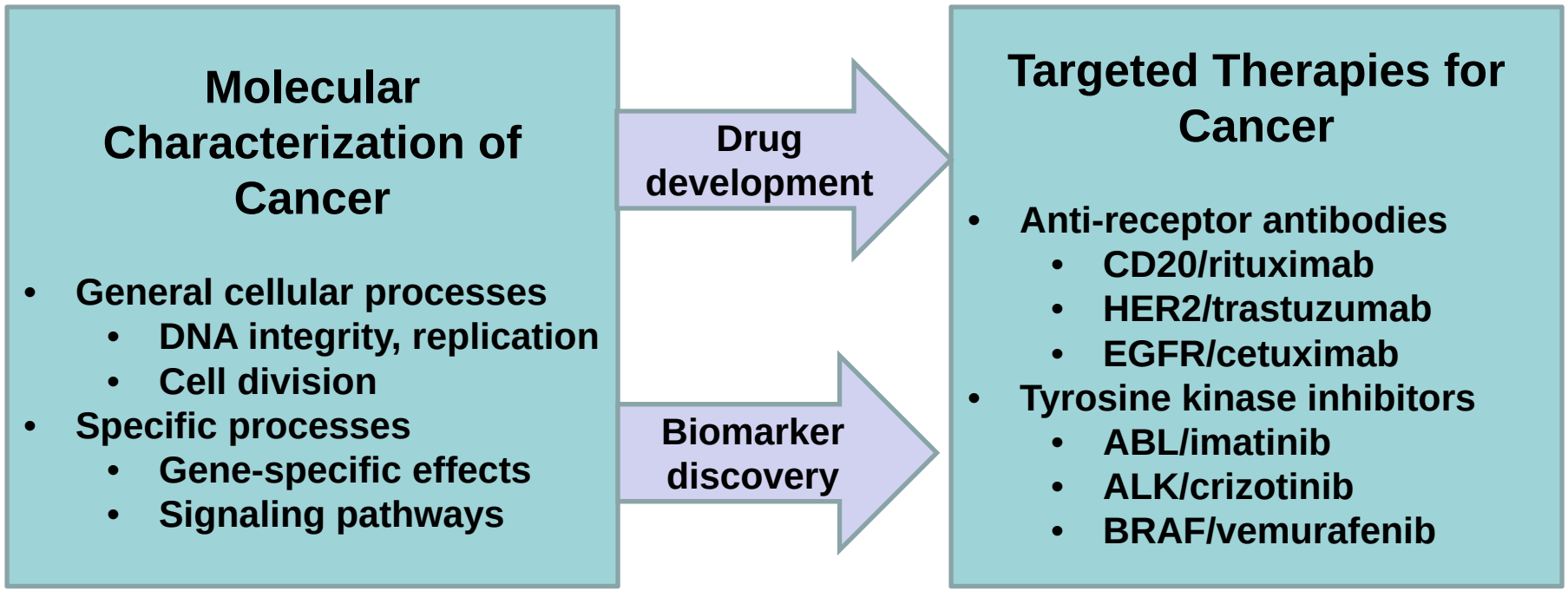
Use of Investigational IVDs in Therapeutic Trials

David Litwack, Ph.D.
Personalized Medicine Staff
OIR/CDRH/FDA


Molecular Characterization of Cancer
General cellular processes
DNA integrity, replication
Cell division
Specific processes
Gene-specific effects
Signaling pathways
Drug development
Biomarker discovery
Targeted Therapies for Cancer
Anti-receptor antibodies
CD20/rituximab
HER2/trastuzumab
EGFR/cetuximab
Tyrosine kinase inhibitors
ABL/imatinib
ALK/crizotinib
BRAF/vemurafenib

