

The Role of the FDA pre-IDE as a Means to Improve Clinical Assays

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Outline

- **The Need**
- **Classes & Uses of Markers**
- **The FDA's Concerns**
- **The FDA Review and Application Process**
- **The Role of the IRB**
- **Recommendation and Summary**

The Need

- Relatively small number of approved/cleared diagnostics
 - Recent increase in companion diagnostics (e.g., Cobas, Vysis)
- However, there are a number of therapies that may benefit a marker + subset more than a marker – (e.g., erlotinib in EGFRmut NSCLC)
- Problem is to assure that results in clinical trials can be moved into clinic
 - This raises issue of standardization of Lab Developed Tests (LDTs)
- FDA has until now generally not enforced its regulatory oversight but may be reconsidering
- This leads to greater emphasis by NCI and other clinical research supporters on more rigorous standards for diagnostics in trials.

Protocols Whose Markers Require Extra Consideration

Protocols whose markers are essential for trials

- because they require extra biopsies or pose a collection risk

or

- because presence or absence of marker may predict response to drug or increase toxicity for patients

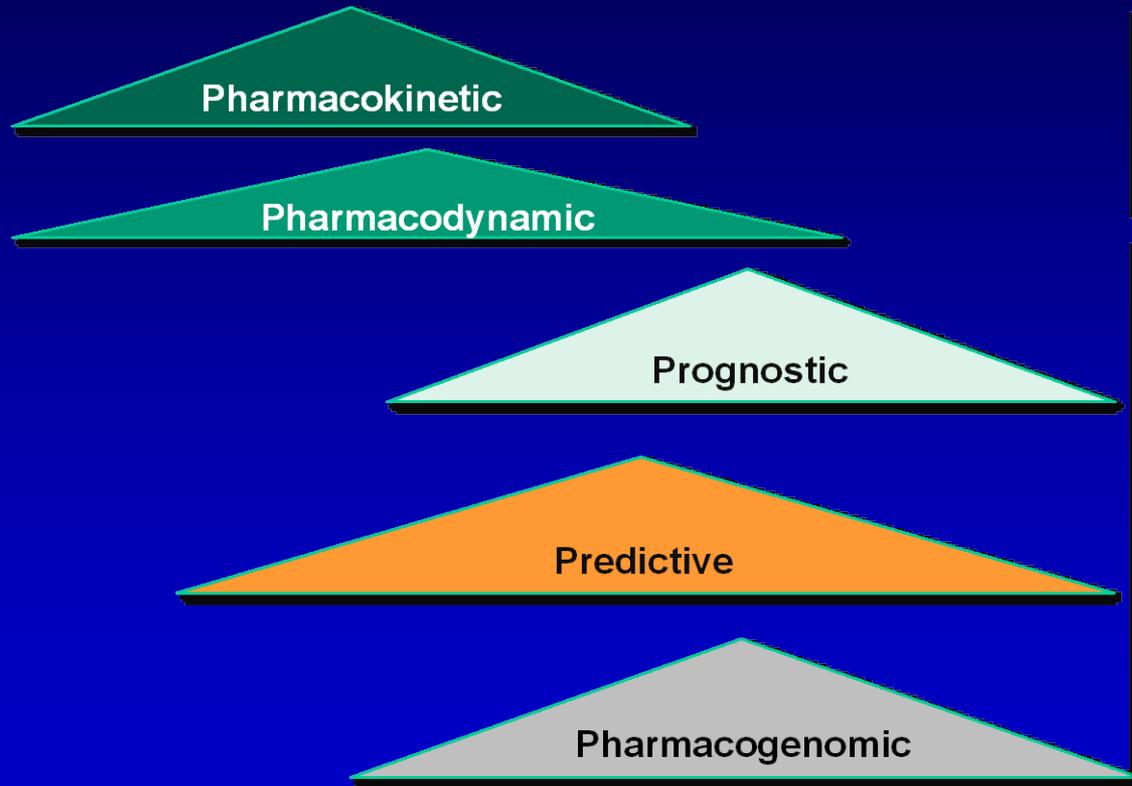
Consider CLASSES and USES of Markers

CLASSES OF MARKERS

Phase of Trial:
Preclinical 0 I II III IV



Clinical Practice



Research
Markers

CLIA
If Assay Used For
Individual Patient
Decision Making
= **Integral Markers**

**FDA/
Pre-IDE Review**

Research Lab

Clinical Lab

Uses of Markers

Integral Markers –

- Markers that are essential for performance of the trial
 - used for medical-decision-making in specimen donor
 - examples: eligibility criterion, treatment assignment, risk stratification, dose modification
 - must be performed in a CLIA-approved laboratory

Integrated Markers –

- Markers that are research markers
 - performed on all subjects but not for medical decision-making
- OR
 - performed on a predefined subset (e.g., QoL studies)
- OR
 - performed to test a hypothesis

Research (Correlative) Markers –

- Markers studied to generate hypotheses - exploratory

Regulations - Significant Risk

The Investigational Device Exemption (IDE) regulations (21 CFR Part 812) require that Significant Risk (SR) device studies follow all of the IDE regulations, and have an IDE application approved by FDA.

In general, a SR device is defined [21 CFR 812.3(m)] as an investigational device that:

- . . .
- Is purported or represented to be for 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.

The SR is independent of whether the device is to be marketed through a 510K or PMA or is to be used primarily as an integral marker in clinical trials

Risk Levels – Integral Markers

- **High risk to patient since the patient may be exposed to harm**
