



# **FDA Laws Pertaining To Human Research Protections, The Use Of Investigational Devices And Considerations For Use of Laboratory Developed Tests (LDTs)**

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# **Overview of IVDs and Investigational Device Exemption Regulation**

# Medical Device Amendments (to the FFDCA) of 1976

Regulation of all Medical Devices includes:

- General controls (e.g., current Good Manufacturing Practices)
- Registration and listing
- Good manufacturing practices
- Reporting of adverse events
- Risk based regulation by intended use

## *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 trial/when its distributed or used? 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**

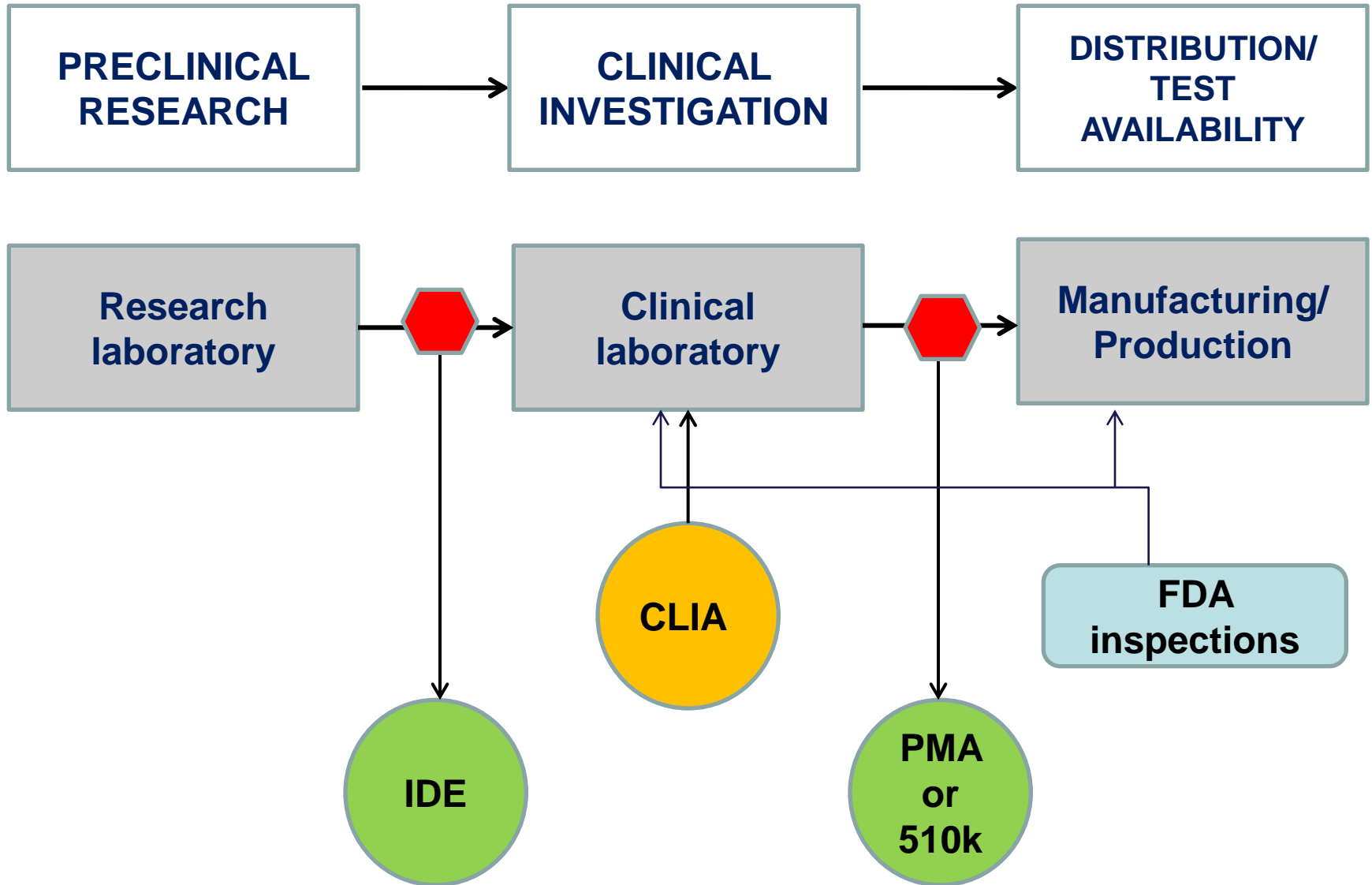
**Indication For Use**

### 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



# 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.
- Investigational device plausibly is effective.

While FDA has provided enforcement discretion from premarket requirements for laboratory developed tests, it has not extended this enforcement discretion to the IDE regulations when an investigation uses an investigational LDT



# What is an investigational IVD?

- 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.
- Intended use: How will the device will be used in the trial?  
e.g., how will test results drive treatment assignment? 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.
