



The Intersection of Genomics Research and the IDE Regulation

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In Vitro Diagnostic (IVD) Regulation



- Through the 1976 medical device amendments to the FDCA, FDA has the authority to regulate all laboratory tests, regardless of whether they are commercially distributed or developed by a laboratory.
- In Vitro Diagnostic tests (IVDs) are a critical component of current clinical care, influencing 80% of all clinical decision-making.
- FDA is charged with ensuring that IVDs are safe and effective (do what they say they will do) for their intended use so that patients are not unnecessarily harmed.
- FDA's policy of enforcement discretion with respect to the regulatory requirements for LDTs does not extend to the IDE regulation.



IVDs as Medical Devices

- 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

Investigational Device Exemption (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.
- Risk-based approach that with some delegation of responsibility
- Even if the purpose of the investigation is not to inform a marketing submission for the IVD (e.g., the test is being used to select the patient population for a drug trial), the use of an IVD in the context of an investigation is generally considered to be investigational and subject to the IDE regulation unless the IVD is legally marketed for that intended use

Genomics Research and the IDE Regulation



- Advancements in NGS have enabled researchers to utilize this technology to interrogate large regions of the genome
 - NGS tests used in research studies may not have been cleared/approved for their intended use
 - Use of RUO components (e.g., instruments, reagents, software)
- Research studies are increasingly including the return of genomic test results to participants
 - Variants related to the study aims
 - Incidental findings (e.g., ACMG 59)
 - The IDE regulation does not prevent the return of genomic data findings, incidental or otherwise
- Is there a reasonable assurance that research test results being returned to participants are analytically valid?
- How are research results being communicated to participants?
 - Important for all types of genomic data findings, incidental or otherwise



Recommendations from *Evolution of Translational Omics: Lessons Learned and the Path Forward* (Institute of Medicine, 2012)

- FDA [should] communicate the IDE requirements for use of omics-based tests in clinical trials to the Office of Human Research Protections (OHRP), IRBs, and other relevant institutional leadership.
- The committee encourages FDA to organize forums with members of the scientific community and have an open and publicly accessible dialogue...This will provide test developers with some insight into FDA's thinking and potential next steps.

CMS on Research Testing and CLIA



What facilities are exempt from needing a CLIA certificate?

“Facilities that only perform testing for forensic purposes are excepted from the CLIA regulatory scheme.

Depending on the circumstances, research testing can be either excepted from CLIA or subject to CLIA.

Specifically, testing facilities may qualify to be excepted from CLIA certification if they meet the description of “research laboratories” provided by the CLIA regulations at 42 C.F.R. § 493.3(b)(2). In accordance with that regulation, **only those facilities performing research testing on human specimens that do not report patient-specific results may qualify to be excepted from CLIA certification.**”

What types of research testing are subject to CLIA?

“In most cases, research testing where patient-specific results are reported from the laboratory, and those results **will be or could be** used “for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings” are presumed to be subject to CLIA absent evidence to the contrary.

In cases where patient-specific test results are maintained by a statistical research center for possible use by investigators in which the results are not reported out as patient-specific and could not be used “for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings,” CLIA would not apply.”



IDE Regulation: A Risk-Based Approach

- IDE requirements depend on the risk of the test use to study subjects in the investigation.
 - Invasive sampling: collection of specimens for testing, if invasive, may pose a risk that would require an IDE submission
 - False results: risks to participants from false test results should be considered
- Risk can change during the course of a study
 - Adaptive trials
 - Protocol changes
 - New information
- If IVD use becomes SR in the middle of a study, an IDE is required
- Ongoing surveillance of risk is recommended



Risk Considerations in Investigations Using Genomic Testing

- What are the clinical indications for testing?
- Has the test been analytically validated?
- Are the results confirmed by an acceptable technique? What is an acceptable technique?
- Are results returned?
- Will results be placed in the medical record?
- How are results communicated to the treating physician?
- What are the risks of an incorrect test result?
 - What clinical actions might be taken based on test results?
 - How urgent are the results?
- For genetic testing, risk may depend on the disease; the risks of treatment/procedure(s) after a screen positive result; the consequences of the genetic result in the medical record; other factors

Risk Determination: A Spectrum



Factors increasing risk

- Clinical actions that may or may not be taken based on test result
- Results placed in medical record
- Healthy population
- Reporting results automatically
- Reporting results for adult onset disorders to pediatric population

Factors mitigating risk

- Seriously ill population
- Reporting through an expert
- Lack of known effective therapies
- Required sessions with genetic counselor