- **The IRB and FDA need to determine whether marker and its assay poses a “Significant Risk (SR)” to patient**
- **If there is Significant Risk, then an Investigational Device Exemption (IDE) needs approval from CDRH**
 - **An IDE may be bundled with an IND (CDRH and CDER/CBER may do a bundled approval)**
- **Even if the marker and its assay are cleared of significant risk, the impact of the marker measurement on the patient needs to be assessed**

What is An Investigational Device Exemption (IDE)?

- IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.
- Investigational use includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.
- All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.
 - The IRB may approve NSR IDEs but all IDEs that may have a Significant Risk need to be reviewed by the FDA
 - If any question about risk, the PI and assay developer should do a pre-IDE review with the FDA

What is An Investigational Device Exemption (IDE)?

- Clinical evaluation of devices that have not been cleared for marketing or deemed Non-Significant Risk by FDA requires:
 - an IDE approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA
 - informed consent from all patients
 - labeling for investigational use only
 - monitoring of the study
 - required records and reports.

Good Clinical Practices (GCP)

- The regulations and requirements that must be complied with while conducting a clinical study.
- Apply to the manufacturers, sponsors, clinical investigators, IRBs, and the medical device.
- Primary regulations are included in the Code of Federal Regulations, Title 21 (21 CFR)

CFR	Title	Area
21 CFR 812	<i>Investigational Device Exemptions:</i>	conduct of clinical studies with medical devices: application, responsibilities of sponsors and investigators, labeling, records, and reports.
21 CFR 50	<i>Protection of Human Subjects:</i>	requirements and general elements of informed consent;
21 CFR 56	<i>Institutional Review Boards:</i>	procedures and responsibilities for IRBs that approve clinical investigations protocols;
21 CFR 54	<i>Financial Disclosure by Clinical Investigators:</i>	disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data.
21 CFR 820 Subpart C	<i>Design Controls of the Quality System Regulation:</i>	requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.

Medical Devices: The Pre-Submission Program and Meetings with FDA Staff

- FDA has recently released a draft guidance on pre-submission for devices (assays)
- Outlines their current recommendations about clinical assay development
- Also suggests how to contact the FDA's Offices

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

IDE (AND Pre-IDE) APPLICATION

Step

Entry

1. Name and address of sponsor

2. Report of prior investigations (§812.27). A report of prior investigations must include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation.

