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# Using sequencing (and other assays) in clinical trials: FDA rules and regulations

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# Using sequencing (and other assays) in clinical trials: FDA rules and regulations

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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.



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

“The committee recommends that FDA 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...IRBs often lack knowledge of the IDE requirements compared to their understanding of the IND requirements; thus, clarification and education by FDA about IDE requirements are necessary. This communication could be conducted online and via technologies such as webcasting in order to reduce FDA’s cost and time requirements.”



# FDA Organization

<b>CDRH</b>	<b>Center for Devices and Radiological Health</b>
<b>CDER</b>	<b>Center for Drug Evaluation and Research</b>
<b>CBER</b>	<b>Center for Biologics Evaluation and Research</b>



# Office of In Vitro Diagnostics and Radiological Health

<b>DIHD</b>	<b>Division of Immunology and Hematological Devices</b>
<b>DMGP</b>	<b>Division of Molecular Genetics and Pathology</b>
<b>DMD</b>	<b>Division of Microbiology Devices</b>
<b>DCTD</b>	<b>Division of Chemistry and Toxicology Devices</b>
<b>DRH</b>	<b>Division of Radiological Health</b>
<b>DMQS</b>	<b>Division of Mammography Quality Standards</b>



# IVD Regulation

- In Vitro Diagnostic tests (IVDs) are a critical component of current clinical care, influencing 80% of all clinical decision-making.
- 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.
- 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.



# Benefits of FDA Oversight

- Independent Premarket Review
  - Independent assessment occurs prior to clinical use of test
  - Ensures test limitations are described
  - Ensures test performance claims are supported
- Clinical Validation
  - Provide assurances that test provides clinically meaningful results
- Post Market Surveillance and Post Market Controls
  - Mechanism to assist manufacturers and FDA in identifying problems with tests and assuring the performance of the IVD through out its life cycle
- Oversight of Investigational-Stage Devices
  - Ensures acceptable risk-benefit ratio in clinical investigations of devices to protect study subjects



# *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 patients' 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

# Things that are or can be medical devices include:

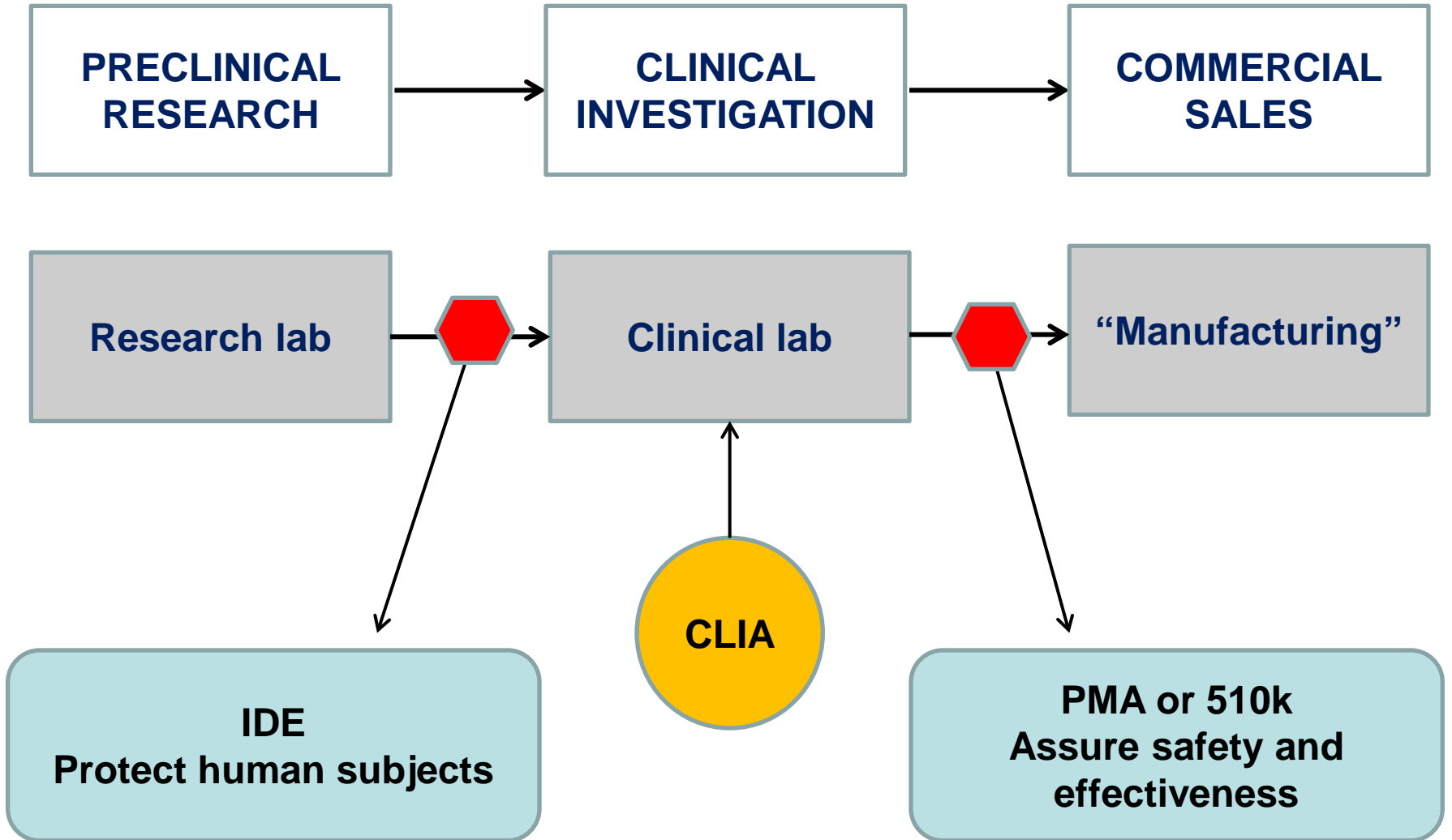
- Instrumentation
- In vitro diagnostic kits
- Reagents used for laboratory testing
- Some apps
- Software
- Algorithms

