In Vitro Diagnostic Tests as Devices

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Precision medicine

Identify patients most likely to benefit (or be harmed) by specific treatments.

- Requires development and testing of new assays
- Both the drug and the test (IVD) may be investigational in the same study

In vitro diagnostics (tests) are devices

- 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).

What is a companion device?

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

Intent is that device and drug are approved together, and refer to each other in their labeling. Exceptions may be for:

- New products to treat serious or life threatening conditions
- Already approved therapeutic products

Companion devices that are not approved/cleared, are considered investigational devices.

What is an LDT?

Laboratory Developed Tests (LDTs)

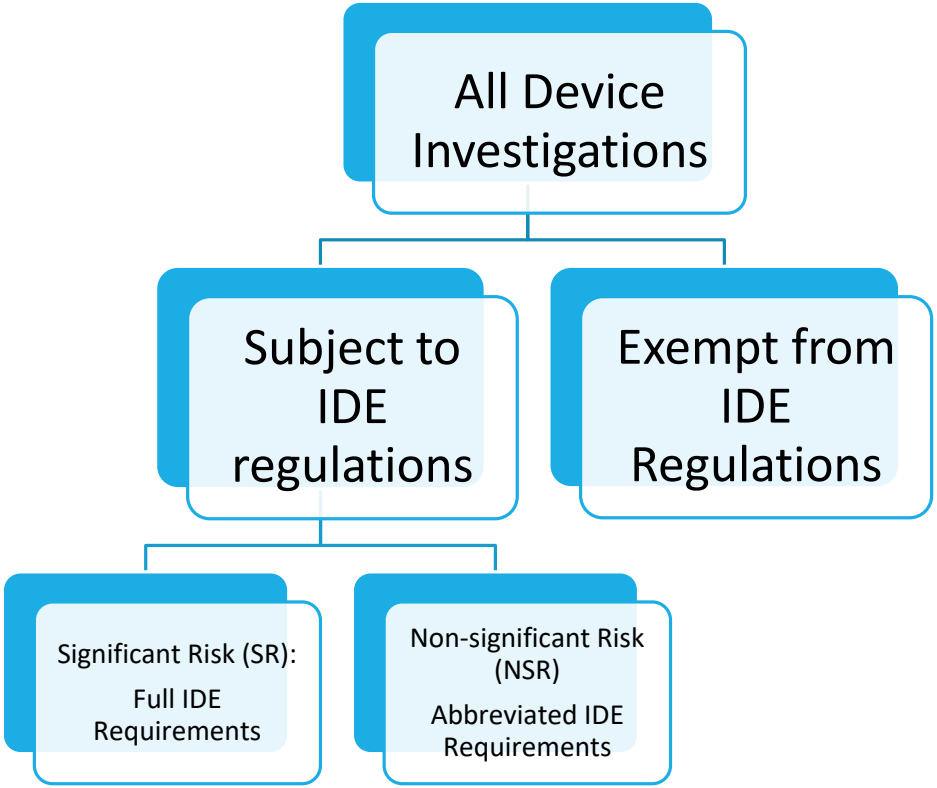
- A laboratory developed test (LDT) is a type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory.

Currently FDA does not enforce pre-market review for LDTs, but this is changing.

When used in research, LDTs may investigational

IRB responsibilities for IVDs

Apply the FDA device regulations



Why?

The results obtained from an IVD can alter the care and/or interventions provided to research participants and patients.

IVDs are routinely used to determine eligibility to trials.

- Many are routine
  - Routine blood work, tissue pathology etc
- Many are new
  - Genetic testing

Example

Investigator initiated pilot study to evaluate the investigational drug 123XYZ in the treatment of FGFR mutation positive recurrent or persistent ovarian carcinoma. All eligible patients will take oral study drug daily. Primary objective is to assess the activity of the drug by evaluating CR+PR and PFS at 6 months. Secondary objectives include toxicity evaluation.

Inclusion/Exclusion criteria

- Patients must have recurrent or persistent ovarian carcinoma which is refractory to curative therapy or established treatments..
- Patients must have a documented FGFR2 activating mutation either on primary, recurrent or metastatic biopsy. Activating mutations are defined as the known FGFR2 hotspots at S252W, P253R, S373C, Y376C, C383R, N550K, N550H, K660E.
- Patients must have had at least one prior chemotherapeutic regimen for management of endometrial carcinoma; this includes prior use of adjuvant chemotherapy.
- Usual other stuff….

IRB considerations

Is the test an IVD?

- Is the test a laboratory assay performed on a sample of blood or tissue obtained from a participant and the result used for trial specific purposes (eligibility, stratification, treatment assignment)?
  - Y=IVD
  - N=No IVD

Examples:

- Tumor histology
- Serum chemistry result
- Diagnostic imaging
- Sequencing for a mutation

IRB considerations: Investigational?

Is the IVD an investigational device in this study?

- If the test is being performed for clinical purposes, and the testing is not dictated solely for purposes of the trial, it may not be investigational.

If the test is not being performed for clinical purposes, it may be investigational. Factors to consider include:

- Is the assay being developed as a companion assay for the investigational drug?
- Are banked specimens being obtained for assay development purposes?
- Does the protocol mandate additional procedures in order to obtain the specimen for testing?

IRB considerations: exempt?

a legally marketed device when used in accordance with its labeling OR

a diagnostic device if it complies with the labeling requirements in §809.10(c) and if the testing:

- is properly labeled in accordance with 21 CFR 809.10(c);
- is noninvasive;
- does not require an invasive sampling procedure that presents significant risk;
- does not by design or intention 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

SR vs NSR

A significant risk device means an investigational device that:

- 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 a use in 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. (21 CFR 812.3(m))

NSR…everything else

IRB considerations SR v NSR

A device may be significant risk based upon either the procedure used to obtain the sample, or the consequences of an inaccurate test result.

If the consequences of an inaccurate test result, or the procedure used to obtain the sample do not meet the definition of significant risk, then the device is non-significant risk.

Considerations for IVD SR determinations

Are patients going to be foregoing alternative effective therapeutic options if the test result is wrong? (E.g., if the there are no other options and clinical trials are the only remaining options, the answer is no.)

Are patients going to be exposed to adverse events that are worse than the SOC?

Is there any information that is known about the test result subsets that makes it worse for someone if the test result is wrong? (for example, if its already known that there is no effect in one marker subset, or adverse events are worse in one subset)

Are there “significant risk” biopsies planned for the sole purpose of testing (serious morbidity or mortality can occur from the biopsy)?

SR v NSR

Would an inaccurate test result lead to misdiagnosis or a change in treatment, and if so, would the change result in an increase risk of harm that is life threatening, or result in permanent impairment of a body function or permanent damage to a body structure?

- Caveat: It is possible that an inaccurate test result might result in a patient receiving the same drug, or drug with a similar risk profile, as they would receive clinically, outside of the trial.

SR vs NSR

Is the sample that is being collected for the test done in a way that would be considered significant risk?

NSR examples

- Skin biopsy
- Biopsy of an easily accessible lymph node
- Bone marrow

SR examples

- Lung
- Mediastinum
- pancreas

What if biopsy unspecified?

- A statement that only NSR procedures may be used for obtaining tissue may be sufficient for making an NSR determination.

SR v NSR: Phase 1 studies

Don’t assume unknown risks mean serious risks.

- Phase 1, First in Human studies…assume safe unless evidence to the contrary.

Consider clinical situation of the patient

- What are their options?