**FREQUENTLY ASKED QUESTIONS**

**Regulatory Assessment of a Clinical Study Involving an**

 **In Vitro Diagnostic (IVD) Device**

In vitro diagnostics (IVDs) meet the definition of a device under the Federal Food, Drug and Cosmetic Act. Section 201(h) of the Act defines a device as: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

1. recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.” 21 U.S.C. 321(h) (emphasis added).

The Investigational Device Exemptions (IDE) regulation, 21 CFR 812, provides regulatory requirements for studies of investigational devices, including those using IVDs. An IVD device (IVDD) is often different from other devices because most other devices function “on” or “in” a patient. Under 21 CFR 812.3(p), however, the definition of a “research subject” includes use of a sample obtained from a person on which an investigational device is tested.

The risks of testing an IVDD include both the risks of obtaining the sample and the risks associated with using the results of the IVDD. The severity of the risks (potential for harm) determine what parts of 21 CFR 812 apply to the study and what information subjects need to be given about the IVDD.

1. **Is the use of an IVDD in the study subject to 21 CFR 812?**

A research study with one or more objectives to test the safety or effectiveness of an IVDD is a device study and is subject to 21 CFR 812. Under FDA guidance documents, this may include determining the performance characteristics of the IVDD, comparing the usefulness of the IVDD to other available tests, and/or validating the utility of the IVDD.

1. **Does the study constitute basic research only?**

One study objective often seen is to determine whether biomarkers correlate with disease state, treatment response, or risk of disease. Based on the study design some of these may be considered ‘basic research’ (not subject to 21 CFR 812) while others would be considered ‘development or testing of an IVDD’ (subject to 21 CFR 812). The following examples illustrate ‘basic research’ versus ‘IVDD development or testing’.

* 1. An investigator is collecting samples as part of a drug, biologic or other study to determine if there are any biomarkers or biomarker combinations (“signatures”) that might correlate, for example, with a particular disease, disease risk, or treatment response. Biomarkers may include proteins, DNA, RNA, metabolites, and/or other molecules found in the body. These samples are merely being used for “fishing” and specific biomarkers have not been previously identified and are not being evaluated. **This type of study would be considered basic research and thus not subject to 21 CFR 812.**
	2. An investigator is collecting samples as part of a drug, biologic or other study with the objective to determine if one or more specific biomarkers or biomarker combination (i.e. “signatures”) might correlate, for example, with a particular disease, disease risk, or treatment response. This example is different than the first in that a specific biomarker has been defined and is being evaluated. **This type of study would be considered the development or testing of an IVDD and subject to 21 CFR 812.**
	3. The study includes the development of an In Vitro Diagnostic Multivariate Index Assay (IVDMIA). An IVDMIA is a diagnostic device that “combines the values of multiple variables using an interpretation function to yield a single, patient-specific result” (e.g. a “classification,” “score,” “index,”, “algorithm,” etc.), that is intended for use in the diagnosis of a disease or condition, or in the cure, mitigation, treatment or prevention” or it “provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.” For example, an investigator is integrating quantitative results from multiple assays to obtain a qualitative “score” that predicts a person’s risk of developing a disease or condition. **This type of study would be considered development or testing of an IVDD and thus subject to 21 CFR 812.**

If the study’s objective is to collect samples for unspecified future use, this would be considered basic research (e.g. a biorepository) and not subject to 21 CFR 812. The use of such samples in later research may, however, be subject to 21 CFR 812 as described above. Consideration of the IVDD risks, including sampling method, would occur in the context of the future study when the samples are being used.

1. **What happens if a study is subject to 21 CFR 812?**

If the FDA has not made a determination of the risk level of the study and/or what parts of 21 CFR 812 apply, the IRB must make this determination.

1. **Is the use of the device in the study IDE exempt?**

Diagnostic device studies are considered exempt from 21 CFR 812 (IDE regulations) if the sponsor complies with applicable labeling requirements in 21 CFR §809.10(c) and **all** of the following criteria are met:

1. **IVDD is non-invasive.**

A noninvasive device is one that:

* Does not penetrate or pierce the skin or mucous membranes of the body, the ocular cavity or urethra; or,
* Does not 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.
1. **The IVDD does not require an invasive sampling procedure that presents significant risk.**
* Noninvasive sampling is defined in the same way as a noninvasive device. Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues left over from those taken for non-investigational purposes is also considered noninvasive (21 CFR 812.3(k)).
* If the testing of the IVDD requires invasive sampling, it may still be considered IDE exempt if the sampling does not present a significant risk.
	+ Risk determination for invasive sampling is based on the potential harm that may result from the sampling. While the types of sampling that may constitute significant risk have not been specified in the regulations, FDA guidance states sampling techniques that require the biopsy of a major organ, use of general anesthesia, or placement of a blood access line into an artery or large vein (subclavian, femoral, or iliac) present a significant risk.
1. **IVDD does not introduce, by design or intention, energy into a subject.**
* ‘Energy’ may include light, heat, sound, or radiation emitted by the IVDD.
1. **IVDD will not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.**
	* As per the FDA guidance, this requirement is met if:
		+ The test results do not influence patient treatment or clinical management decisions before the diagnosis is established by a medically established product or procedure.
		+ If an investigational test uses a new technology or represents a significant technological advance, established diagnostic products or procedures may not be adequate to confirm the diagnosis provided by the investigational IVDD and the study cannot be IDE exempt.

