this draft guidance, 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 guidance documents means that something is suggested or recommended, but not required.

II. Background

In contrast to other types of devices that act on or in a patient, IVDs are usually used on samples that are removed from or originate in the patient's body.[5] Despite their use *ex vivo*, IVDs may pose risk to patients, e.g., when they provide inaccurate test results that misinform patients' healthcare management decisions. This risk extends to the use of investigational IVDs when their results are used to guide the management of subjects in therapeutic product trials, e.g., to select or classify subjects, assign subjects to therapeutic product arms or doses, or monitor responses to treatment. Such uses have become more common given the increasing number of targeted therapeutic product development programs and potential response biomarkers.

[4] As used in this guidance, *therapeutic product* includes therapeutic, preventive, and prophylactic drugs and biological products. Although this guidance does not expressly address therapeutic devices as therapeutic products intended for use with *in vitro* diagnostics, the principles discussed in this guidance may also be relevant to such devices.

[5] Note, however, that specimen collection devices are also considered IVD devices.

An investigational IVD is an IVD (i.e., a reagent, instrument, or system intended for use in the diagnosis of disease or other conditions[6]) that is the object of an investigation,[7] and thus is subject to the IDE regulation (21 CFR Part 812). Compliance with the IDE regulation allows the shipment of investigational IVDs and their use in investigations while at the same time providing measures to protect the safety of study subjects. Under the IDE regulation, an approved IDE is required for an investigational device unless it is exempted under 21 CFR 812.2(c). Investigational IVDs are often exempt under 21 CFR 812.2(c) from most of the IDE regulation.

As specified in 21 CFR 812.40, the sponsor is responsible for ensuring IRB review and approval of an investigation.[8] Sponsor-investigators,[9] who serve as both sponsors and investigators[10] in an investigation, also assume the responsibility for ensuring IRB review and approval. Sponsors may fail to appropriately recognize and identify to their IRBs the investigational status of IVDs used in therapeutic product trials. FDA is also concerned that sponsors and/or IRBs may not adequately assess and/or describe the risks associated with investigational IVDs. The following sections are intended to provide additional information to sponsors and IRBs to clarify issues relating to the investigational status of IVDs, risk assessment(s) that should be undertaken, and the requirements applicable to investigational IVDs in 21 CFR Parts 50, 56, and 812.

III. Policy[11]

A. What is an Investigational 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)).[12] When an investigational IVD is used to guide the therapeutic management of subjects in a therapeutic

[6] See 21 CFR 809.3(a) for the complete definition of *in vitro* diagnostic product.

[7] See 21 CFR 812.3(g) for the complete definition of an investigational device and see 21 CFR 812.3(h) for the definition of investigation.

[8] *Sponsor* means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators (21 CFR 812.3(n)).

[9] *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, an investigation (i.e., an individual under whose immediate direction the investigational device is administered, dispensed, or used). The term does not include any person other than an individual. The obligations of a sponsor-investigator under 21 CFR Part 812 include those of an investigator and those of a sponsor (21 CFR 812.3(o)).

[10] *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team (21 CFR 812.3(i)).

[11] This guidance is not intended to address investigations of combination products as defined in 21 CFR 3.2(e).

[12] For determining the applicability of the IDE regulation, the relevant definition of investigation is the one found in 21 CFR 812.3(h), not the one found in 21 CFR 56.102(c).

product trial, and trial results provide information on the safety and effectiveness of the investigational IVD in addition to the safety and effectiveness of the investigational therapeutic product, FDA believes that the trial falls within the definition in 21 CFR 812.3(h). An investigational IVD used in a therapeutic product study might be, for example, a novel IVD, an IVD that is legally marketed[13] in the U.S. for a different intended use[14], or a legally marketed IVD that has been significantly modified with respect to its technological characteristics. It is important that sponsors and IRBs consider whether changes made to a legally marketed IVD, including changes to IVD labeling, result in it being investigational and, if so, subject to the IDE regulation. For example, changes to a cleared or approved IVD that would identify a new patient population, new specimen type, or both, would render the IVD investigational for the new intended use. An illustration of this would be a test approved for measuring HER2 levels *in breast cancer patients* for the purposes of determining if the patient should receive treatment with trastuzumab would be considered investigational in a clinical trial when used for measuring HER2 levels *in lung cancer patients* for the purposes of determining if the patient should receive treatment with trastuzumab).[15] Legally marketed IVDs that are used in therapeutic product trials in accordance with the intended use and indications for use for which they were cleared or approved (and that have not been modified) are not considered to be investigational, and hence are not subject to the IDE regulation.

B. IDE Regulation and Investigational IVD Risk in Investigations

Investigational devices are subject to the IDE regulation. The regulatory requirements for an investigational IVD are determined by the risk posed to subjects by use of that IVD. The IDE regulation describes three categories of device studies: significant risk (SR) studies, non-significant risk (NSR) studies, and exempt studies. It is important for sponsors and IRBs to understand the differences between these categories and appropriately evaluate the risks associated with the use of investigational IVDs in therapeutic product trials. Each investigational IVD (including those that are legally marketed for a different intended use and those that are legally marketed but significantly modified) should be assessed to determine if it is SR, NSR, or exempt.

The intended use of an investigational IVD in a therapeutic product trial, which is needed to determine if the IVD is SR, NSR, or exempt, depends upon how that IVD is incorporated in the clinical protocol, including how test results will drive treatment assignment or otherwise influence the clinical management of study subjects. When describing the intended use of an investigational IVD in a study risk determination Q-submission (see section III.H for additional information on submitting a study risk

[13] For purposes of this document, a legally marketed IVD is one that is approved, cleared, or Class I or Class II exempt. For purposes of this document, cleared or approved IVDs include those that were granted *de novo* classification.

[14] See Appendix for a description of "intended use."

[15] Another example of an investigational use is modifying the use of the device such that quantitative results can be obtained rather than qualitative results, e.g., use in titration studies.

determination Q-submission utilizing the Q-Submission process) or an investigational plan contained in an IDE submission (21 CFR 812.25(a)), the types of information discussed in the "Intended Use" section of this guidance's Appendix should be addressed.