- Those IVD devices that are used in studies according to the intended use/indications for use described in their cleared or approved labels, i.e., on-label use, are not considered investigational.
- Investigational use requires an exemption from premarket approval requirements for new drugs and devices.

# Specimens are people too!

- *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.



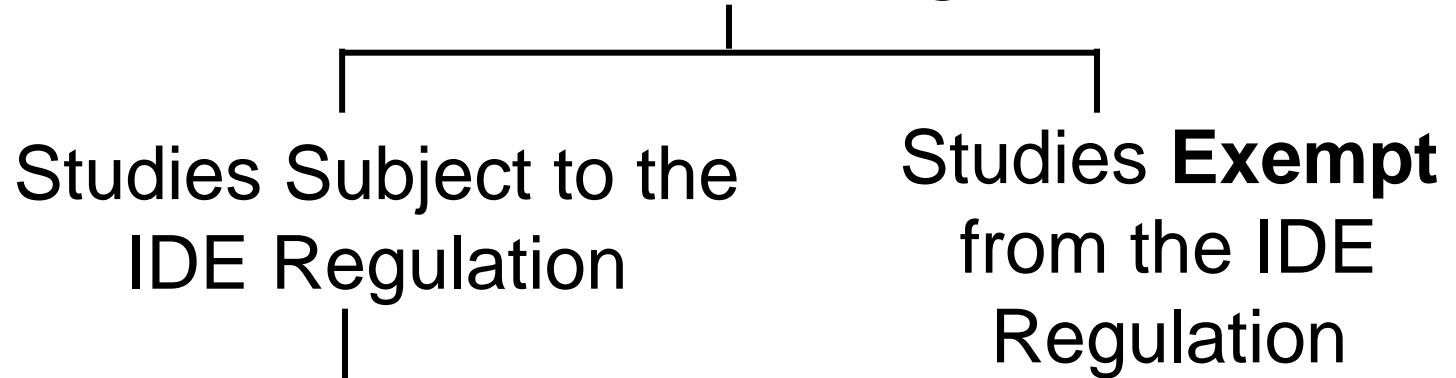
# **Risk assessment**

# Risk in Investigations using IVDs

- Need to think about the benefits and risks of a test, and impact of test use on patients in the trial
- Does specimen acquisition require an invasive sampling procedure that presents significant risk?
- Are the results confirmed by an acceptable technique? What is an acceptable technique?
- Are results returned?
- What are the risks of an incorrect test result, both false positives and false negatives
  - What clinical actions might be taken based on test results?
  - How urgent are the results?
- For newborn screening, this may depend on the disease; the risks of treatment/procedure(s) after a screen positive result.



# All Device Investigations



**Significant Risk (SR)**

**Non-Significant Risk (NSR)**

Full Requirements

Abbreviated Requirements

# 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 a NBS test in a retrospective study of residual DBS (without return of results).
- Example: Use of a NBS test in a prospective study where the results of the screening test are confirmed by an FDA cleared screening test before results are returned.
- Depends on interpretation of “medically established”.