If all four exemption criteria are met, the study is considered IDE exempt. The study may still FDA-regulated under 21 CFR 50 and 56, however, (and require IRB review and subject consent, for example) even 21 CFR 812 does not apply.

If the study does not meet all four criteria, a determination of the risk level of the device study must be made (i.e. whether the use of the IVDD in the study does or does not pose a significant risk).

As a point of clarification, an IVDD is not likely to be considered a “custom device” as described in 812.2(b)(7) as one of the IDE exempt categories. The definition of a “custom device” is provided below, and is more commonly associated with items produced to suit the specific (physical) needs of one patient, such as a modified prosthetic or dental implant.

Custom device means a device that:

(1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;

(2) Is not generally available to, or generally used by, other physicians or dentists;

(3) Is not generally available in finished form for purchase or for dispensing upon prescription;

(4) Is not offered for commercial distribution through labeling or advertising; and

(5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.

1. **If the study is not exempt, can the study be run under an abbreviated IDE or does it require an IDE application to the FDA?**

The determination of whether a study will require an IDE application to the FDA is based on the risk to subjects in the study. This requires an assessment of whether or not the device as used in the study is considered Non-Significant Risk (NSR) or Significant Risk (SR). If the FDA has not made this assessment, the IRB must determine the risk level of the study.

If the study is SR, and IDE application to the FDA is required and the IDE must be in effect prior to IRB approval.

If the sponsor is submitting the study as NSR without a determination from the FDA, the sponsor should provide a rationale for why the study is NSR (under 21 CFR 812.2(b)(ii)) prior to IRB approval.

If the IRB determines the study is NSR, the study is considered to have an approved IDE under the abbreviated requirements of 21 CFR 812.2 and no IDE application to the FDA is needed.

If the IRB and sponsor disagree regarding the SR/NSR assessment, the FDA can assist in making the risk determination. If sent to the FDA for review, the risk determination made by the FDA is final. The most common way of soliciting FDA feedback is through a NSR/SR risk determination Q-submission.

**4. What are the considerations for determining if use of the device in the study poses a “significant risk” (SR)?**

Under 21 CFR 812.3(m), an SR device:

* Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
* Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
* 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
* Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The risks of an IVDD come from the sampling procedure and/or the decisions made based on the results of the IVD testing. The FDA guidance (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf>) describes the following considerations for making the NSR/SR determination:

* The risk determination is based on the proposed use of a device in an investigation and not on the device alone. Therefore, the risk associated with the study as a whole, and not just the risk associated with the device itself, should be evaluated. The same device can be used in two different protocols and, based on how it is used, one study can be considered SR, while the other study could be NSR.
* Any additional procedures such as surgery, prolonged anesthesia, radiation exposure, prolonged hospitalization, etc., required for the evaluation of the IVDD should be considered.
* The risk of any invasive sampling procedure should be evaluated, for example;:
	+ Is the sample collected for research purposes only?
	+ Is the sampling from the biopsy of a major organ or obtained under general anesthesia?
* The potential for misdiagnosis and/or error in treatment caused by inaccurate test results that could be life-threatening or could result in permanent impairment of a body function or permanent damage to the body structure should be evaluated. For example:
	+ False positive results can lead to unnecessary confirmatory testing, unnecessary treatment that can be invasive or have harmful side effects, and/or unnecessary psychological trauma when serious or life-threatening diseases or conditions are involved.
	+ False negatives can result in a delay in establishing the correct diagnosis, failure to start or continue needed treatment, prevent timely follow-up and retesting and contribute to the potential spread of infectious agents to others.

**If the study is run under an IND, do I need to submit an IDE application to the FDA?**

If the study is being conducted under an IND and involves a device, the determination of whether your study is subject to 21 CFR 812 remains the same as described above. If the use of the device in the study does not meet IDE exemption criteria, the sponsor should provide a rationale for why the use of the device does not pose a significant risk. If the use of the device meets the definition of significant risk, the sponsor should provide either the IDE number or confirmation that the FDA device section (CDRH) has agreed to oversee the testing of the device under the IND application.

References:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf>

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf>

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.pdf>