Specific contents of the report must include:

- a bibliography of all publications, whether adverse or supportive,
- copies of all published and unpublished adverse information
- copies of other significant publications if requested by IRB or FDA
- a summary of all other unpublished information (whether adverse or supportive) relevant to evaluation of the safety and effectiveness of the device
- if nonclinical laboratory data are provided, a statement that such studies have been conducted in compliance with the Good Laboratory Practice (GLP) regulation in 21 CFR Part 58. If not conducted in compliance with the GLP regulation, include a brief statement of the reason for noncompliance.

IDE (AND Pre-IDE) APPLICATION

Step

Entry

3. Investigational plan (§812.25) shall include the following items in order:

- purpose (the name and intended use of the device and the objectives and duration of the investigation)
- protocol (a written protocol describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness)
- risk analysis (a description and analysis of all increased risks to the research subjects and how these risks will be minimized)
- a justification for the investigation
- a description of the patient population including the number, age, sex, and condition)
- description of this device (a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation)
- monitoring procedures (the sponsor's written procedures for monitoring the investigation and the name and address of each monitor).
- additional records and reports (a description of any records or reports of the investigation other than those required in Subpart G of the IDE regulation).

IDE (AND Pre-IDE) APPLICATION

Step

Entry

4. A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device
5. An example of the agreement to be signed by the investigators and a list of the names and addresses of all investigators. Information that must be included in the written agreement are found in § 812.43
6. Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study
7. A list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available)
8. The name and address of any institution (other than those above) where a part of the investigation may be conducted
9. The amount, if any, charged for the device and an explanation of why sale does not constitute commercialization

Meshinchi et al. Clin Cancer Res 18:1547–54, 2012

IDE (AND Pre-IDE) APPLICATION

Step

Entry

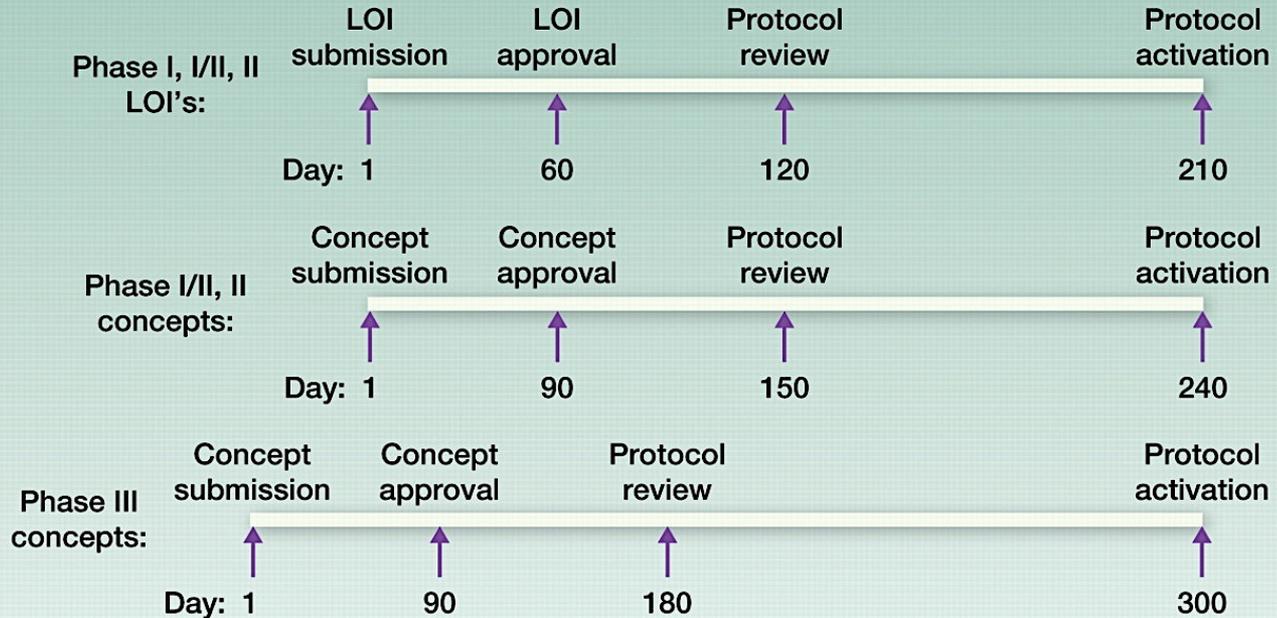
10. Please note that an environmental assessment as required under 21 CFR 25.40 or a claim for categorical exclusion under 21 CFR 25.30 or 25.34 is no longer required. [§25.34(g)]
11. Copies of all labeling for the device
12. Copies of all informed consent forms and all related information materials to be provided to subjects as required by 21 CFR 50, Protection of Human Subjects
13. Any other relevant information that FDA requests for review of the IDE application. Information previously submitted to FDA in accordance with Part 812 may be incorporated by reference.