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



# 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>





# Risk-Based Classification

- For IVDs, the risk is based on the **consequences of a false result**
- Examples:
  - High risk – HIV
  - Lower risk – pregnancy
- 3 classification levels
  - Class I: common, low-risk devices – 510k (usually exempt)
  - Class II: more complex, moderate risk – 510k
  - Class III: most complex, high risk - PMA

# Elements of FDA Premarket Review

- Analytical validity
  - Correctly detects analyte
  - Accuracy, precision, limits of detection/measurement
- Clinical validity
  - Correctly identifies disease/condition
  - Clinical sensitivity, clinical specificity, predictive values
- Labeling



# ILLUMINA MiSeqDx™ PLATFORM AND UNIVERSAL KIT 1.0

- The MiSeqDx Platform is a sequencing instrument that measures fluorescence signals of labeled nucleotides through the use of instrument specific reagents and flow cells (MiSeqDx Universal Kit 1.0), imaging hardware, and data analysis software. The MiSeqDx Platform is intended for targeted sequencing of human genomic DNA from peripheral whole blood samples. The MiSeqDx Platform is not intended for whole genome or de novo sequencing.
- The MiSeqDx Universal Kit 1.0 is a set of reagents and consumables used in the processing of human genomic DNA samples derived from peripheral whole blood, and in the subsequent targeted re-sequencing of the resulting sample libraries. User-supplied analyte specific reagents are required for the preparation of libraries targeting specific genomic regions of interest. The MiSeqDx Universal Kit 1.0 is intended for use with the MiSeqDx instrument.





# Illumina MiSeqDx™ Cystic Fibrosis 139 Variant Assay

The Illumina MiSeqDx™ Cystic Fibrosis 139-Variant Assay is a qualitative in vitro diagnostic system used to **simultaneously detect 139 clinically relevant cystic fibrosis disease-causing mutations and variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene** in genomic DNA isolated from human peripheral whole blood -specimens. The variants include those recommended in 2004 by the American College of Medical Genetics (ACMG) and in 2011 by the American College of Obstetricians and Gynecologists (ACOG). The test is intended for carrier screening in adults of reproductive age, in confirmatory diagnostic testing of newborns and children, and as an initial test to aid in the diagnosis of individuals with suspected cystic fibrosis. The results of this test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available laboratory and clinical information.

This test is not indicated for use for newborn screening, fetal diagnostic testing, pre-implantation testing, or for standalone diagnostic purposes.

-The test is intended to be used on the Illumina MiSeqDx™ instrument.

