AMDM 2013 Focus Meeting

Companion Diagnostics: IDE Considerations for CDx

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DISCLAIMER

- Thoughts presented here regarding new policy / regulatory issues are preliminary and do not represent finalized FDA policy

- I have no financial relationships to disclose.

IVDs: Companion Diagnostics

- Companion diagnostics are a special class of 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.
- Drugs and their companion tests refer to each other in their labels.
- Draft Guidance for Industry and FDA Staff. In Vitro Companion Diagnostics. Issued on July 14, 2011.
- www.fda.gov/CompanionDiagnostics

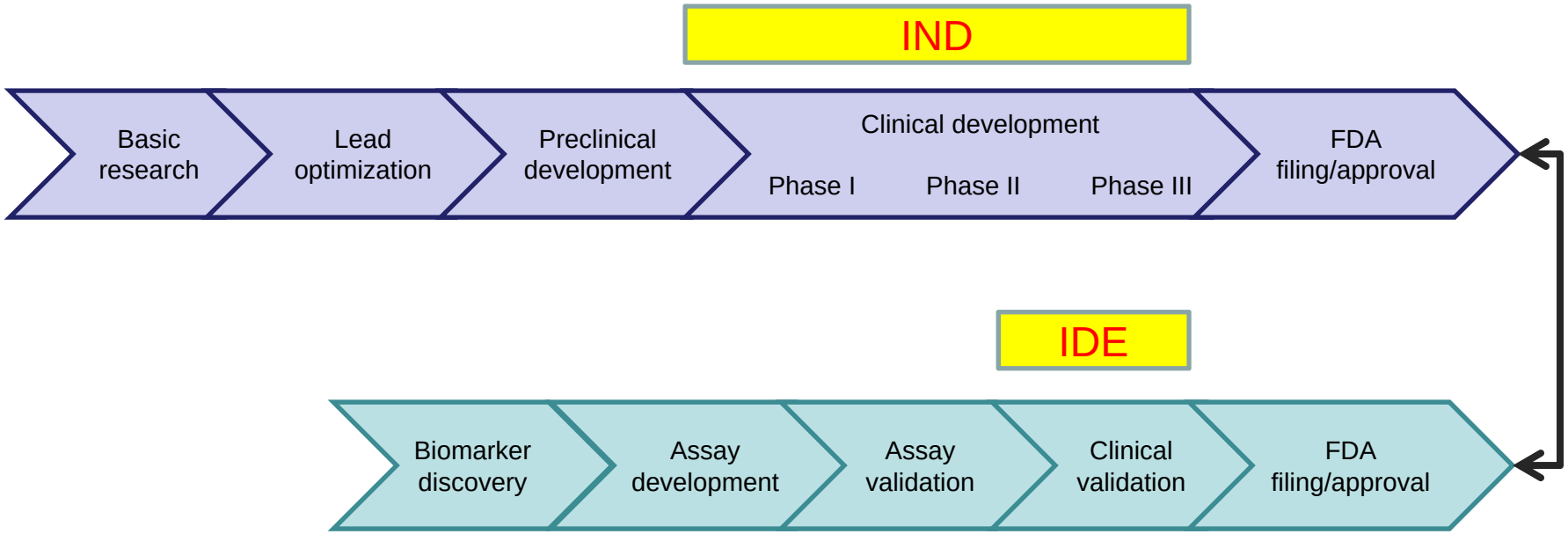
Companion Diagnostic IVD and Drug Labels Cross-reference Each Other

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.
- Biomarker discovery and test development can occur anytime during the drug development process.
- From a regulatory perspective, the goal is to get simultaneous approval of the drug and diagnostic.