Pre-IDE (Sub) Review vs Application

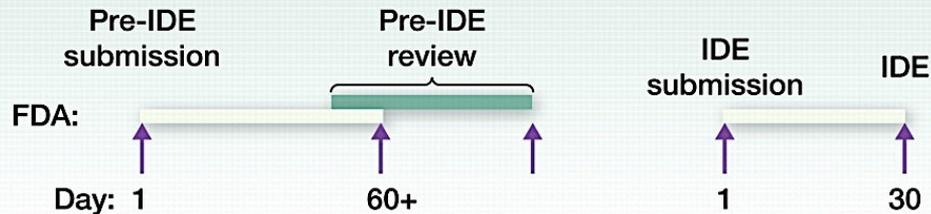
	Pre-IDE review	IDE application
Review time:	~60 Days	30 Days
Risk assessment:	Assay performance (rate of FP/FN within samples of intended use) impact of FP/FN on patient within state of disease in trial	
Elements of trial document reviewed for risk:	Background/significance/rationale, primary and secondary endpoints, eligibility criteria, statistical design, correlative science section, informed consent	
Assay assessment:	Analytical performance of assay within intended clinical use accuracy, precision, reliability, reproducibility	
Elements of trial document reviewed for assay:	Not currently included in LOIs, concepts or protocols but information required is generally that needed for any test in a CLIA-accredited laboratory*	

Pre-IDE Review Meets OEWG

A Operational efficiency working group (OEWG) timelines



B FDA Pre-IDE and IDE timelines



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FDA Guidance for IRBs

A draft guidance was issued this month on IRB procedures for both IND and IDE reviews:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM328855.pdf>

The guidance is to remind institutional review boards (IRBs) of their longstanding role in the review of:

- 1) the qualifications of the clinical investigator
- 2) the adequacy of the facility in which the research will take place
- 3) the determination of whether an investigational new drug application (IND) or investigational device exemption (IDE) application is necessary for the proposed clinical investigation.

If Assay is an Integral Marker, IRB Should Know Its Potential For Risk

- What is the risk to the patient of a false positive (FP) or negative assay (FN) result?
- This requires understanding the analytical performance of assays:
 - accuracy, reproducibility, precision and
 - how these characteristics translate into false positive or negatives
- Then IRB must consider consequences of FP and FN

Areas of Special Focus In Protocols for IRB and FDA

Background/Significance/Rational

Primary and Secondary Endpoints

Eligibility Criteria

Statistical Design

Correlative Science Section

Informed Consent

Need to know what patients are told

Clinical Assay Development Resources From NCI

Clinical Assay Development Program: <http://cadp.cancer.gov/>

Cancer Diagnosis Program: <http://cdp.cancer.gov>

Cancer Diagnosis Program Templates for IHC, FISH/CISH, or Somatic Mutations: <http://cdp.cancer.gov/diagnostics/templates.htm>

- also available on the CTEP website under templates and documents for protocols
- provide documentation of clinical assay performance for trials

 LOI/Concept/Protocol #: _____ Protocol Investigator: UName, Phone _____

Immunohistochemical (IHC) Marker Template For Integral Markers in Clinical Trials

This is a template to describe the analytical and clinical performance of an assay that is essential for performance of a trial. It will be used to assess whether assays are ready for use in a trial by Disease Steering Committees and CTEP. The FDA may also use it to evaluate integral assays and diagnostics for their pre-CE evaluation. Not all parameters may be known a priori. Please enter as much information as you can and N/A for not available or applicable where appropriate.