The following discussion of the nature of risks is specific to device studies under the IDE regulation and is not intended to inform FDA's risk evaluation in other contexts, including FDA's assessment of potential risk during FDA's classification of IVDs. Furthermore, the evaluation of risk, or the determination of exemption under the IDE regulation, for investigational IVDs in therapeutic product trials is independent of the determination of whether an IND is required for that same trial. For a general discussion of this topic, please refer to the guidance entitled "Significant Risk and Nonsignificant Risk Medical Device Studies" (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf).

1) Significant Risk (SR) Devices

As defined in 21 CFR 812.3(m), a significant risk (SR) device means an investigational device that:

> (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.

Sections 812.3(m)(3) and (4) are especially relevant to the use of investigational IVDs in therapeutic product trials as described in this guidance. Incorrect test results can present significant risk when they lead to misdiagnosis and/or mismanagement of subjects' care. For example, if the treatment is a drug that has significant toxicity and efficacy is expected only in the marker-positive population, false positive test results may lead subjects without the marker to be treated with the drug, and therefore risk experiencing serious adverse events without any expectation of benefit. Note that under 21 CFR 812.3(m), the relevant consideration is whether there is a potential for serious risk, but not the likelihood for serious harm occurring. Invasive sampling[16] (e.g., certain biopsies or sampling procedures) may also introduce significant risk, even if the selection of therapy is not guided by results from the investigational IVD.

[16] See 21 CFR 812.2(c)(3)(ii); see also 21 CFR 812.3(k) for a definition of *noninvasive*.

For a more detailed discussion on the subject of risk assessment, see section III.C in this guidance.

2) Non-Significant Risk (NSR) Devices

FDA may consider certain non-exempt investigational IVDs in a therapeutic product trial to present risks that are not considered significant (21 CFR 812.3(m)). In such cases, the investigational IVD is considered to be non-significant risk (NSR).

If an investigational IVD in a therapeutic product trial is considered to be NSR, the trial is considered to have an approved IDE, i.e., the sponsor does not need to submit an IDE application and obtain FDA approval before starting the trial, if the sponsor complies with the abbreviated IDE requirements described in 21 CFR 812.2(b), including obtaining IRB approval of the trial and complying with the informed consent requirements under 21 CFR part 50.[17]

There is no requirement to inform the relevant FDA device review Center (whether the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER)) of NSR studies, even when the device is used in a therapeutic product study.[18] When the sponsor determines that an investigational IVD used in a therapeutic product trial is NSR and submits the investigation to the IRB, the IRB provides initial review, approval if appropriate, and continuing review of the trial (see Section III.D of this guidance). If information becomes available that the investigational IVD represents an unreasonable risk to the safety of the subjects (for example, the information indicates that significant harm has been incurred as a result of using an investigational IVD that was considered NSR in a therapeutic product trial, even if the IRB concurred with the sponsor that the device in question was NSR), FDA may place a clinical hold on the trial,[19] and may require submission and approval of an IDE prior to continuation of the trial (21 CFR 812.20(a)).

[17] However, if FDA notifies the sponsor that the investigational IVD is significant risk, the sponsor must submit an IDE application to FDA and obtain approval before starting the investigation (21 CFR 812.2(b) and 812.20(a)).

[18] However, the sponsor must notify the applicable FDA device review Center (CDRH or CBER) of any unanticipated adverse device effect, withdrawal of IRB approval, device recall or disposition, failure to obtain informed consent, or when otherwise directed by the IRB or FDA (21 CFR 812.150). All records associated with an NSR study are subject to inspection by FDA, particularly if the data collected in the investigation are used to support a subsequent U.S. device marketing application (21 CFR 812.145).

[19] The Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. No. 112-144, 126 Stat. 1054), enacted in 2012, amended section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by adding a new paragraph (8) that gave FDA explicit authority to place a study on "clinical hold" when the device involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation and for such other reasons as FDA may by regulation establish.

3) IDE Exempt Investigations

Trials involving investigational IVDs are exempt from most requirements found under the IDE regulation if they meet the criteria outlined in 21 CFR 812.2(c).[20] These trials are considered "exempted investigations." Most pertinent to this guidance, to be an exempted investigation under 21 CFR 812.2(c)(3), the investigational IVD used in the study must be labeled in accordance with 21 CFR 809.10(c) and the testing (i) must be noninvasive, (ii) must not require an invasive sampling procedure that presents significant risk, (iii) must not by design or intention introduce energy into a subject, and (iv) must not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.[21] Under 21 CFR 809.10(c)(2)(ii), for such a device, when being shipped or delivered for product testing prior to full commercial marketing, all labeling must bear the following statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."

Even if a device investigation is exempt under 21 CFR 812.2(c) from most requirements of the IDE regulation, such studies are subject to applicable requirements under 21 CFR 812.119 (disqualification of a clinical investigator), 21 CFR Part 50 (informed consent) and 21 CFR Part 56 (IRB).[22,23] For more information on exempted investigational IVD investigations, see the guidance entitled "In Vitro Diagnostic Device Studies – Frequently Asked Questions" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf).

C. Evaluating Whether an Investigational IVD Used in a Clinical Investigation of a Therapeutic Product is Significant Risk

Because the regulatory requirements for use of a non-exempt investigational IVD differ based on the risk of its use, sponsors should assess IVD risk during the planning phase of a clinical investigation. In large part, the risk will depend on the clinical consequences of erroneous or inaccurate results from the IVD (e.g., false positives or false negatives). Risk determinations should take into consideration factors that may be unique to each trial and the investigational therapeutic product and investigational IVD used.

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[20] Sponsors of investigational IVDs that are exempt under 21 CFR 812.2(c) must comply with applicable requirements under 21 CFR 809.10(c), 812.119, Part 50, and Part 56.

[21] We consider "diagnosis" here to mean diagnosis of a disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae (21 CFR 809.3(a)).

[22] Sponsors and IRBs who have questions about these requirements may contact Elaine Katrivanos (Elaine.Katrivanos@fda.hhs.gov), Division of Program Operations and Management, Office of *In Vitro* Diagnostics and Radiological Health.

