In Vitro Diagnostic (IVD) Devices: How they Differ from Other Devices and How FDA Regulates Them

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What is an in vitro diagnostic device?

“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 etc..

2. Intended for use in the diagnosis of disease or other condition, or in the cure, mitigation, treatment, or prevention of disease, in man and which does not achieve its primary intended use through chemical action or depend on being metabolized within or on the body.
Q: What should study investigators and sponsors use as goals when conducting an IVD device study?

- Produce scientific evidence to demonstrate safety and effectiveness
  - Data to support proposed indications for use
  - Is data reliable and accurate?

- Ensure rights and welfare of study subjects protected
  - Has data been generated ethically?
What does FDA consider to be valid scientific evidence?

- 21 CFR Part 860.7(c)(2)

“Evidence from well controlled investigations, partially controlled studies, and objective trials without matched controls, well documented case histories conducted by qualified experts, and reports of significant human experience with marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its condition of use”
Chronology of a typical IVD study

Pre-IDE
- Qualify trial sites
- Identify principal investigators
- Review protocol
- Negotiate contract
- IRB reviews
- Enroll patients
- Bank specimens

FDA Submissions
- Analyze date
- Close out and audit sites
- Complete trial
- Interim site visits
- Collect fresh specimens
- Start trial-initiation visit
- Ship supplies and train

Essential docs. in place
Discuss FDA regulations applicable to IVD studies to ensure data is **reliable, accurate and ethically generated**

This presentation addresses studies using IVD devices which are approved or cleared under **device regulations** (21 CFR 800 series)
Q. What are the applicable FDA regulations for IVD studies?

- Under certain circumstances, IVDs are exempt from most requirements of the IDE regulation (21CFR 812.2 (c)(3))

Exception: Disqualification of an Investigator (812.119)
Q. What are the applicable FDA regulations for IVD studies? (Cont’d)

◆ All are subject to many Parts of Title 21 CFR including:
  
  ◆ Informed Consent (Part 50)
  ◆ IRB (Part 56)
  ◆ Financial Disclosure (Part 54)
  ◆ Electronic Records (Part 11)
  ◆ Dissemination of Information on Unapproved/New Uses… (Part 99)
  ◆ Labeling (Part 809.10)
  ◆ Quality System Regulation (Part 820)
  ◆ Premarket Approval (Part 814)

Note: This is not an all-inclusive list
Q. Does the study need an IDE?

A study is exempt from most provisions of the IDE Reg. if it fits into any one of the following scenarios:

- Pre-amendment device i.e. available prior to 1976
- Found substantially equivalent to a pre-amendment device
Q. Does the study need an IDE?
(Cont’d)

◆ If the IVD….  
  ◆ is properly labeled as investigational (21 CFR 809.10(c))
  ◆ is noninvasive
  ◆ does not require an invasive sampling procedure….  
  ◆ does not introduce energy into a subject  and
  ◆ is not used as a diagnostic procedure without confirmation of the diagnosis by another , medically established diagnostic product or procedure
Q. Does the study need an IDE?

(Cont’d)

- Requirements for an IDE also depends on level of risk to the study subjects
- Sponsor is responsible for making initial risk determination and presenting to IRB
- FDA makes final decision
Q. What type of risks are associated with the use of an investigational IVD device and how is it determined if the study is a significant or non-significant risk study?

- IVD Regulatory path determined by public health risk and intended use

- **Class I:** Low risk. Subject to GMP regulations, facility registration, and device listing. Majority exempt from FDA pre-market review

- **Class II:** Intermediate risk. Subject to special labeling and general controls. Generally require a 510(k) submission. Contact Div. regarding appropriate study design and need for IDE

- **Class III:** Highest risk. Stringent regulation. Require a PMA submission, pre-market approval. See above.
FDA concerned that device is

- Reliable
- Health care professional /patient understands both value and limitations
- Device is safe
- Low risk of misdiagnosis due to a false positive or false negative result
- Device is effective and has clinical utility
Q What are the responsibilities of the sponsor or investigator of a non-significant risk study that is exempt from most of the IDE requirements?