IVDS: COMPANION DIAGNOSTICS

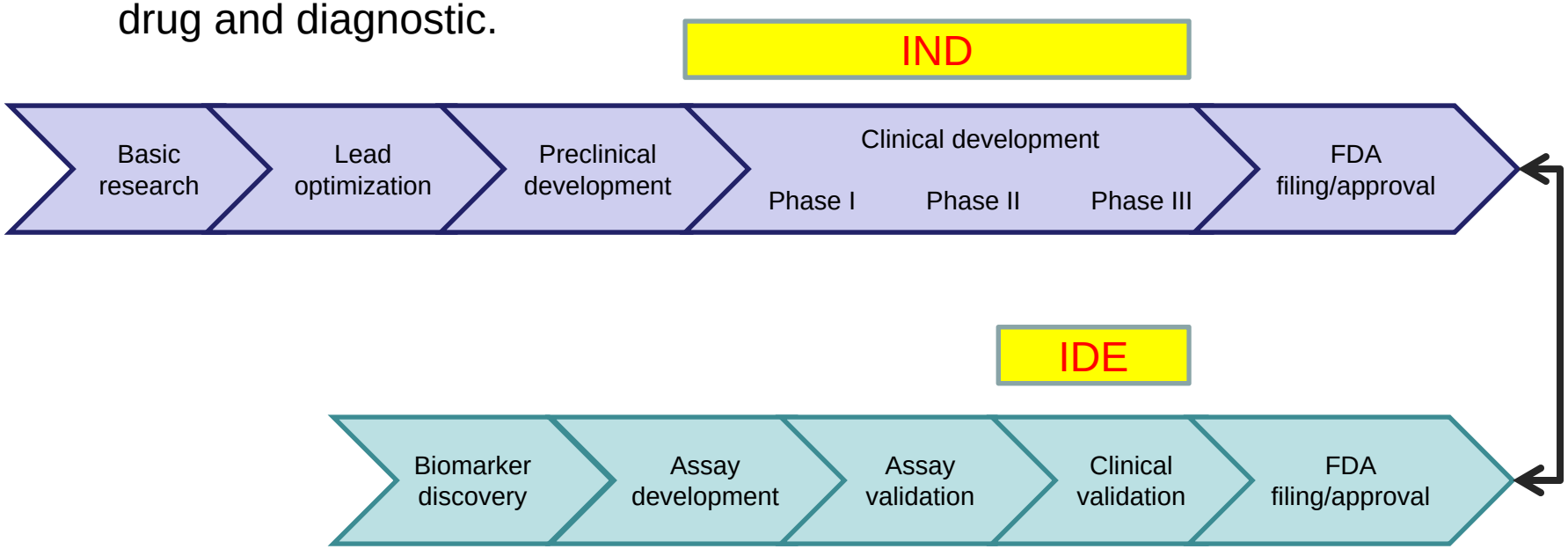
- An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
- Drugs and their companion tests refer to each other in their labels.
- The drug and device are typically studied in the same clinical trial.
- **These investigations are then subject to:**
  - **Investigational New Drug (IND) regulation, 21 CFR 312**
  - **Investigational Device Exemption (IDE) regulation, 21 CFR 812**

XALKORI® (crizotinib) Capsules, oral
XALKORI is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive *as detected by an FDA-approved test.*

Vysis ALK Break Apart FISH Probe Kit
The Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed parraffin-embedded (FFPE) non-small cell lung cancers (NSCLC) tissue specimens *to aid in identifying those patients eligible for treatment with XALKORI® (crizotinib).*

Codevelopment

- The development of paired therapeutic products and diagnostic devices with interdependent uses (e.g., a drug and a companion diagnostic).
- Biomarker discovery and test development can occur anytime during the drug development process.
- Safety and efficacy of the new drug and new diagnostic is typically demonstrated in the same clinical trial.
- From a regulatory perspective, the goal is simultaneous approval of the drug and diagnostic.



"A bad test is every bit as bad as a bad drug."

- Wrong biomarker
  - Wasted rx development effort
  - Lost treatment opportunity

- Poor analytical performance
  - Obscures drug's effect
  - Wrong patients treated

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.

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 therapeutic product 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 therapeutic product 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.

What's in an IDE Application?

- Detailed in 21CFR812.20
- 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.

Common Problems in Drug Trials

- Failure to recognize that the biomarker test is an investigational medical device.
- Expectation that compliance with IND regulation supplants the IDE requirement.
  - OIR will often be alerted to the use of an investigational IVD in the study by the therapeutic product Center.
- 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.

A Risk-Based Approach to IVD Regulation

- Need to think about the benefits and risks of a test

- For an IVD tests, it is important to think about the **risks associated with false positives or false negatives**. What would happen if the test results are wrong? Are the benefits greater than the risks of inaccurate results?
  - False positive: the patient would receive unneeded treatment, be exposed to treatment risk without benefit
  - False negative: the patient would not receive needed treatment.