[23] For questions related to a CBER-regulated IVD, please contact the Regulatory Project Manager (RPM) in the CBER Office where your product will be reviewed. If you don't know or are unsure of whom to contact, please contact CBER's Office of Communication, Outreach and Development (OCOD) as listed on the title page of this guidance.

The sections below present questions to help sponsors and IRBs evaluate critical factors when making risk determinations for investigational IVDs in therapeutic product trials and describe how clinical trial designs generally affect the risk of investigational IVD use.

1) Factors to Consider in Making a Risk Determination

This section presents key questions that sponsors and IRBs should consider when assessing the risk of investigational IVD use in a therapeutic product study. These questions are focused on considerations regarding how results from the IVD will be used, the potential consequences of such use, and a number of other factors pertaining to the specific circumstances of the study. Answers to these questions will assist sponsors and IRBs in assessing whether the trial involves a significant risk device as defined in 21 CFR 812.3(m).

a. Will use of the results from an investigational IVD lead to some study subjects foregoing or delaying a treatment that is known to be effective?

When the result from an investigational IVD directs subjects to an investigational therapeutic product, the availability of alternative therapies and the nature of those alternatives may influence the level of risk to the subject from an erroneous result. For example, in an investigation for a population that has no other treatment options, has exhausted all other treatment options, or for which standard of care provides only marginal benefit, the potential harm caused by an erroneous result from the investigational IVD use may be lower, because the investigational therapeutic product may not present greater risks than the alternatives available to the subject. Likewise, if treatment with the investigational therapeutic product will not interfere with the likely effectiveness of later treatment with a known effective therapy (i.e., a delay in receiving the known effective therapy will not irreversibly degrade the condition of the subject), the risk of an erroneous investigational IVD result may be lower. If, however, the standard of care or other alternatives are reasonably effective, or a delay in receiving known effective therapy would irreversibly degrade the condition of the subject, then the potential harm caused by an erroneous investigational IVD result may be greater.

b. Will use of the results from an investigational IVD expose study subjects to safety risks (e.g., adverse events from the investigational therapeutic product) that exceed the risks encountered with the control arm therapy or non-trial standard of care?

The risk(s) of the investigational therapeutic product should be considered in assessing the risk of investigational IVD use. When a drug has minimal side effects, for instance, the risk associated with use of the investigational IVD for enrollment or assignment to treatment arms will generally be lower because an

erroneous test result would not be expected to cause serious harm. However, in a study of an investigational therapeutic product with significant toxicity, the risk associated with investigational IVD use will generally be greater because an erroneous test result could unnecessarily expose a subject to the therapeutic product's toxicity.

c. Is it likely, based on existing knowledge about the relationship between the biomarker and the investigational therapeutic product, that incorrect results from the investigational IVD would present a potential for serious risk to study subjects?

Existing knowledge about the relationship of the result obtained from the investigational IVD and the potential safety and efficacy of the investigational therapeutic product should be considered independently of the answers to questions posed in sections III.C.1.a and b. For instance, if there is strong (e.g., clinical) evidence that an investigational therapeutic product with serious side effects may be effective only in a marker-positive population, then an investigational IVD used to identify marker-positive subjects is likely to be of higher risk, regardless of the relative safety and efficacy of the standard of care or alternative therapies.

A determination that the investigational therapeutic product should be restricted to a test-defined population may rely on preclinical studies. However, evidence needed to define a biomarker-positive or –negative population is oftentimes obtained during early clinical trials or in the course of an ongoing trial. For this reason, an investigational IVD that is initially NSR (e.g., used for stratification) could become SR in a later phase investigation of the same therapeutic product, or even in the middle of a particular trial. Surveillance and changing risk is discussed in section III.C.3 below.

d. Does use of the investigational IVD require invasive sampling that is not part of standard of care?

If invasive sampling is used to collect samples for testing with the investigational IVD, and that sampling is not part of the standard of care (for example, if extra biopsies of a tumor or an additional surgical procedure to obtain a specimen for testing is required), then the IVD may be SR, regardless of the risks associated with erroneous results.

2) Investigational IVD Risk and the Design of Clinical Investigations for Therapeutic Products

This section describes some intended uses for investigational IVDs in the context of some commonly used therapeutic product trial designs. To assess risk, it is important to understand how the intended use of the investigational IVD affects trial subjects' medical treatment.

Note that the risks associated with the trial designs and other uses described in the examples below are presented without reference to other information that may affect the overall risk from an erroneous result. As discussed in the previous section (section III.C.1), predicted side effects of the investigational therapeutic product and other factors should also be taken into account when making a final risk determination.

- **Study enrollment**. Investigational IVDs can be used to identify subjects for enrollment eligibility. The goal is usually to identify for inclusion those subjects most likely to benefit from therapy (efficacy), or to identify for exclusion those subjects most likely to suffer toxicity without significant benefit. Misclassification of subjects due to erroneous investigational IVD results can lead to treatment that might unnecessarily expose them to toxicities or suboptimal treatment.

- **Predicting serious adverse reactions**. An investigational IVD can be used to identify study subjects likely to be at increased risk for serious adverse reactions as a result of treatment with an investigational therapeutic product, and who, thus, should be subjected to additional or different monitoring or therapeutic procedures. Similarly, the investigational IVD may be used to identify subjects at decreased risk for adverse reactions, and thus results from that IVD may justify reduced monitoring. This use of the IVD, given its role in predicting risk for serious adverse reactions to the investigational therapeutic product, is potentially of higher risk due to the probable harm that may be incurred from acting on incorrect test results. The potential use of an investigational IVD to predict the risk of serious adverse reactions may be identified while the trial of an investigational therapeutic product is already underway. This may lead to a change in the use of the investigational IVD and its associated risk from lower risk at the start of the trial to higher risk during the course of the trial (see section III.C.3 below).

- **Dosing**. Safety and efficacy of a therapeutic product is often closely related to the dose administered if that product has a narrow therapeutic window and/or has harmful effects outside of the efficacy window. When over- or under-dosing may pose serious risks and an investigational IVD is used to determine the dose a study subject should receive, that use is likely to be of higher risk.

