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Investigational device exemption

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Investigational Device Exemption (IDE)

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DISCLAIMER

- Thoughts presented here regarding new policy / regulatory issues are preliminary and do not represent finalized FDA policy
- FDA cannot comment on specific investigations.



ISSUES

- FDA is seeing more researchers apply discoveries in the clinic.
- Most academic researchers do not understand their obligations under the IDE regulation.
- Most academic institutions do not provide adequate regulatory support.

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.

Intended Use

What assay measures, how to use results

Intended Population

Analyte

Indication For Use

Example:

*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 ≤ 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



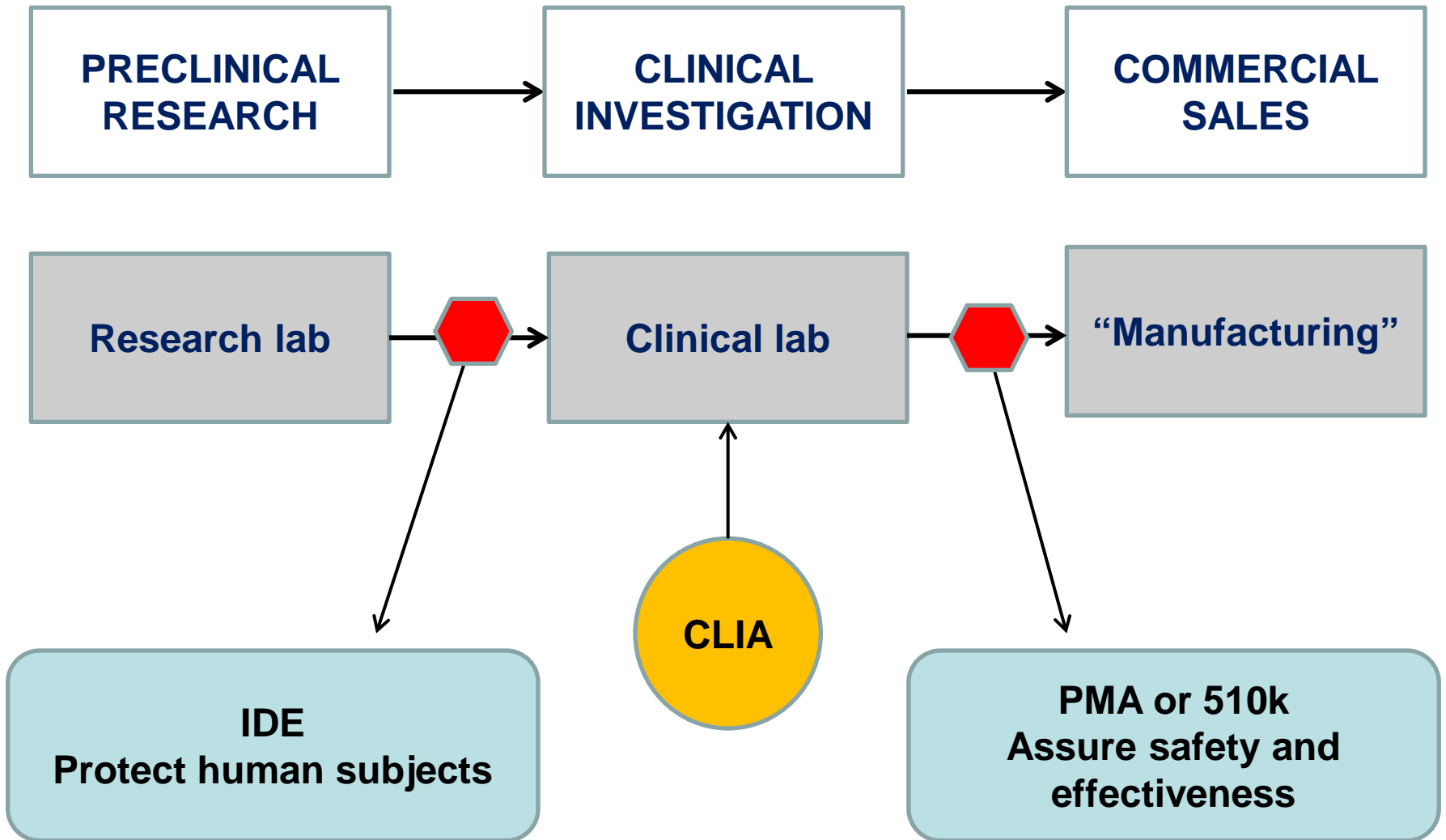
Things that are or can be medical devices include:

- Instrumentation
- In vitro diagnostic kits
- Reagents used for laboratory testing
- Some apps
- Software
- Algorithms

Medical devices are subject to regulatory requirements even though they may only be investigational.