For companion diagnostics, this will depend on the disease, the risks of treatment with the drug, and other treatment options (e.g., standard of care).

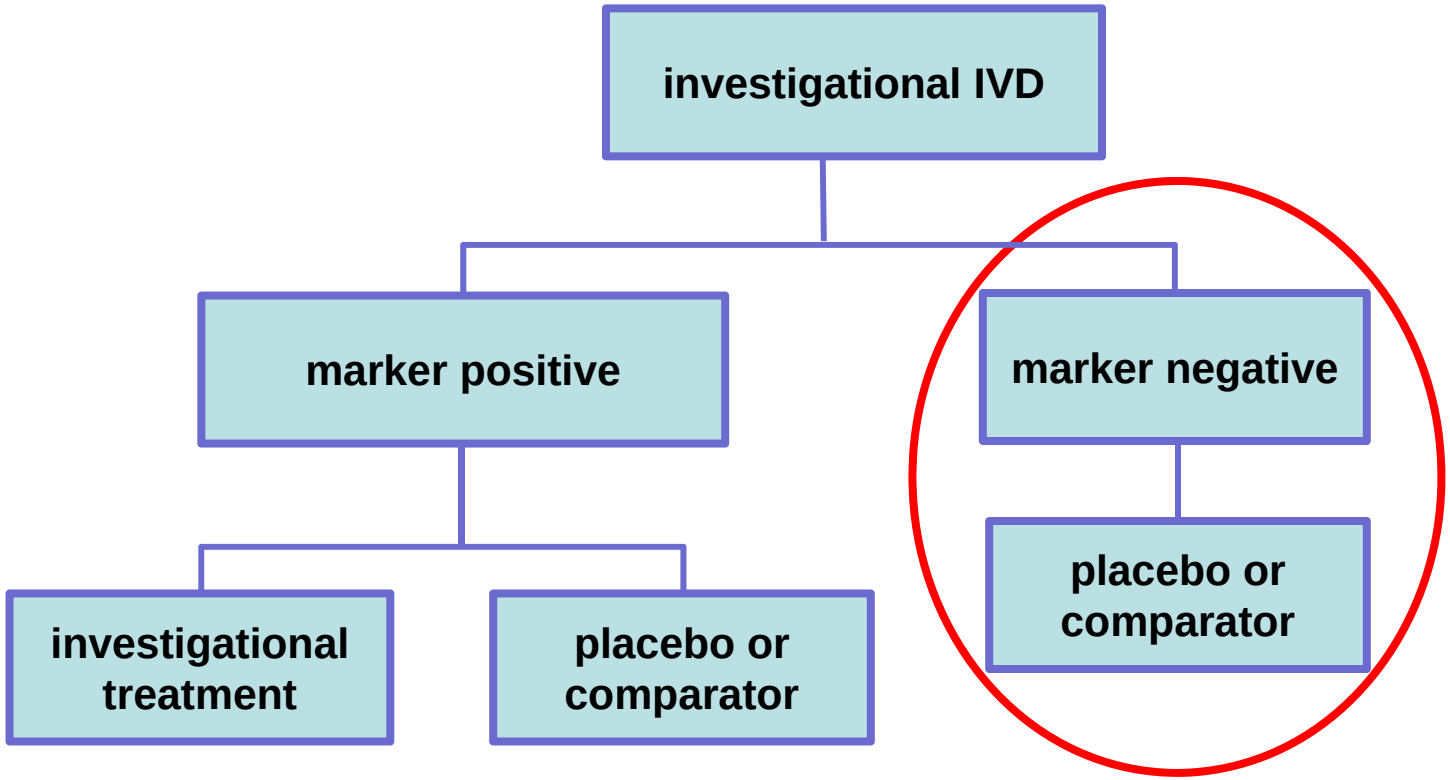
Uses of an Investigational IVD Device in a Therapeutic Product Trial

- The safety and effectiveness of the device is linked to that of the therapeutic product.