- **Monitoring**. An investigational IVD generally has higher risk when it is used to determine response to an investigational therapeutic product for the purpose of adjusting that treatment (e.g., schedule, dose, discontinuation) to maintain an appropriate therapeutic or safety margin.

- **Assigning subjects to study arms**. An investigational IVD can be used to assign enrolled subjects to a particular study arm. The risks associated with assignment depend on the study design (some examples noted below). However, if a study design involves a combination of different trial designs, the investigational IVD will be of higher risk if its use is of high risk within any particular component of the trial.

- A stratification study design utilizes an investigational IVD result to classify subjects into test-positive or test-negative subgroups, followed by randomization to the investigational therapeutic product or control group within each of the subgroups. When each subject has an equal chance of being in the investigational therapeutic product or control group, the investigational IVD is generally of lower risk because its use does not determine treatment selection. In some cases, the result contributes to a probability of being assigned to a particular treatment, but is not the sole determinant. In such cases, the degree of risk related to investigational IVD use will depend on the degree to which the result contributes to that probability.

- Adaptive study designs typically advance in stages, with inclusion/exclusion criteria or methodologies for assigning study subjects to treatment arms in later stages based on the outcome of earlier stages.[24] In such trials, early use of the investigational IVD may be NSR; however, use of the IVD in subsequent phases may be different and may present additional risk. When investigational IVD use becomes SR in a later stage of an adaptive trial, FDA approval of an IDE application will be required for continued use of the investigational IVD in the trial (see section III.C.3 below).

- **Retrospective studies.** Retrospective studies involve the analysis of specimens after subjects are enrolled in the trial or the trial is complete. In most cases, if the investigational IVD result does not influence treatment, that IVD would be considered lower risk and may be exempt from most IDE regulation requirements if the criteria in 21 CFR 812.2(c)(3) are met (see section III.B.3 above). Prospective retrospective studies, where specimens are collected expressly for the purpose of retrospective analysis, would carry the risk associated with specimen collection occurring outside of standard patient care.

Note that certain trial features do not inherently influence an investigational IVD risk determination. Among these are the size and the phase of the trial, the "line" of therapy proposed for the investigational therapeutic product, and the potential access of patients to other trials.

[24] For more discussion of adaptive study designs, see the guidance entitled "Adaptive Designs for Medical Device Clinical Studies (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446729.pdf) and the draft guidance entitled "Adaptive Design Clinical Trials for Drugs and Biologics" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf) (This draft guidance represents FDA's proposed approach on this topic. When final, this guidance will represent FDA's current thinking on this topic.).

3) How Investigational IVD Risk May Change During the Course of a Clinical Investigation

When an investigational IVD is NSR at the beginning of a clinical investigation but becomes SR at a later stage, or when a SR investigational IVD is introduced into a clinical investigation, FDA approval of an IDE application, in accordance with 21 CFR 812.20(a)(2) and 21 CFR 812.30(a), is required prior to use of the SR investigational IVD in the clinical investigation. There are several ways in which an investigational IVD may be introduced into a clinical investigation or an investigational IVD's use may change during the course of a clinical trial.

- Safety and outcomes data, and other information gathered during the trial may change the risk of the investigational IVD. For example, if results from early subjects in the trial indicate more severe side effects or less improvement in a biomarker-positive population than expected, the assessment of risk from use of an investigational IVD to detect that biomarker may change.

- Adaptive clinical trial designs that incorporate pre-planned and conditional alterations in trial conduct may change the use of an investigational IVD as the trial progresses. Risk posed by altered use of the IVD should be considered.

- A new or amended study protocol for an existing investigational new drug application (IND) may introduce or alter the risk of an investigational IVD. For instance, a Phase 1 trial may not include an IVD or it may include an IDE exempt or a NSR IVD. However, a later Phase 2 trial conducted under the same IND may add a SR device or may change the use of an investigational IVD in such a way as to make the IVD SR. In such a case, the sponsor would be required to submit an IDE application to FDA in accordance with 21 CFR 812.20; the investigational IVD could not be used in the Phase 2 trial until FDA approves the IDE application (21 CFR 812.20(a)(2) and 812.30(a)).

Ongoing surveillance during a clinical investigation is recommended to monitor the risk of the investigational IVD. For a SR investigation, the timing of an IDE application is at the sponsor's discretion and should be planned to allow sufficient time for FDA review before the use of the SR investigational IVD in the clinical investigation. FDA recommends interacting with the applicable Center (CDRH or CBER) via the Q-Submission process (see section III.H) prior to initiating the first stage of the trial. This interaction may facilitate FDA review of a future IDE application if required and may provide the sponsor with greater predictability in regard to the IDE process.

D. Recommendations for IRBs and Sponsors in Evaluating Investigational IVDs in the Context of Clinical Investigations for Therapeutic Products

Each U.S. site that performs testing using the investigational IVD is considered a study site. Whether a trial involves only one site or many sites, it is the responsibility of the trial sponsor to ensure that IRB review and approval are obtained (21 CFR 812.40).

Each reviewing IRB must, as part of its review of the clinical investigation, consider the sponsor's risk determination of the investigational IVD (21 CFR 56.108, 56.111, 812.2(b)(1)(ii), 812.62, and 812.66). If a sponsor and its IRB cannot agree on the level of risk presented by the investigational IVD, the sponsor may request a study risk determination from FDA through the Q-Submission process (see section III.H).

If the IRB concurs with a sponsor's NSR determination and approves the investigation, and the sponsor complies with the abbreviated requirements in 21 CFR 812.2(b)(1), the sponsor is considered to have an approved IDE for use of the investigational IVD in the therapeutic product trial, unless FDA has notified the sponsor under 21 CFR 812.20(a) that approval of an IDE application is required. Failure of a sponsor and an IRB to recognize or correctly assess the risks of use of an investigational IVD in a therapeutic product trial may deprive the study subjects of the additional protections associated with significant risk device investigations. In addition to other IDE requirements, a significant risk device study entails FDA evaluation of the investigational IVD to determine, among other things, whether the IVD has been adequately validated for its use in the study. For this reason, it is important for IRBs to be aware of how investigational IVDs are used and the risks associated with their use in the context of therapeutic product trials.