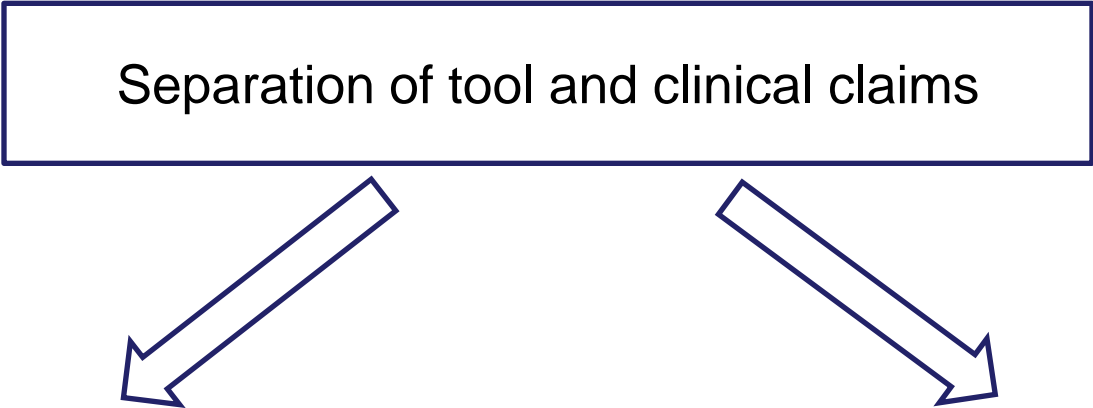


# Illumina MiSeqDx™ Cystic Fibrosis Clinical Sequencing Assay

The Illumina MiSeqDx™ Cystic Fibrosis Clinical Sequencing Assay is a targeted sequencing in vitro diagnostic system that re-sequences the protein coding regions and intron/exon boundaries of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood specimens collected in K2EDTA. The test detects single nucleotide variants, and small InDels within the region sequenced, and additionally reports on two deep intronic mutations and two large deletions. The test is intended to be used on the Illumina MiSeqDx Instrument. **The test is intended to be used as an aid in the diagnosis of individuals with suspected cystic fibrosis (CF).** The test is most appropriate when the patient has an atypical or non-classic presentation of CF or when other mutation panels have failed to identify both causative mutations. The results of the test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available information including clinical symptoms, other diagnostic tests, and family history. This test is not indicated for use for stand-alone diagnostic purposes, fetal diagnostic testing, for pre-implantation testing, carrier screening, newborn screening, or population screening.

# Lessons from the Illumina Clearances

Separation of tool and clinical claims



## **Tool: MiSeqDx instrument**

Use: Sequences DNA

Analytical validation

- Clinical and cell line samples
- Well-standardized panel with known variants
- Performance demonstrated on a representative set of variants