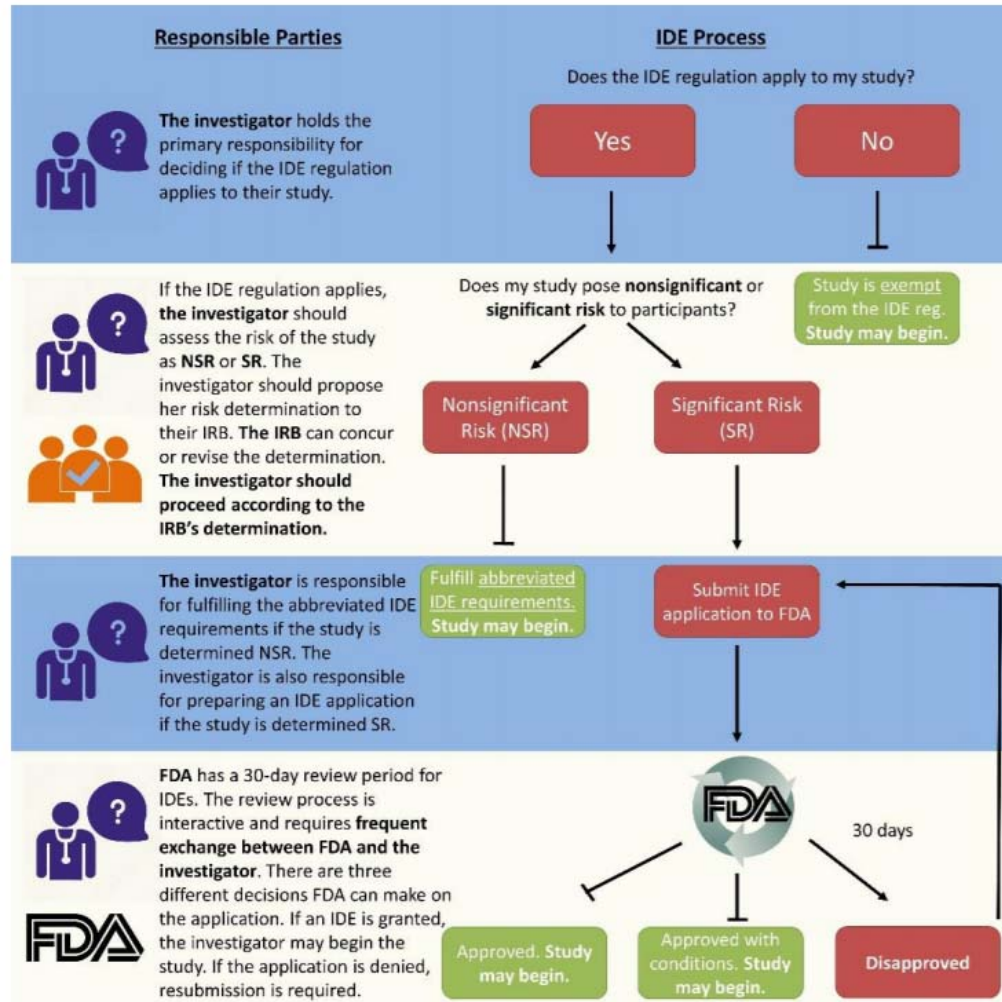
Risk Determination: Delegation of Responsibility

- Sponsor makes initial determination and presents to IRB
- IRB reviews determination; agrees or modifies
- FDA can help; FDA determination is final





Does the Study Need an IDE?





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).



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. Meeting the abbreviated requirements (including IRB approval) means that you have an approved application for an IDE.
- Example: Use of an investigational IVD test to stratify patients for treatment in a clinical trial.



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 in vitro diagnostic test to select patients for a clinical trial.

IDE Decisions for SR Investigations



- Sponsor submits IDE application to FDA for SR studies
- FDA **approves, approves with conditions, or disapproves** IDE within 30 calendar days
- Sponsor obtains IRB approval
- After **both** FDA and IRB approve the investigation, study may begin
- Changes in an existing study → amendments
- New studies with the same device → supplements
- **“Approved with Conditions”** signifies that the study may begin, but that certain conditions have been stipulated and must be met by the sponsor within 45 calendar days
- **Minor and Major Study Design Considerations** are recommendations (but not requirements) regarding study design to help study achieve its goals

General Challenges for Academic Researchers



- No prior interaction with FDA
- No prior experience with IDE regulation
- Lack of adequate regulatory support
- Time-sensitive nature of funding mechanisms



Pre-submission Meetings

- Sponsors can 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.
- *Can obtain a formal risk determination during risk determination Q-submissions*
- Guidance on the pre-submission process
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

FDA Guidances Related to IDEs



- FDA Decisions for Investigational Device Exemption Clinical Investigations (<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf>), Food and Drug Administration, August 2014.
- In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf>), Food and Drug Administration, June 2010.
- IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites and the Determination of Whether an IND/IDE is Needed (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM328855.pdf>), Food and Drug Administration, August 2013.
- Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf>), Food and Drug Administration, April 2006.



More Resources

- **Medical Device Databases**

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm>

- **Device Advice**

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

- **CDRH Learn** <http://www.fda.gov/Training/CDRHLearn/default.htm>

- **NHGRI website** <https://www.genome.gov/10002335/regulation-of-genetic-tests/#al-4>

FDA Efforts – We are here to help!



- Educational
 - Conferences
 - Discussion with IRBs, academic investigators, and institutions
- Work with NIH to disseminate information early in the granting process
- NHGRI website on genetic studies
 - <https://www.genome.gov/10002335>
 - Contains case studies
- Contact us with questions at any point in the process – the earlier the better



Thank You

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