The information described below is intended to provide assistance to sponsors and IRBs in understanding FDA's regulations, and to aid in the development of a risk assessment process for investigational IVDs intended for use in therapeutic product trials.

1) Information the Sponsor Should Include in Its Submission to the IRB

The sponsor should provide an assessment of whether or not any IVD being used in a study is an investigational IVD, along with supporting information. The sponsor should also provide its assessment of the investigational IVD as SR, NSR, or exempt from most requirements of the IDE regulation, and provide a rationale for the assessment.[25] Note that this should be done even if the forms provided by the IRB to the sponsor do not specifically request such information. If the IRB determines that the investigational IVD is SR and notifies the sponsor of such determination, then the sponsor may either seek a study risk determination from FDA (if the sponsor disagrees with the IRB's determination) or submit an IDE application to FDA and comply with other applicable regulatory requirements in the IDE regulation.[26]

[25] Under 21 CFR 812.2(b)(1)(ii), if the sponsor believes its investigational device is NSR, the sponsor must present the IRB with a brief explanation of why the device is NSR.

[26] Under 21 CFR 812.150(b)(9), if the IRB disagrees with an NSR determination by the sponsor and determines that the device poses a significant risk, the sponsor must report this finding to the FDA within five working days.

In reviewing a clinical investigation, an IRB considers whether the criteria in 21 CFR 56.111 are met, including that the risks to subjects are minimized and are reasonable in relation to the anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. So that IRBs may make such a determination, in the submission of a therapeutic product trial to an IRB, a sponsor should identify each investigational IVD and its use in the trial.[27]

2) Recommendations for Review Questions for IRBs

In order to carry out its obligations under 21 CFR Part 56, including that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25 (as required by 21 CFR 56.109(b)) and that a clinical investigation meets the criteria for approval in 21 CFR 56.111, IRBs should assess the risks of use of proposed investigational IVDs in all therapeutic product trials. IRBs should request follow-up information if they believe that the sponsor did not identify or adequately describe the use of an investigational IVD and its associated risks in such trials.

To correctly identify whether an investigational IVD is used in a study, and to assess the risks of use of an investigational IVD in such study, FDA recommends that IRBs consider the following questions when reviewing applications for therapeutic product trials:

1) Are one or more IVDs being used in this study? If so, the answers to the following questions should be assessed separately for each IVD.

2) Is the IVD investigational?

   a. Is the IVD legally marketed (see footnote 13)? If not, its use in the clinical trial should be considered investigational.

   b. If the IVD is legally marketed, does the use of the IVD in the therapeutic product study represent a new use (see section III.A.)? A new use for a cleared or approved IVD will make that device investigational and subject to the IDE regulation. New uses may involve use of the IVD on patient populations for which it was not cleared or approved, or use in the same patient population but with a different specimen type or with a different therapeutic product than for which it was cleared or approved. Other modifications to a cleared or approved IVD, including changes to the instructions for use, may also render it investigational and subject to the IDE regulation.

If the IVD is investigational:

[27] Under 21 CFR 50.25(a), the informed consent form must include, among other things, a description of any experimental procedures and of any reasonably foreseeable risks or discomforts to the subject. Therefore, the informed consent form must identify investigational IVD use and the risks associated with that use in the clinical investigation. Description and acceptance of investigational IVD risk does not constitute mitigation of that risk.

3) Does it meet the exemption criteria under 21 CFR 812.2(c)? For example, does it meet the criteria in 21 CFR 812.2(c)(3), which are specific to diagnostic devices? Note that even if it is exempt under 21 CFR 812.2(c), sponsors must comply with applicable requirements under 21 CFR 809.10(c), 812.119, Part 50, and Part 56..

4) If not exempt under 21 CFR 812.2(c), what are the risks of investigational IVD use in this investigation (see section III.C)? In particular:

   a. Would inaccurate results from use of the investigational IVD present a potential for serious risk to the health, safety, or welfare of a subject? Consideration of the trial's design (see section III.C.2 above) may help in addressing the key questions about significant risk that are set forth in section III.C.1. Examples of specific questions to consider are:

      1. Does the investigational IVD determine whether a subject is enrolled in a study, or to which treatment arm within that study a subject will be assigned? If so, what are the consequences of an incorrect investigational IVD result?

      2. Will the investigational IVD be used for subject monitoring or adjusting dosage? Again, the risk associated with erroneous investigational IVD results should be considered.

   b. Does specimen collection for use of the investigational IVD present a potential for serious risk to the health, safety, or welfare of a subject? If use of the investigational IVD involves invasive procedures for the subject that would not normally be performed as part of standard of care or patient management, then it may be considered SR.

5) Is an IDE application required for the investigation? It is important to understand that compliance with the IND regulation does not exempt the investigation from the IDE regulation (see sections III.E - III.G).

6) If an IDE application is required, what is the status of the IDE application? While an IRB is not involved in the review of an IDE application, the IRB may wish to be made aware of FDA's comments and decision on the IDE application.

7) Do informed consent documents clearly explain the investigational nature of the IVD and its risks (e.g., the risks of inaccurate test results)? In accordance with 21 CFR 50.25(a)(1) and (2), informed consent documents must identify any procedures which are experimental and provide a description of any reasonably foreseeable risks or discomforts to the subjects. Thus, the informed consent documents for the types of investigations discussed in this guidance must describe any reasonably foreseeable risks or discomforts associated with the investigational therapeutic product and the fact that an investigational IVD would be used along with any reasonably foreseeable risks or discomforts associated with that use. For the investigational IVD, these risks include the risks associated with inaccurate results (in the context of IVD use in the study), and the risks associated with specimen collection and use as part of the study.

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3) When Can a Sponsor Begin a Therapeutic Product Trial Involving Use of an Investigational IVD?