Some common misconceptions:

- *It is not a test, it is a process.*
- *It is not an IVD if it is in the research and development stage.*
- *It is not an IVD if I don't plan to market the test.*
- *The IDE regulation does not apply if I don't plan to market the test.*
- *I have CLIA certification, so I don't need to worry about the IDE regulation.*
- *I can never generate enough data to submit an IDE.*





What is an investigation?

- *Investigation* means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.



Definition of “Subject” for Investigations

- *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 is an Investigational Device?

- *Investigational device* means a device...that is the object of an investigation.
- 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.
- Important to distinguish from off-label use or practice of medicine.
- Investigational use requires an exemption from premarket approval requirements for new drugs and devices.

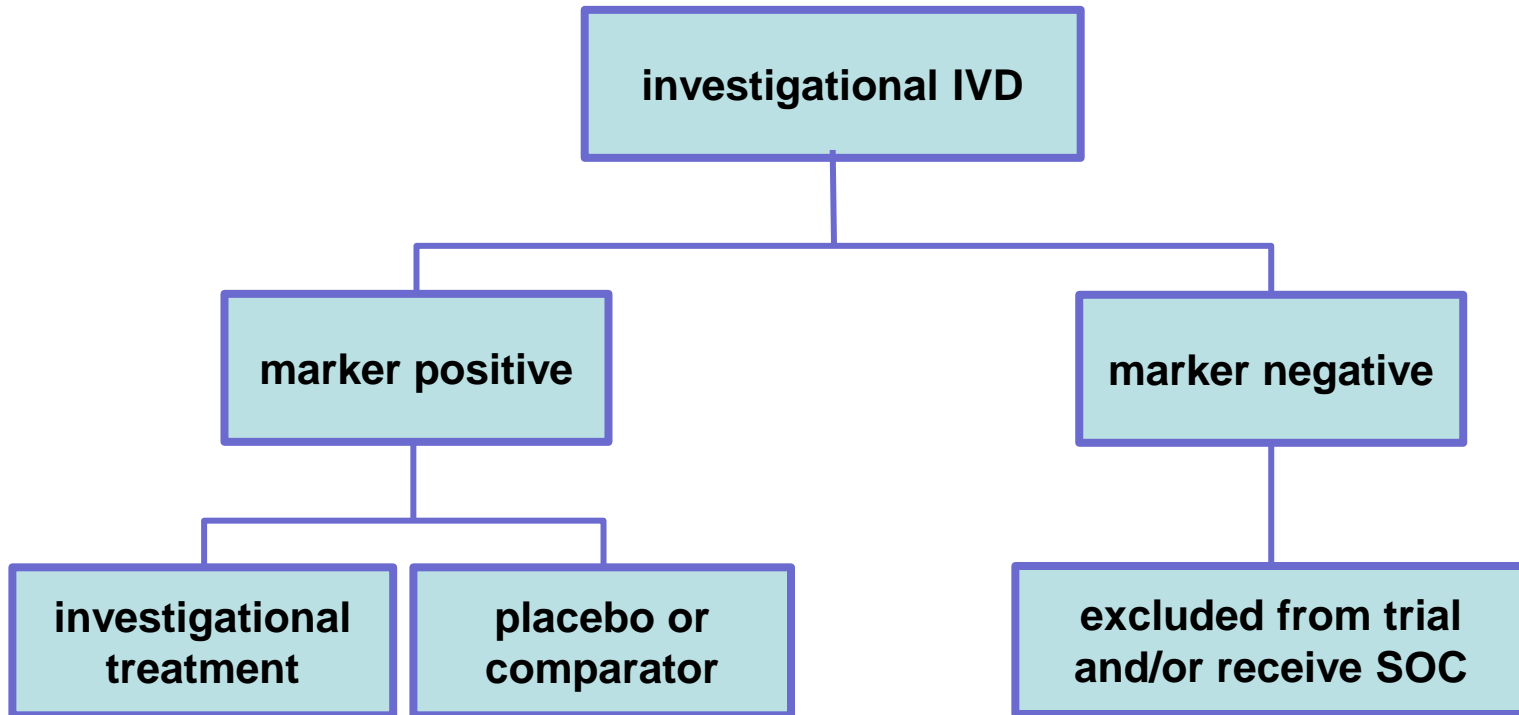


IVDs: Companion Diagnostics

- Companion diagnostics are IVDs
- 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.
 - **Note:** it is important to recognize, for example, that when a validated prognostic test is used to select patients for treatment, the ability to select patients who are expected to benefit from the treatment is an investigational use for which the test has not been validated until the investigational therapeutic product has demonstrated safety and efficacy in the test-selected population.
- Drugs and their companion tests refer to each other in their labels.
- Draft guidance. In vitro companion diagnostic devices.
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm>