- Common uses:
  - Patient selection
  - Stratification
  - Predicting adverse reactions
  - Dosing
  - Monitoring

MARKER USED TO SELECT TREATMENT

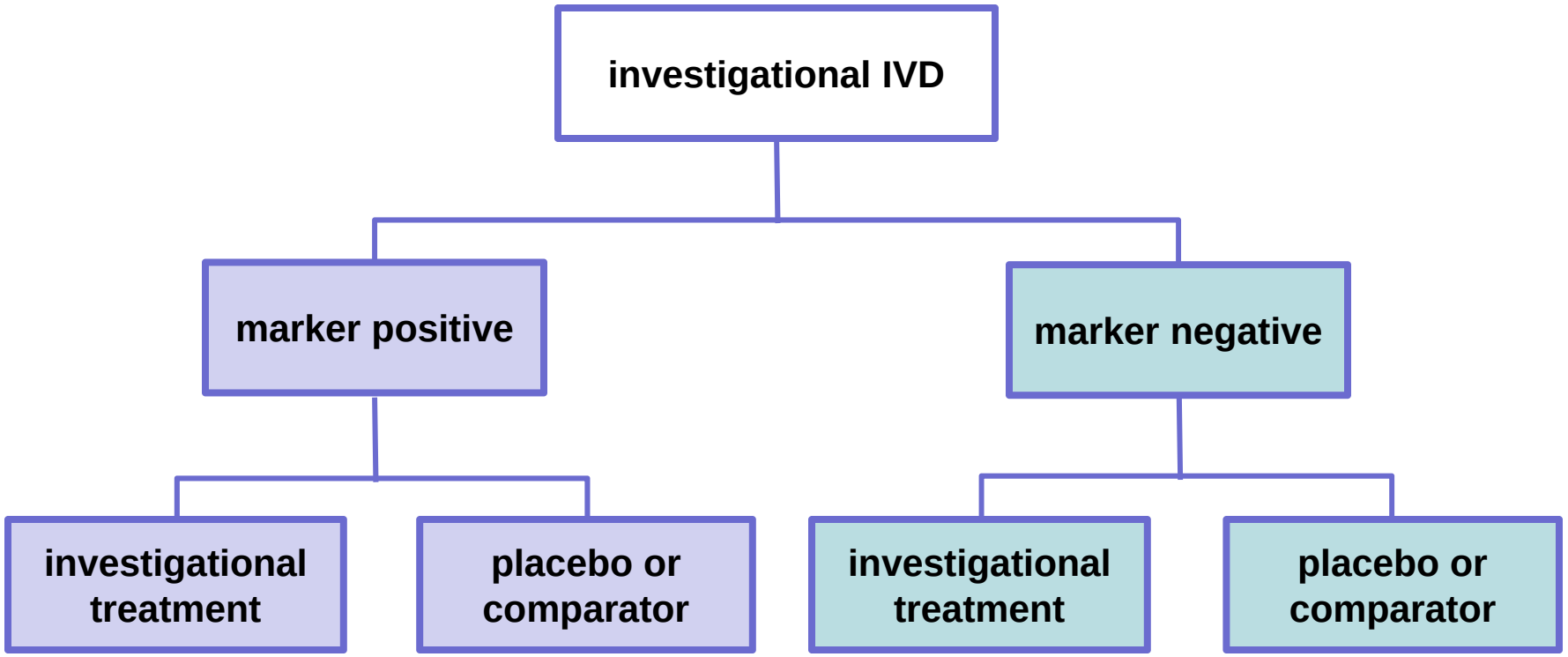
Test result influences treatment.



Sometimes not enrolled

MARKER USED FOR STRATIFICATION

Test result does not influence treatment.



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.
- e.g., retrospective studies

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 means that you have an approved application for an IDE
- Example: Stratification

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.
- In other words, does the use of the IVD guide patient care?
- Eg, patient selection

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

- Will use of the investigational test results lead to some trial subjects foregoing or delaying a treatment that is known to be effective?

- 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?

- 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?

- Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?

Some Features with Lesser Relevance for IVD Risk Determination

- "Line" of therapy
- Disease stage
- Size of trial
- Access to "other trials"
- Exclusion from a trial

Risk in Ongoing Trials

- Risk can change during the course of a trial.
  - Adaptive trials
  - Protocol changes
  - New protocols
  - 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.

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 will typically be 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.

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!

- 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

Contact Information

Ernest.Litwack@fda.hhs.gov

Personalized Medicine Staff

Office of In Vitro Diagnostics & Radiological Health/ CDRH/FDA