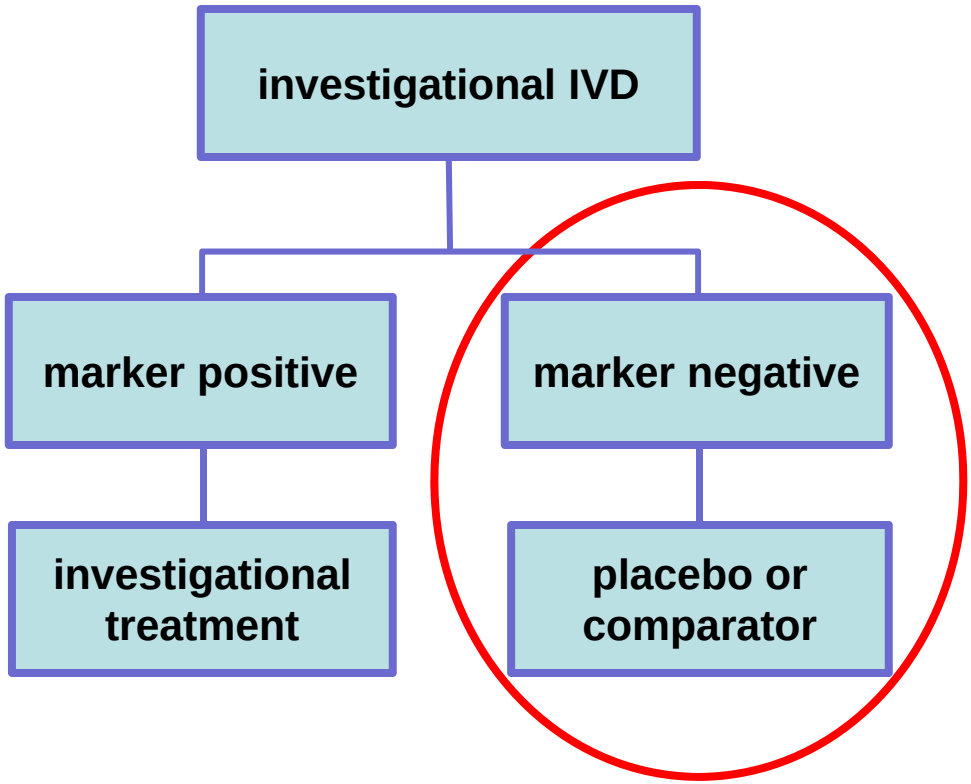
Uses of an Investigational IVD Device in a Therapeutic Product Trial

- 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

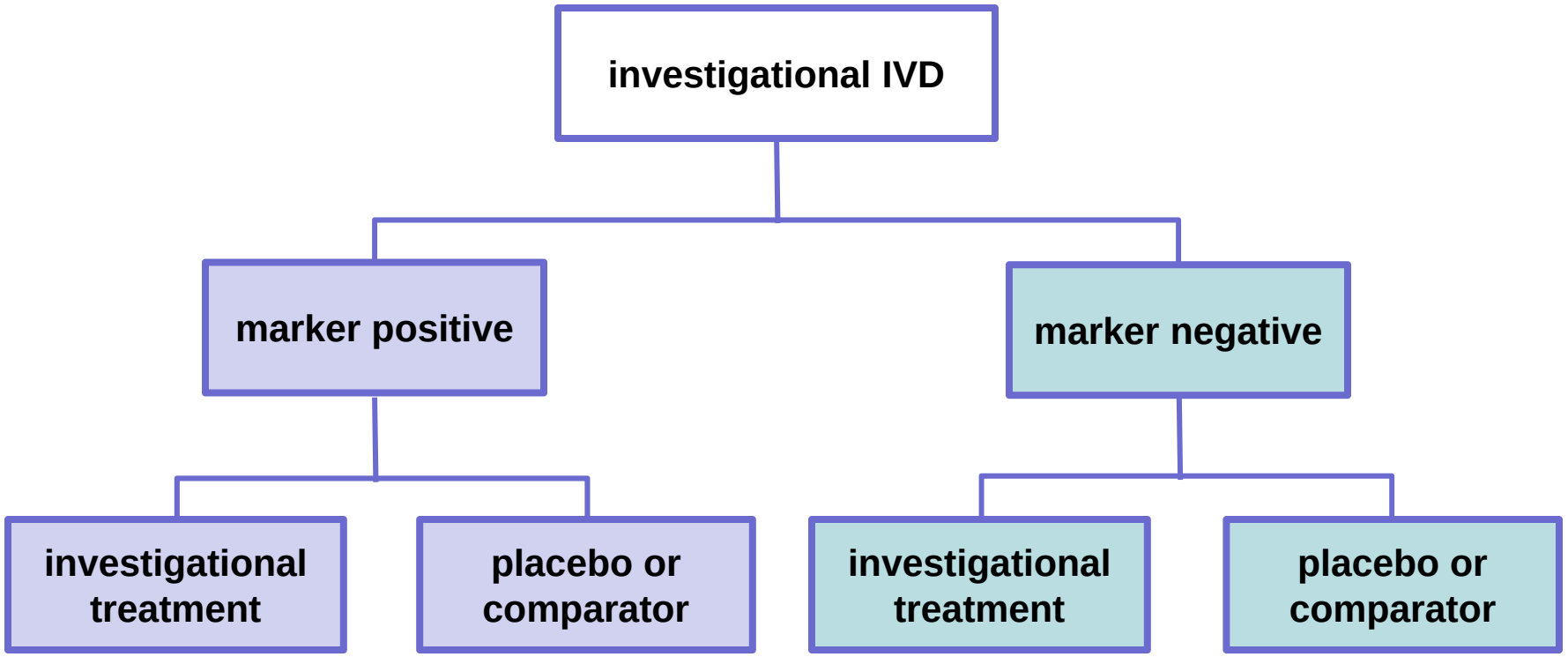
Test result influences treatment.