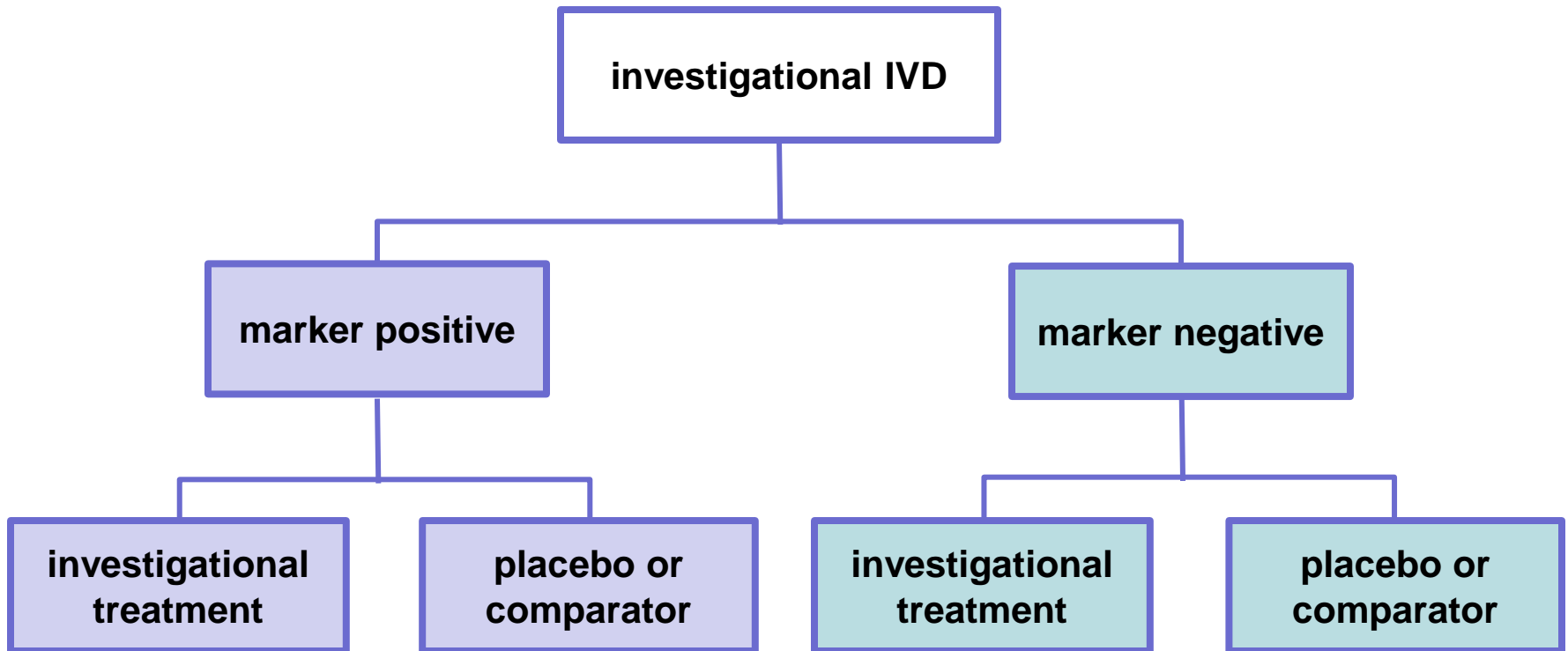
MARKER USED TO SELECT TREATMENT

Test result influences treatment.



MARKER USED FOR STRATIFICATION

Test result does not influence treatment.