## Nonsignificant risk (NSR)

- Does not meet the definition of significant risk (SR) (21 CFR 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.
- Example: Use of an investigational IVD NBS test to identify newborns that may have a serious condition; confirmatory testing process well-established and FDA-approved treatment available

## 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 IVD test to select patients for a clinical trial evaluating an unapproved drug.



# What's in an IDE Application?

- Detailed in 21 CFR 812.20
- Administrative elements
- Fully specified device or test system from sample collection to test report
- Sufficient analytical validation and clinical information
- Report of prior investigations
- Investigational plan
  - Purpose
  - Protocol
  - Risk analysis
  - Monitoring procedures
  - 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 newborn screening assay, analytical performance around the cutoff/reference range is critical.



# Human Subject Protections Regulations for FDA regulated research

- 21 CFR 50
- Unlike 45 CFR 46 (HHS), FDA regulations do not allow IRBs to waive consent or to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent
- Consent can be written or oral, provided that the IRB approves content conveyed orally (21 CFR 50.27(b)(2))
- FDA extends exercise enforcement discretion to the use, without informed consent, of leftover human specimens in exempt investigations as long as specimens are not individually identifiable.



## What might this mean for you?

- If you're using an investigational test (kit or LDT) in a pilot where results are being returned (exempt, NSR or SR), you should be obtaining informed consent
- FDA believes you should inform the participant in the informed consent process that an investigational device is being used.



# 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](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>



# Presubmission Process

- You can (and should) 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!
  
- Guidance on the pre-submission process  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>



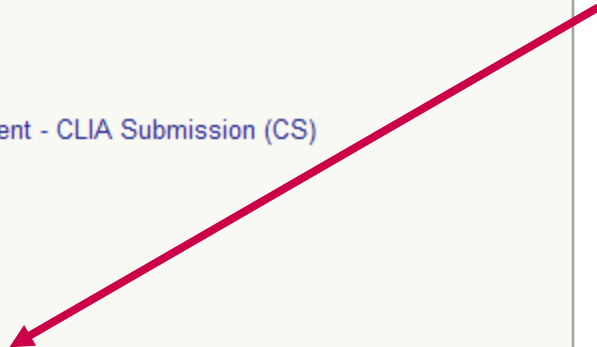
# Transparency

510(k) Database: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>



# Transparency

<a href="#">New Search</a>		<a href="#">Back To Search Results</a>
Device Classification Name	<a href="#">System, Test, Amino Acids, Free Carnitines And Acylcarnitines Tandem Mass Spectrometry</a>	
510(K) Number	K083130	
Device Name	NEOBASE NON-DERIVATIZED MSMS KIT, MODEL 3040	
Applicant	PERKINELMER, INC. 8275 Carloway Road Indianapolis, IN 46236	
Contact	Kay A Taylor	
Regulation Number	<a href="#">862.1055</a>	
Classification Product Code	<a href="#">NQL</a>	
Date Received	11/13/2008	
Decision Date	07/09/2009	
Decision	Substantially Equivalent - CLIA Submission (CS)	
Classification Advisory Committee	Clinical Chemistry	
Review Advisory Committee	Clinical Chemistry	
Summary	<a href="#">Summary</a>	
FDA Review	<a href="#">Decision Summary</a>	
Type	Traditional	
Reviewed By Third Party	No	
Expedited Review	No	







# Transparency

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY  
ASSAY ONLY TEMPLATE**

**A. 510(k) Number:**

k083130

**B. Purpose for Submission:**

New device

**C. Measurand:**

Amino acids, free carnitine, acylcarnitines, and succinylacetone

**D. Type of Test:**

Quantitative measurement by mass spectrometry

**E. Applicant:**

PerkinElmer, Inc.

**F. Proprietary and Established Names:**

NeoBase Non-derivatized MSMS kit

**G. Regulatory Information:**

1. Regulation section:

21 CFR §862.1055 Newborn screening test system for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry

2. Classification:



**Thank you!**

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