Sometimes not enrolled

MARKER USED FOR STRATIFICATION

Test result does not influence treatment.



IMPORTANT CONSIDERATIONS FOR THE INVESTIGATIONAL USE OF COMPANION DIAGNOSTICS

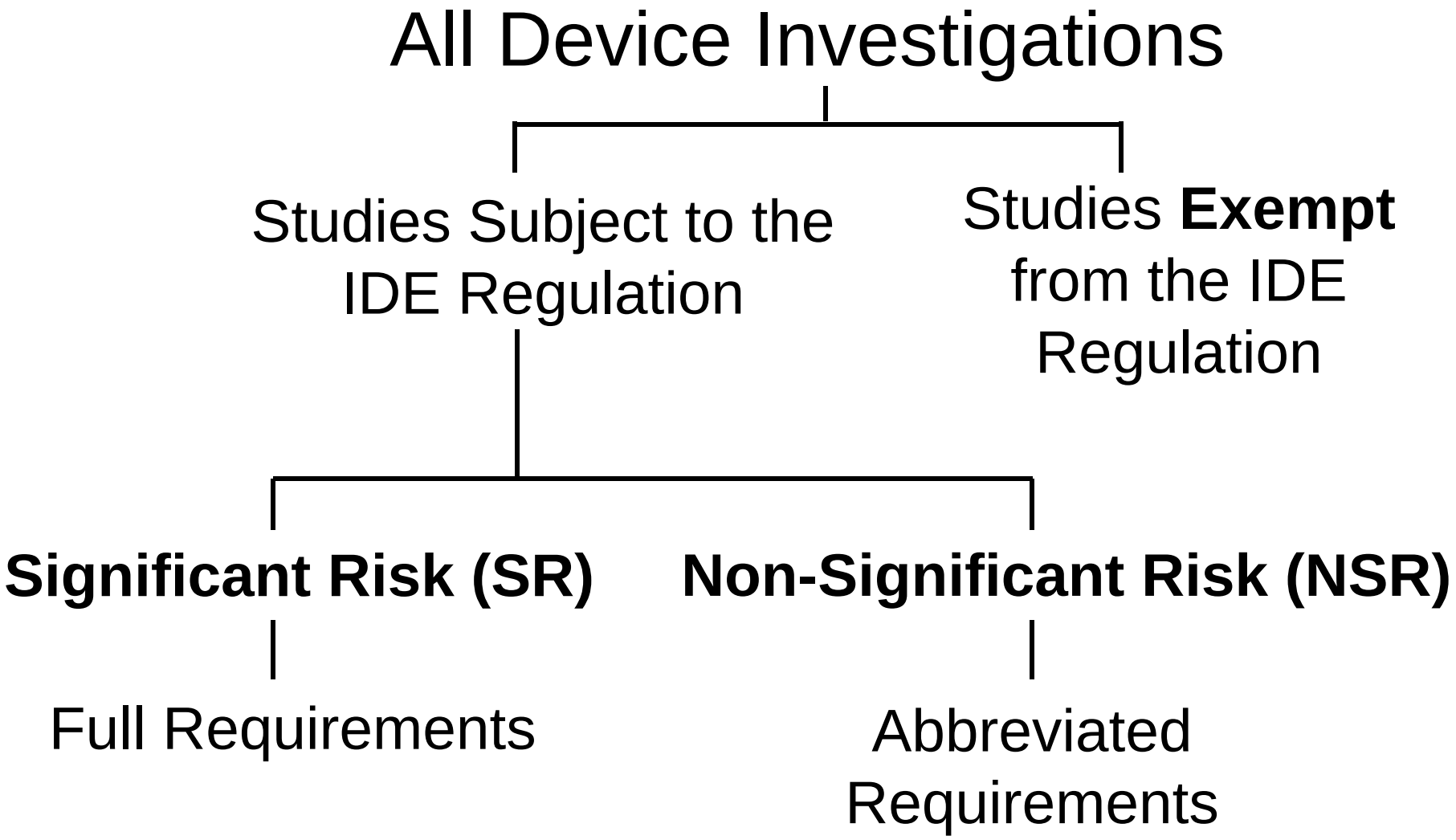
- Sponsors of therapeutic product trials that incorporate an investigational IVD must consider regulations that pertain to both drugs and devices.
- Exemptions from premarket approval requirements for new drugs and devices.
  - Investigational Device Exemption (IDE) regulation (21 CFR 812)
  - Investigational New Drug (IND) regulation (21 CFR 312)
- IDE and IND regulations have different requirements!
- For trials involving both an investigational IVD and a new drug (e.g., for companion diagnostics), both an IND and an IDE may be required. The requirement for an IDE is independent of the requirement for an IND.
- Intent to market the IVD is not relevant to the IDE regulation.