Clinical validation not needed

## **Clinical: CF 139 variant and whole gene tests**

Use: Sequences 139 variants or whole CFTR gene

Analytical validation

- Specific validation of 139 variants, plus validation of CFTR normal sequence

Clinical validation

- Use of the CFTR2 database (JHU) for evidence



# 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

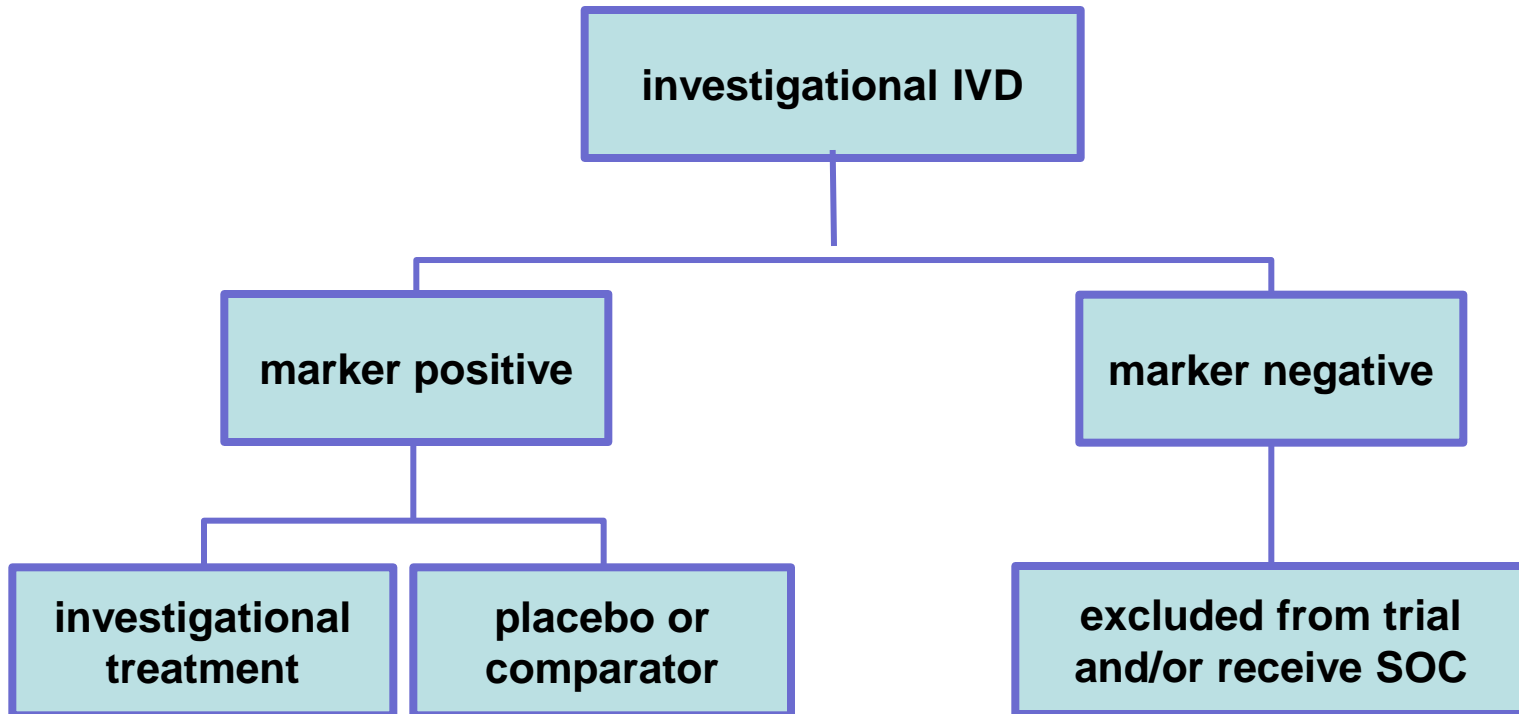
- *Subject* means a human who participates in an investigation, either as an individual on whom or on whose **specimen** an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