- Follow abbreviated requirements (812.2(b))
- Label the device in accordance with 812.5 i.e. IUO
- Comply with 812.46 with respect to monitoring investigations
- Maintain records (812.140(b) (4) & (5)) reports (812.150 (b) (1-3) (5,7))
- Comply with 812.7 against promotion and other practices
- Comply with selection of investigators (812.43)
- Human subject protection regs.
Q. Responsibilities of a sponsor or investigator for significant risk studies?

- Additional requirements include an investigational plan (812.25), report of prior studies (812.20(b)(2)) & (812.27), IDE progress and final reports.

- FDA must approve study IDE application before start of study.
Q: What FDA human subject research protection regulations apply to IVD device studies?

- 21 CFR Part 50: Informed consent and limited emergency exceptions
- 21 CFR Part 56: IRB review
- 21 CFR Part 812: IDE
- Apply to all clinical investigations including IVD devices regulated by FDA

Note: 45 CFR Part 46 Subpart A does not apply
What is FDA’s definition of clinical investigation/research?

- Any experiment involving a test article and one or more human subjects that:
  - Must meet requirements for prior submission to FDA or
  - Results of experiments intended to be submitted to FDA as part of application for research or marketing permission (21 CFR 812.3 (p))
Does every IVD study require IRB review?

- IRB review and approval is **required for any clinical investigation** that must meet the requirements of prior submission to FDA

- Any **changes** to the protocol should also be reviewed
Can an IVD Study receive expedited IRB review?

- Yes
- If risk to study subject is no more than minimal
How does FDA define a human subject?

- **Human** who participates in research either as a recipient of the test article or as a control. A healthy human or a patient.

- **Subject** is an individual on whom or on whose **specimen** an investigational device is used.
Under 21CFR 50 there is a requirement to obtain informed consent of subject or legally authorized representative.

There are limited exemptions to requirement:
- emergency, life threatening situations, (need independent physician opinion.)
- military operations.
Enforcement discretion proposed for not identifiable, leftover human specimens in new guidance published 4/25/06

- FDA intends to exercise enforcement discretion, under certain circumstances, with respect to requiring informed consent when human specimens are used in FDA-regulated IVD Device investigations

- New guidance, not a change in the regulation
Enforcement discretion: Applicable in what circumstances?

- Investigation meets the IDE exemption criteria at 21 CFR 812.2 (c)(3)
- The study uses leftover specimens – remnants from routine clinical care or analysis that would have been discarded or;
- Repository specimens – leftover or previously collected for other unrelated research purpose
- Specimens may be coded but not individually identifiable by the investigator, sponsor, or any individual directly associated with the study
Enforcement discretion: Applicable in what circumstances? (Cont.)

- Specimen may be accompanied by clinical information if source not identifiable to anyone associated with study

- Individuals caring for patients are different from those conducting the study

- Supplier of specimen has established policies and procedures to prevent release of identifiable information

- Study protocol must be reviewed by an IRB (21 CFR Part 56)
What type of records should be kept for these studies?

◆ Sponsor should
  ◆ Maintain **written documentation** regarding circumstances described in the guidance
  ◆ Ensure **specimen provider** has written documentation regarding subject non identifiability
  ◆ Consider if sufficient clinical information about subject available to support a device pre market clearance/approval. If not, submission rejected
**IRB Role**

- Check documentation regarding circumstances described in guidance

- IRB review should pay attention to privacy, confidentially, and whether potential for information from study influencing patient management
Closing reflections: Close out of IVD device studies

- Has the sponsor demonstrated the safety and effectiveness of their IVD device?
- Did they protect the rights and welfare of study subjects?
- Can they “survive” an audit of their study document?

If yes……

- They are ready to present study results to FDA to support the device’s “Intended/indications for use”
FDA Information – Websites

http://www.fda.gov/oc/gcp/default-htm
   Regulations and FDA information sheets

http://www.fda.gov/cdrh/oivd/guidance/1588.html
   Guidance on Informed Consent for IVD studies using leftover non-identifiable specimen