Other trial designs

- Adaptive
- Basket trials

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

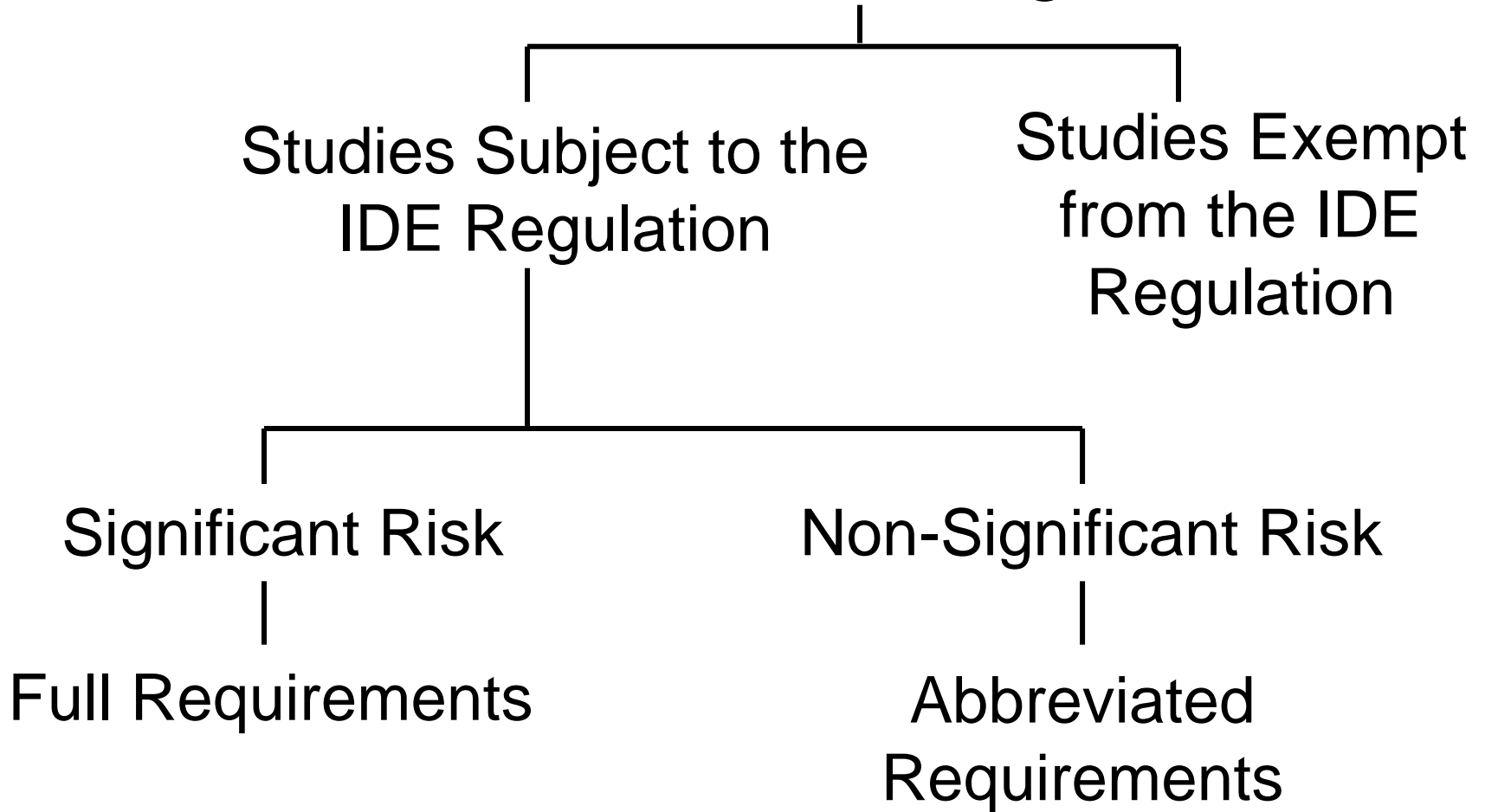


IDE approval aims to ensure that:

- Risks are outweighed by anticipated benefits to subjects and importance of knowledge to be gained.
- Informed consent is adequate.
- Investigation is scientifically sound.



All Device Investigations



IDE: A Risk-Based Approach to IVD Regulation

- IDE requirements depend on the risk of the test use to study subjects in the investigation.
- For IVD tests, it is important to think about the risks associated with erroneous test results. What would happen if the test results are wrong?
 - False positive or false negative results mean that a patient may be diverted from therapeutic options which may be more beneficial to them.
 - Patients may be subject to adverse events from the investigational trial when they are not intended to be the subject of the investigation.



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

BALANCED APPROACH TO IVD RISK

Context and effect of an incorrect test result

Cancer is a serious disease. Any effect on a treatment decision arising from IVD use poses significant risk.

More Risk



Less Risk

Cancer is a serious disease. Large and unmet medical need makes any IVD risk minor.