This template requires detailed information that may be known only by laboratorians, scientists who work in clinical laboratories, and should be collaborating closely with clinical trials. Please be sure to indicate the appropriate responses before filling out this form. The template has the following sections with information needed from trialists and laboratorians:

1. Assay, Patient and Specimen Information - Trialists and Laboratorians
2. Primary Antibody Characteristics - Laboratorians
3. Design of Immunohistochemical Assay - Laboratorians
4. Assay Performance - Laboratorians
5. Laboratory Information - Trialists and Laboratorians

 Study Chair: _____ LOI/Concept/Protocol # _____

DNA-based in situ hybridization biomarker template (FISH, CISH)

This is a template for use in outlining the known status of a FISH or CISH assay that is to be used in a trial. It is intended to be used for assays measuring BPOE genetic variations such as specific translocations, gene amplifications or deletions. It is not intended for array CISH or similar multiple DNA in situ hybridization assays. Not all parameters may be known a priori. Please enter as much information as you can. Enter N/A for not available or applicable where appropriate.

It is recommended that Ventura et al., FISH analysis for the detection of lymphoma-associated chromosome abnormalities in routine paraffin-embedded tissue. *J Mol. Diagn.* 8:141-151, 2006 be read as a reference before completing this template.

This template requires detailed information that may be known only by laboratorians, scientists who work in clinical laboratories and should be collaborating closely with clinical trials. Please be sure to indicate the appropriate responses before filling out this form. The template has the following sections with information needed from both trialists and laboratorians:

Section	Heading
1.	Assay, Patient and Specimen Parameters - Trialists and Laboratorians
2-4.	Probe Characteristics - Laboratorians
7.	Design of In Situ Hybridization Assay - Laboratorians
8.	Assay Performance - Laboratorians
9.	Laboratory Information - Trialists and Laboratorians

 Study Chair: _____ LOI/Concept/Protocol # _____

DNA-based Mutation Assays

This is a template for use in outlining the known status of an assay that is to be used in a trial. The Clinical Laboratory Scientists who will be performing the tests should fill out this form. Not all parameters will be known a priori. Please enter as much information as you can. Enter N/A for not available or applicable where appropriate. This template is intended only for DNA-based somatic mutations and not for FISH-based mutations. It is also primarily intended for assays for markers that are integral for a trial. The information provided will be useful for an FDA pre-IDE review.

It is recommended that Jennings et al., Recommended Principles and Practices for Validating Clinical Molecular Pathology Tests. *Arch Pathol Lab Med* 133:743-755, 2009 be read as a reference before completing this template.

Section	Heading
1	Assay, Patient and Specimen Parameters
2	Design of Mutation Assay
3	Assay Performance
4	Laboratory that is performing this assay

RECOMMENDATIONS

IRBs may want their institution's protocols to include a section that concisely documents whether an IND or IDE is required

AND

For protocols that include integral markers the risk of FP and FN assay results and their consequences should be described for patients.

Also may need to include clinical assay developers on the IRBs for protocols with integral markers.

SUMMARY

- IRB needs to review role of the protocol investigators, assay developers and performers, and sponsors to determine if IND/IDE may be needed
- If trial has an integral marker, then an IDE is likely and IRB, investigator and sponsor need a pre-IDE Submission to FDA
- Can be hard for IRB and FDA to find the risk attendant to an integral marker
 - Need to know how to define false positive and negative rates and what that means for toxicity to patient
- Both IRB and FDA need to know what patient is told about the risk for patient in the consent

Whether this increased attention to development of Molecular Diagnostics improves quality will need to be assessed