In addition to IRB approval, it is important for sponsors to understand that even if a therapeutic product trial is permitted under the IND regulation, or is exempt from the requirements of the IND regulation under 21 CFR 312.2(b), the sponsor must still have an IDE that is approved or approved with conditions by the FDA if the trial includes a SR investigational IVD.

As explained in FDA's guidance entitled "FDA Decisions for Investigational Device Exemption Clinical Investigations" (www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf), approval with conditions for an IDE indicates that: (i) FDA believes the sponsor has provided sufficient data to support initiation of subject enrollment in a clinical investigation; (ii) there are no subject protection concerns that preclude initiation of subject enrollment; (iii) there *are* additional conditions that must be met to address certain outstanding issues; and (iv) the investigation may proceed, but the additional conditions are to be fulfilled within 45 days of the date of FDA's decision letter. FDA recommends that IRBs ensure that any investigation incorporating an SR investigational IVD has an FDA-approved or conditionally approved IDE by obtaining a copy of FDA's IDE approval letter from the sponsor of the investigation.

Sponsors and IRBs should be aware of protocol amendments that may change subject monitoring as outlined in 21 CFR 312.30(b)(1)(iii).[28] They should also be aware of other modifications to the protocol that alter the investigational IVD risk from NSR to SR, or that add the use of an SR investigational IVD to a therapeutic product trial which originally did not involve any investigational IVD, or involved the use of an investigational IVD that met the criteria for exemption under 21 CFR 812.2(c)(3), or involved the use of an NSR investigational device. Attention to such protocol amendments by IRBs is critical in protecting study subjects (see section III.C.3) Changes that introduce a SR investigational IVD to the trial will require FDA approval of a new IDE or approval of a supplement to an existing IDE independent of any amendments to an existing IND (21 CFR 812.20).

E. Common Questions about Investigational IVD Use in Clinical Investigations of Therapeutic Products and Compliance with the IDE Regulation

The IDE regulation applies to *all* clinical investigations of devices to determine safety and effectiveness (see section III.A) except as provided in 21 CFR 812.2(c) (21 CFR 812.2(a)). FDA has identified several situations in which sponsors and IRBs had questions as to whether an IDE was required. These include:

[28] 21 CFR 312.30(b)(1)(iii) requires the submission of a protocol amendment for "[t]he addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety."

- Use of an investigational IVD in a therapeutic product trial that was exempt from the IND regulation. Even if the therapeutic product(s) in the trial is/are exempt from the requirements of 21 CFR Part 312 under 21 CFR 312.2(b), the investigational IVD in the trial is subject to the IDE regulation (21 CFR Part 812). If the investigational IVD does not meet the exemption criteria under 21 CFR 812.2(c), then a risk assessment should be conducted to determine whether the IVD is NSR or SR. If the investigational IVD is SR, then in accordance with 21 CFR 812.42, a sponsor shall not begin an investigation or part of an investigation involving the IVD until FDA has approved an IDE application.

- Use of an investigational IVD without intent to commercialize. If the investigation uses an investigational IVD for directing the management of subjects but the IVD manufacturer does not intend to seek FDA clearance or approval for the commercial distribution of the IVD, the IDE regulation may still apply, as 21 CFR 812.2(a) states that Part 812 applies to all clinical investigations of devices to determine safety and effectiveness[29] except as provided in 21 CFR 812.2(c), which addresses investigations exempted from most of the IDE regulation.

F. Inclusion of Investigational IVD Information in an IND

Increasingly, the use of diagnostic tests for markers of interest in therapeutic treatment selection in protocols submitted to therapeutic product INDs has necessitated consultation between the device review Center (CDRH or CBER) and the therapeutic product review Center (CDER or CBER). Sponsors should be aware that all investigational IVDs used in therapeutic product trials are also subject to the IDE regulation (21 CFR Part 812), and may also require the submission of a separate IDE application if determined to be SR. A therapeutic product trial that also incorporates the use of an SR investigational IVD may not be initiated without an approved IDE application.[30] Parts of the therapeutic product trial unrelated to the investigational IVD may still proceed, however, unless the trial is placed on clinical hold by the therapeutic product review Center.

Although studies with NSR investigational IVDs do not require the submission of an IDE, they must still comply with the abbreviated IDE requirements described in 21 CFR 812.2(b).

[29] See section III.A for further discussion.

[30] When an approved IVD is used to guide the therapeutic management of subjects in a clinical trial of a new therapeutic product (e.g., a HER2 test that is approved for use with trastuzumab is used to guide the therapeutic management of subjects in a clinical trial of a new breast cancer drug), generally the use of the IVD would be considered investigational (see section III.A). However, for such IVDs, FDA does not intend to examine whether they comply with the requirement for IDE approval under the FD&C Act and 21 CFR Part 812 when IRB approval is obtained and maintained for the investigation using such IVD, the investigation meets the abbreviated requirements under 21 CFR 812.2(b)(1)(i), (iii)-(vii), and assurance is provided to the IND that the IVD is used with the new therapeutic product in accordance with the instructions for use (IFU) that are provided in the device's approved labeling. Assurance of adherence to the IFU should minimally address the intent-to-test criteria (e.g., disease type [such as lung cancer, colon cancer], specimen type [such as plasma, serum, tissue], and specimen adequacy), the test methodology, and the classification criteria (i.e., cutoff, if used).

In addition, under the IND regulation, clinical protocols for INDs must contain a description of laboratory tests used to monitor the effects of the drug in human subjects and to minimize risk (21 CFR 312.23(a)(6)(iii)(*g*)). Further, FDA may request that the sponsor submit in the IND other relevant information concerning the IVD(s) used in the trial as needed (21 CFR 312.23(a)(10)(iv),(11)). For instance, the therapeutic product review Center (CDER or CBER) may request submission of IVD data, including performance data, to an IND should such information be needed to assess the clinical trial as a part of the IND review.