# 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.

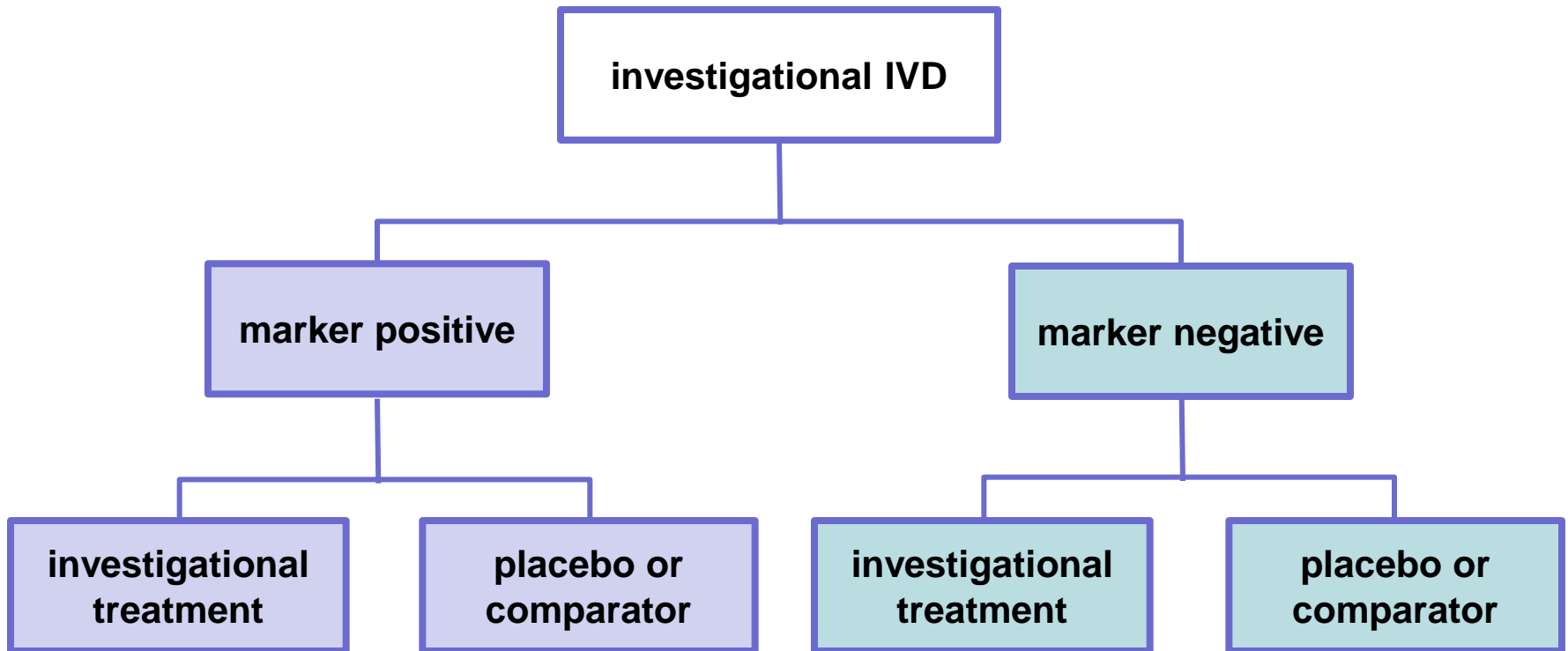
# MARKER USED TO SELECT TREATMENT

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



Several parts of the Code of Federal Regulations (21 CFR) pertain to IDEs:

- Part 812 - Investigational Device Exemptions
- Part 50 - Protection of Human Subjects and Informed Consent
- Part 54 - Financial Disclosure of Investigators
- Part 56 - Institutional Review Boards
- Part 820 Section 30 – Design Controls (Quality Systems Regulation)



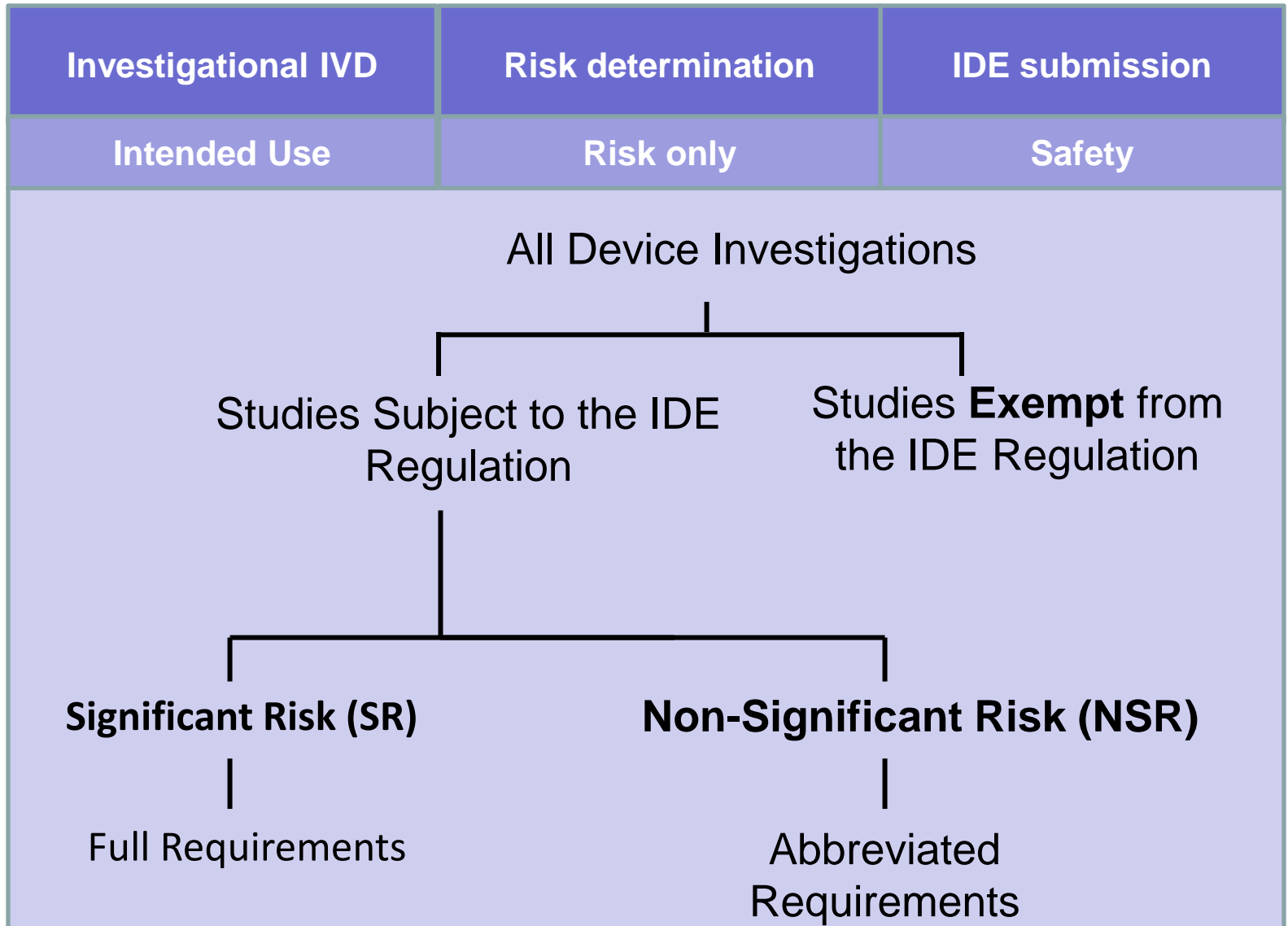
An IDE allows you to ship an IVD without meeting the following requirements:

- Misbranding
- Registration and listing
- Performance standards
- Premarket notification
- Premarket approval
- Banned device regulation
- Restricted device regulation
- Good manufacturing practice/Quality System regulations (except design controls)



## 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.



# IDE Requirements (non-inclusive)

- Detailed in 21CFR812.20
- Fully specified device
- Sufficient analytical validation and clinical information
  - Does the test measure the correct analyte reliably?
- Pre-specified investigational plan
- Informed consent – Include, as part of the IDE, the actual text of the Informed consent that will be used in the proposed study.
- If there are physician investigators in the study ensure that they have a current license to practice medicine, and this will be included in the IDE and subsequent annual reports.

# 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 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
- Targeted biomarker
- Invasive sampling

- All-comers accrual
- Stratification
- No “known effective” Rx
- Convenience biomarker
- Non-invasive sampling



# Some Features with Lesser Relevance for IVD Risk Determination

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



# 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?
- 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 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.



# 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





## 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 presub 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.

## IDE Submissions

- 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 → 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
- Annual reports

# IDE Submissions

- Example of “approved with conditions” letter:

*Your application is conditionally approved, and you may begin your investigation at the following institutions after you have obtained IRB approvals and submitted certifications of IRB approvals to FDA: Centers X, Y, and Z. Your investigation is limited to 3 institutions and 20 subjects.*

*This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:*

# IDE Requirements (non-inclusive)

- Fully specified device
- Sufficient analytical validation and clinical information
- Pre-specified investigational plan
- Informed consent – Include, as part of the IDE, the actual text of the Informed consent that will be used in the proposed study.
- If there are physician investigators in the study ensure that they have a current license to practice medicine, and this will be included in the IDE and subsequent annual reports.



# What's in an IDE Application?

- Detailed in 21 CFR 812.20
- Administrative elements
- Report of prior investigations
- Investigational plan
  - Purpose
  - Protocol
  - Risk analysis
  - Description of device
  - Monitoring procedures
  - Labeling
  - 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 companion diagnostic, analytical performance around the cutoff/reference range is critical.



## 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.*



# Interacting with FDA...for Sponsors

## **PRESUBMISSION**

- 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.
- Guidance on the pre-submission process  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

## **DURING REVIEW OF A SUBMISSION**

- Acceptance Review Communication
- Substantive Interaction
- Interactive Review



# Resources

- Medical Device Databases
  - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm>
- 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](http://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
- FDA outreach
  - Presentations and presence at meetings
  - Webinars
  - Guidance, etc.
- FDA participation in internal and external working groups
- Workshops
- Other opportunities



Thank you!

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