IDE: A Risk-Based Approach to IVD Regulation

- Need to think about the benefits and risks of a test, and impact of test use on patients in the trial.

- For an IVD tests, it is important to think about the risks associated with incorrect 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).


All Device Investigations
Studies Subject to the IDE Regulation
Studies **Exempt** from the IDE Regulation
Significant Risk (SR)
Non-Significant Risk (NSR)
Full Requirements
Abbreviated Requirements

IMPORTANT CONSIDERATIONS FOR THE INVESTIGATIONAL USE OF COMPANION DIAGNOSTICS

- Key question: SR or NSR?
- A significant risk IVD will usually be one that influences how a patient is treated.
- When the IVD is SR, 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.
- An IDE is not required for an NSR IVD. Some information on the test may be requested in the IND (based on IND regulation).
- A trial may not proceed until it has received IND and/or IDE approval AND IRB approval.

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?

Balanced Approach to IVD Risk

Context and Effect of FP or FN test result?

- Accrual by test result
- Rx assignment
- Safety signal for Rx
- Targeted biomarker
- Survival endpoint
- Invasive sampling
- Strong biomarker effect known

- All-comers accrual
- Stratification
- No “known effective” Rx
- Convenience biomarker
- Response endpoint
- Non-invasive sampling
- Weak/conflicting info on biomarker effect

Some Features with Lesser Relevance for IVD Risk Determination

- “Line” of therapy
- Disease stage
- Size of trial
- Access to “other trials”

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.

What Should IRBs Ask About Therapeutic Product Trials?

1. Are one or more IVD devices being used in this study?
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?

Delegated Responsibilities and Risk Determination

Sponsor makes initial determination and presents to IRB

WARNING: CONFLICT OF INTEREST!

IRB reviews determination; agrees or modifies

FDA can help; FDA determination is final

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

- How well does the test measure the analyte?
- Does the test measure the correct analyte?
- Does the test measure the analyte reliably?
- Precision, reproducibility, sensitivity, specificity, etc.
- For a companion diagnostic, analytical performance around the cutoff/reference range is critical.
- What is impact of analytical performance on erroneous results?

Common Problems

- 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.

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.

Contact Information

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