- Accrual by test result
- Rx assignment
- Safety signal for Rx
- Convenience biomarker
- Weak/conflicting info on biomarker effect
- Invasive sampling

- All-comers accrual
- Stratification
- No “known effective” Rx
- Targeted biomarker
- Strong biomarker effect known
- Non-invasive sampling



Assessing Risk

1. Will use of the investigational test results lead to some trial subjects foregoing or delaying a treatment that is known to be effective?
2. Will use of the investigational test results expose trial subjects to safety risks (e.g., adverse events from the experimental therapy) that (in some “net” sense) exceed the risks encountered with control therapies or non-trial standard of care?
3. Is it likely, based on a priori information about the investigational therapy, that incorrect test results would degrade the safety or efficacy of subjects’ treatment?
4. Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?

Risk in Investigations Using Genetic Testing

- What are the clinical indications for testing?
- 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?



Some Features with Lesser Relevance for IVD Risk Determination

- Size of trial
- Access to “other trials”
- Clinical trial phase



Risk in Ongoing Trials

- Risk can change during the course of a trial.
 - Adaptive trials
 - Protocol changes
 - New information (DSMB review)
- If IVD use becomes SR in the middle of a trial, an IDE is required.
- Ongoing surveillance is recommended.



Example 1

Researchers have identified a biomarker that they hypothesize will predict response to a new drug for colorectal cancer. They develop an IVD to detect the biomarker, and design a clinical trial in which only those patients that are positive for the biomarker will receive the drug. Other inclusion criteria specify that the patients have exhausted all other lines of therapy.

- What is the risk of the use of IVD in the trial?
- If an earlier trial of the drug identified potentially serious or life-threatening toxicities, would your risk assessment change?

Example 1

- Initial decision: NSR. Although the IVD is used for selection, there are no known effective therapies remaining for patients. Therefore, false results do not pose added risk to patients.
- Modified decision: SR. Although there are no known effective therapies remaining, side effects from the drug may unreasonably degrade quality of life or lead to death earlier than would be predicted from the normal course of the disease. False positive patients would be exposed to these risks without any reasonable expectation of benefit.

Example 2

Researchers have developed a test to detect a biomarker in bone marrow, and design a clinical trial to use the IVD to select patients with pancreatic cancer to receive a drug that is approved for use in prostate cancer. To enter the trial, patients must have additional bone marrow biopsies, and have not received any prior lines of therapy. The toxicities of the drug are well-understood and can be mitigated with appropriate monitoring.

- What is the risk of the use of IVD in the trial?
- What if an earlier trial suggested that marker-positive patients with pancreatic cancer could respond to the new drug?



Example 2

- Initial decision: SR. The IVD is used for selection. False results will divert patients from standard of care or known effective therapies.
- Modified decision: NSR. Given preliminary indications that the biomarker predicts response to the drug, test-positive patients have a reasonable expectation of benefit. False results can be mitigated by monitoring. While extra bone marrow biopsies are invasive, they may not pose high enough risk to qualify the study as significant risk.
- In real life, this scenario should be discussed with FDA.

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





Some Recommended Questions for IRBs

1. Are one or more IVD devices being used in this study to select patients for treatment?
2. Is the device investigational?
 - a. Has the device been cleared or approved by the FDA?
 - b. If the IVD has been cleared or approved, is it being put to a new use in the trial?
3. What are the risks of IVD use in the study?
 - a. Does specimen collection present a risk?
 - b. What are the risks of inaccurate results?
 - i. Is the IVD used for enrollment or assignment to an arm?
 - ii. Will the IVD be used for patient monitoring or adjusting dosage?
 - iii. Are the benefits of treatment greater than the risks of an inaccurate IVD result?
4. Will results from the IVD device be supported by use of an independent confirmatory test?
5. Does the informed consent cover the use of the investigational IVD?



FDA Policy for CDx Trials

- **SR IVD:** An IDE is required for an investigation *even if* there is an IND for use of the drug, or if the drug is IND exempt.
- **NSR IVD:** An IDE is not required, and cannot be accepted for review.
 - The trial still has to comply with the abbreviated requirements.
 - Some information on the test may be requested in the IND.
 - A presubmission with CDRH is recommended.
- A trial may not proceed until it has received IND and/or IDE approval AND IRB approval.



Common Problems

- Failure to recognize that the biomarker test is an investigational medical device.
- Expectation that compliance with IND regulation is sufficient to satisfy requirements under the IDE regulation.
- Risk misdetermination. 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 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!

- Draft Guidance on the presubmission process
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm>.



Resources

- Guidance
 - 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>
 - FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations.
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf>
 - Significant Risk and Nonsignificant Risk Medical Device Studies.
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf>
 - 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>

Other FDA efforts

- Educational –
 - Conferences
 - Discussion with IRBs, academic investigators, and institutions
- Work with NIH to disseminate information early in the granting process