G. Managing IDEs and INDs for the Same Study

To simplify the application process, the IDE submission for a therapeutic product trial that is under an IND should cite the corresponding IND number. IDEs and INDs may also cross-reference each other through a letter of authorization (LOA) or, in cases where either an IND or IDE is not required, information about the non-submitted investigational product may be provided through use of a master file.[31] Master files allow one party to submit information for confidential review by FDA without granting access to other parties. For instance, if the manufacturer of the investigational IVD wishes to refer to confidential information about an investigational drug product to which it does not have access, the therapeutic product manufacturer can submit a master file containing that information and authorize the IVD manufacturer to reference it. FDA will then review the information in the master file as part of its review of the IDE for the investigational IVD. Similarly, an IVD manufacturer may submit a master file and authorize a therapeutic product manufacturer to reference that file, so that the confidential information about the investigational IVD can be included in FDA's review of the therapeutic product IND. In cases in which the relevant confidential information has been submitted in another regulatory submission, such as an IND or an IDE, the owner of the submission may simply provide the third party an LOA to reference specific sections of the regulatory submission. The LOA may grant the FDA either the *right to reference* or the *right to reference* ***and*** *discuss* the information in the regulatory submission with the third party.

An IND and IDE may be held by the same sponsor or each may be held by different sponsors representing different entities (e.g., a pharmaceutical company and an IVD company). The investigation conducted under the IND is subject to clinical hold under 21 CFR 312.42.[32] For example, CDER may place an investigation on clinical hold under 21 CFR 312.42(b)(1)(i) or (b)(2)(i) if the agency determines that the investigation places subjects at an unreasonable and significant risk of illness or injury. For example, this determination could be made because an investigational IVD used to identify subjects for inclusion in the clinical trial of

[31] For more information, see Introduction to Master Files for Devices (MAFs) (http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/ucm142714.htm) and Guideline for Drug Master Files (DMF) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm). For information on master files relating to biologics license applications, contact the Center responsible for review of that biological product.

[32] This is in addition to the authority granted under FDASIA to place investigations subject to the IDE regulation on clinical hold. See footnote 19, above.

an investigational therapeutic product with significant toxicity was deficient and therefore might not reliably select subjects. Regardless of whether the IND and IDE are held by the same or different sponsors, sponsors should understand the regulatory requirements applicable to investigations involving both an investigational therapeutic product and an investigational IVD.

An approved IDE for an investigational IVD used in a therapeutic product trial may make it easier for sponsors to use that same investigational IVD for a separate therapeutic product trial, as only an approved supplement to the IDE (in addition to IRB approval) may be needed to commence the new trial if the IVD indication is the same or very similar (21 CFR 812.35).[33]

H. Q-Submission Meetings

FDA recognizes that many factors must be considered in designing therapeutic product trials that involve the use of investigational IVDs for subject selection or other purposes. As the testing and therapeutic strategy is being developed, sponsors and sponsor-investigators are encouraged to meet with FDA in a Q-submission meeting prior to starting the trial to discuss questions about IVD risk, study design, and regulatory requirements. It is often helpful to have both the IVD and the therapeutic product sponsors at these Q-Submission meetings. In addition, a sponsor wishing to obtain a written study risk determination of the proposed study from FDA may submit a study risk determination Q-submission. For further information, see the guidance entitled "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf).

[33] Note that certain changes (e.g., a significant change to the design of the device or a change in its indication) may require approval of an IDE supplement. See 21 CFR 812.35; see also guidance entitled "Changes or Modifications During the Conduct of a Clinical Investigation" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082158.pdf).

APPENDIX. Important Considerations for Sponsors

This section describes important considerations for sponsors as they prepare an IDE application.[34] When applicable, sponsors should also ensure that laboratories using the investigational IVD in the investigation are compliant with the Clinical Laboratory Improvement Amendments and related regulations (42 U.S.C. 263a; 42 CFR Part 493), and that the investigation is compliant with all applicable statutes, regulations, and conditions of IRB and/or FDA approval (21 CFR 812.30(b)(1)).

A. Contents of an IDE Application

- The contents of an IDE application are detailed in 21 CFR 812.20, 812.25, and 812.27. Broadly, these regulations address administrative requirements, description of the IVD, prior investigations with the IVD, and the proposed investigational plan.
- For investigational IVDs that will be part of a therapeutic product trial, sponsors should also address the following issues, if applicable, in IDE applications:
    - **Investigational IVD description.** The investigational plan must include a description of the investigational device (21 CFR 812.25(d)). The investigational IVD description should include test principles and technology, all equipment, reagents and supplies (including calibration or control materials), and procedures used to conduct the test, as well as a description of installation requirements and calibration parameters. All analytes detected by the investigational IVD should be described. As an example, for genetic tests, a list of all assayed mutations (e.g., SNPs or gene rearrangements) should be supplied, as well as PCR primers and probe design, if applicable.

      As part of the investigational IVD description, all necessary instruments and/or software should be listed and described. Information pertaining to the level of software validation that has been performed for the investigational IVD will be critical in evaluating whether the investigational IVD is being used appropriately in the context of the study. For investigational IVDs with highly complex, multivariate algorithmic software, this may be the largest portion of data submitted to support the IDE.[35]

[34] For general information on IDEs, see "Guidance on IDE Policies and Procedures" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm). Additionally, sponsors may consider various resources for information on IVD validation, for example, Mansfield et al., Biomarkers for pharmacogenetic and pharmacogenomic studies: Locking down analytical performance, (2007a) *Drug Discovery Today: Technologies* 4:17, and Mansfield et al., Biomarkers for pharmacogenetic and pharmacogenomic studies: special issues in analytical performance, (2007b) *Drug Discovery Today: Technologies* 4:21.

[35] For information on the type of documentation FDA will expect for device software, please reference "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf), issued May 11, 2005.

- **Sample type, acquisition, and processing**. Descriptions of the type of specimen(s) to be tested, specimen collection, processing, storage, sample identification, and acceptance/rejection criteria should be provided.

- **Intended use**. The investigational plan must include the intended use of the investigational device (21 CFR 812.25(a)). The intended use for the investigational IVD should encompass information on the analyte to be detected and how it relates to the investigational therapeutic product; whether the IVD produces a quantitative, semi-quantitative, or qualitative result; specimen type(s); conditions for use; the condition or disease to be screened, monitored, treated, or diagnosed; the intended use population (i.e., the population that will be tested using the investigational IVD); frequency of use; and physiological basis. The intended use population should be adequately described and justified. From the standpoint of the therapeutic product trial, testing with the investigational IVD should reflect the appropriate intent-to-treat (or not-to-treat) population.

