FDA Regulation of *In Vitro* Diagnostic Devices Used in Investigations

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Overview of IVDs and IDE regulation
In Vitro Diagnostics (IVDs)

• In vitro diagnostic devices include “…those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act” (21 CFR § 809.3)

• Intended use: How will the device will be used in the therapeutic product trial? Encompasses:
  – Analyte to be detected
  – Type of result (quantitative, semi-quantitative, qualitative)
  – Specimen type(s)
  – Disease to be screened, monitored, treated, or diagnosed
  – Target subject population
  – etc.
MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the gene expression profile of fresh frozen breast cancer tissue samples to assess a patient's risk for distant metastasis.

The test is performed for breast cancer patients who are less than 61 years old, with Stage I or Stage II disease, with tumor size \(\leq 5.0\) cm and who are lymph node negative. The MammaPrint® result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.

Types of studies depend on IU claims; less dependent on the technology or assay format.
IDE Regulation (21 CFR 812)

• “…purpose…is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose.”

• An IDE is a regulatory submission that permits clinical investigation of devices/IVDs.

• An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution.

• Focused on risk

• Delegated responsibilities
IDE approval aims to ensure that:

- Risks are outweighed by anticipated benefits to subjects and importance of knowledge to be gained.
- Informed consent is adequate.
- Investigation is scientifically sound.
- Investigational device plausibly is effective.
What is an investigational IVD?

• An investigational IVD is not legally marketed for the intended use or indication for use identified in that study, whether or not it has been previously cleared or approved for a separate intended use.

• Intended use: How will the device will be used in the trial? e.g., how will test results drive treatment assignment? Encompasses:
  – Analyte to be detected
  – Type of result (quantitative, semi-quantitative, qualitative)
  – Specimen type(s)
  – Disease to be screened, monitored, treated, or diagnosed
  – Target subject population
  – etc.

• Those IVD devices that are used in studies according to the intended use/indications for use described in their cleared or approved labels, i.e., on-label use, are not considered investigational.

• Investigational use requires an exemption from premarket approval requirements for new drugs and devices.
Specimens are people too!

- *Subject* means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.
What’s in an IDE Application?

• Detailed in 21 CFR 812.20
• Administrative elements
• Fully specified device or test system from sample collection to test report
• Sufficient analytical validation and clinical information
• Report of prior investigations
• Investigational plan

• Purpose
• Protocol
• Risk analysis
• Monitoring procedures

• Consent materials
• IRB information
• Other institutions
• Additional records and reports
Analytical Performance/Validity in an IDE

- Does the test measure the correct analyte?
- Does the test measure the analyte reliably?
- Precision, reproducibility, sensitivity, specificity, etc.
- Risk dependent. The extent of analytical validation required for a pivotal trial exceeds what is required for feasibility studies.
- For a newborn screening assay, analytical performance around the cutoff/reference range is critical.
Risk assessment
Risk in Investigations using IVDs

- Need to think about the benefits and risks of a test, and impact of test use on patients in the trial
- Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?
- Are the results confirmed by an acceptable technique? What is an acceptable technique?
- Are results returned?
- What are the risks of an incorrect test result, both false positives and false negatives
  - What clinical actions might be taken based on test results?
  - How urgent are the results?
- For newborn screening, this may depend on the disease; the risks of treatment/procedure(s) after a screen positive result.
Risk in Ongoing Trials

- Risk can change during the course of a trial.
  - Adaptive trials
  - Protocol changes
  - New protocols
  - New information (DSMB review)

- If IVD use becomes SR in the middle of a trial, an IDE is required.

- Ongoing surveillance is recommended.
All Device Investigations

- Studies Subject to the IDE Regulation
  - Significant Risk (SR)
    - Full Requirements
  - Non-Significant Risk (NSR)
    - Abbreviated Requirements
- Studies Exempt from the IDE Regulation
IDE Exempt

• 812.2(c)(3): A diagnostic device [is exempt], if the sponsor complies with applicable requirements in 809.10(c) [labeling] and if the testing:
  – (i) Is noninvasive,
  – (ii) Does not require an invasive sampling procedure that presents significant risk,
  – (iii) Does not by design or intention introduce energy into a subject, and
  – (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

• Example: Use of an in vitro diagnostic in a retrospective study of accrued specimens (without return of results).

• Example: Whole genome sequencing to diagnose genetic disorders when all results are confirmed by Sanger sequencing.

• Depends on interpretation of “medically established”.
Nonsignificant risk (NSR)

- Does not meet the definition of significant risk (SR) in 812.3(m).
- Abbreviated requirements:
  - Labeling (812.5)
  - IRB approval
  - Informed consent (part 50)
  - Monitoring (812.46)
  - Records (812.140) and reporting (812.150) (sponsor and investigator)
    - Prohibition against promotion and other practices (812.7.)
- No IDE application to the FDA required.
- Example: Use of an investigational IVD NBS test to identify newborns that may have a serious condition; confirmatory testing process well-established and FDA-approved treatment available
Significant Risk (SR)

- Significant risk device (812.3(m)) 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.
- Example: Use of an IVD test to select patients for a clinical trial.
Delegated Responsibilities and Risk Determination

• Sponsor makes initial determination and presents to IRB

• IRB reviews determination; agrees or modifies

• FDA can help; FDA determination is final
Common Problems

• Failure to recognize that the test is an investigational medical device.
• Mistaking classification risk for investigational risk.
• Expectation that compliance with IND regulation supplants the IDE requirement.
• Risk mis-determination. If the IRB agrees the device is NSR, FDA will never see a submission, and will be unaware of the trial.
• Change in risk during course of trial.
Presubmission Process

– You can (and should) meet with the FDA for nonbinding discussions and advice:
  • *before* conducting studies, including clinical trials
  • *before* submitting a marketing application

– This is an opportunity to address new scientific and regulatory issues.

– Particularly important when developing new technologies.

– The earlier the better!

– Guidance on the pre-submission process
Resources

• Guidance
  – Others at www.fda.gov

• Device Advice
  – http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

• CDRH Learn (including information about sponsor responsibilities, investigator responsibilities, IRBs, and the Bioresearch Monitoring Program)
  – http://www.fda.gov/Training/CDRHLearn/default.htm
Thank you!

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