- **Description of investigational IVD cut-offs**. Cut-off values (i.e., clinical decision points) that distinguish relevant trial populations should be established for the investigational IVD. The cut-off value should represent a point where the investigational IVD's analytical performance characteristics support reliable discrimination of the subject populations. If indeterminate (or gray) zone values will be produced, the sponsor should discuss how subjects with test values in the zone will be classified, and the use of indeterminate zone values in managing subjects in the therapeutic product trial.[36]

- **Test performance**. The investigational IVD has demonstrated analytical validity, such that it is able to give accurate measurements from subject specimens. In the context of a therapeutic product trial, where results from the investigational IVD will be used to guide subject treatment, FDA is particularly concerned with analytical validity, including precision, reproducibility, analytic sensitivity, analytic specificity, and accuracy. Depending on the type of assay, matrix comparison, linearity, and interference may also be important.

[36] An example of use of a cutoff with a gray zone is the 2+ result of the immunohistochemistry HER2 tests. Reproducibility studies revealed that readers had a difficult time separating 2+ from 1+ and 3+ results. The clinical trial confirmed that fewer persons with 2+ results were having positive drug outcomes than persons with clear 3+ results, and, as a result, 2+ results were re-categorized as representing equivocal rather than positive results. To address uncertainty of values in this gray zone, clinical practice guidelines recommend retesting 2+ results with another type of test. Wolff et al., Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer, (2014) *Arch Pathol Lab Med* 138:241.

Analytical performance around cut-off values is likely to have the largest impact on subject safety. Failure to select an appropriate cutoff, or failure of the investigational IVD to perform adequately around the cutoff, may result in the assignment of subjects to inappropriate treatments.

The amount of information on analytical performance of an investigational IVD will depend on the nature of the IVD and the therapeutic product trial in which it is used. For instance, while more limited information on analytical performance may be sufficient when a IVD is used in an early feasibility study,[37] more comprehensive information on analytical performance will likely be needed for a registrational or pivotal trial.[38]

- **Preclinical and/or clinical information**. The preclinical and/or clinical information provided should justify the subjects' exposure to the investigational IVD.

- **Clinical study design**. Questions or hypotheses should be clearly stated and should be addressed by a well-designed and sufficiently powered study.

- **Benefit/Risk assessment**. The IDE submission must include a risk analysis that includes a justification for the investigation (21 CFR 812.25(c)). Further, in reviewing an IDE application, FDA considers, among other things, whether the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained (21 CFR 812.30(b)(4)). Therefore, the application should contain information on why the anticipated benefits to the study subjects (or why the importance of the knowledge to be gained from the trial) outweigh the risks of exposure to the investigational IVD. The type, magnitude, duration, and probability of the anticipated benefits should be weighed against the type, severity, duration, and probability of the risks associated with the use of invasive sampling techniques, as well as the potential harms that could result from an erroneous test result by the investigational IVD (such as a false positive or false negative). The risk of investigational IVD use in therapeutic product trials is closely related to that posed by the investigational therapeutic product, and therefore benefit/risk associated with the therapeutic product needs to be considered in this analysis.

[37] For further information about early feasibility device clinical studies, see guidance entitled "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf).

[38] Note that under 21 CFR 812.20(b)(2) and 812.27(a), the IDE application must include a complete and comprehensive report of prior investigations of the device (including clinical, animal, and lab testing).

B. FDA Review of IDE Applications

Sponsors should submit their signed IDE application together with accompanying materials to CDRH's or CBER's Document Control Center (DCC) in accordance with the guidance entitled "eCopy Program for Medical Device Submissions" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313794.pdf). Upon receipt of an IDE application, sponsors are notified in writing of the date that FDA received the original application and the IDE number assigned. The 30 day review clock for the IDE application begins on the date stated in the acknowledgement letter to the sponsor.

Each IDE application received in CDRH's DCC or CBER's DCC is routed to the appropriate Division, and assigned to a reviewer or review team. The IDE application is first screened for required content. If the IDE application contains adequate information for review, the review team then reviews the IDE application within 30 days of receipt. FDA will inform the sponsor of its decision, or notify the sponsor that the investigation may not begin, within 30 days from the date of receipt of the IDE application.[39]

If an IDE application is approved or approved with conditions, the sponsor may begin subject enrollment, up to the number of subjects and investigational sites specified in FDA's decision letter, once allowed to proceed under IND, if applicable, and upon receipt of IRB approval, which may occur prior to FDA approval. If FDA does not have outstanding issues that the sponsor needs to address to support the study of the subject cohort under the proposed investigational plan, the IDE will be approved without conditions. Alternatively, if FDA has identified issues that need to be addressed in a timely manner but do not preclude initiation of subject enrollment in the clinical investigation, the IDE will be approved *with* conditions. In the case of approval with conditions, approval is granted and study enrollment may begin immediately on the condition that, within 45 days from the date of FDA's decision letter, the sponsor submits information addressing the issues identified in FDA's letter.

In certain instances, resolution of outstanding issues may be necessary before initiation of subject enrollment. In these instances, the IDE will be disapproved in accordance with 21 CFR 812.30, meaning that the sponsor may not initiate subject enrollment in the investigation until the sponsor addresses the issues identified in FDA's letter and receives an approval or approval with conditions letter. In cases of disapproval of the IDE, a sponsor has the opportunity to respond to the deficiencies by submitting an amendment or, in accordance with 21 CFR 812.30(c)(1), to request a regulatory hearing under 21 CFR Part 16.

The guidance entitled "FDA Decisions for Investigational Device Exemption Clinical Investigations" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf) provides additional information on this topic.

[39] If FDA does not, within 30 days, notify the sponsor that the study may not begin, the IDE application will be deemed approved, unless the device is a banned device, in accordance with 21 CFR 812.30(a).