

Issues in Clinical Trial Design for Companion Diagnostic Devices

Clinical Trials Investigator Training Course
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Center for Devices and Radiological Health (CDRH)

OHT7: Office of In Vitro Diagnostics and Radiological Health (OIR)

Presentation Overview

- Overview of Regulation of In Vitro Diagnostic Devices (IVDs)
- Key Regulatory Questions:
 - Drug/Device Codevelopment
 - Challenges & Solutions
- Useful Tips & Tools

The contents of this presentation are for discussion and summary purposes only and do not describe the full extent of requirements applicable to devices, including IVDs and Companion Diagnostic Devices. Please see the Federal Food, Drug, and Cosmetic Act and 21 CFR Subchapter H for requirements applicable to medical devices.

Definition: In Vitro Diagnostic Device

“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. ... for use in the collection, preparation, and examination of specimens from the human body.”

[21 CFR 809.3]

Human Subject Regulations

Definition of a “Human Subject”

- A human who participates in an investigation, either as a recipient of the test article or as a control. Includes both persons in normal health and patients.
- Subject is an individual on whom or on *whose specimen* an investigational device is used.

FDA Human Subject Protection Regulations

- **21 CFR Part 50:** Protection of Human Subjects and Informed Consent
- **21 CFR Part 54:** Financial Disclosure of Investigators
- **21 CFR Part 56:** Institutional Review Boards
- **21CFR 812:** Investigational Device Exemption
 - Includes disqualification of investigators
 - Applies to all FDA clinical investigations

Drug/Device Co-development: Key Regulatory Questions



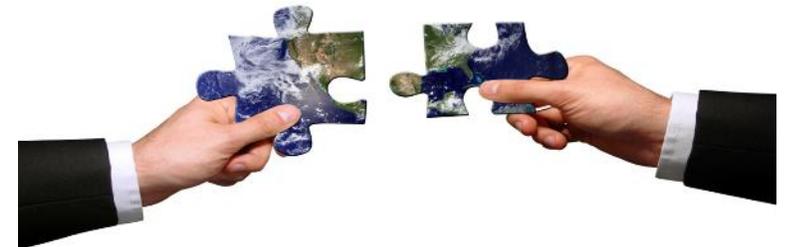
- Will an IDE be required?
- If the drug development program is based on a biomarker, will the test for the biomarker result in a companion diagnostic device?
- Does the companion diagnostic device have adequate performance data to be approved contemporaneously with the drug?
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Is the Test Investigational?

- An investigational device is a device that is **used in a clinical investigation** involving one or more subjects that will generate data about the safety and effectiveness of the IVD as used in the study (i.e., for the clinical indication)
- 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
- You can find the IVDs that have been cleared or approved on FDA's website <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm>
- Investigational Device Exemption (IDE) regulation (21 CFR 812)

Investigational Use of tests: IDEs and INDs

- Sponsors of therapeutic product trials that incorporate an investigational test must consider regulations that pertain to both drugs and devices.
- Exemptions from premarket approval requirements for new drugs and devices.
- IDE and IND regulations have different requirements!
 - Investigational Device Exemption (IDE) regulation (21 CFR 812)
 - Investigational New Drug (IND) regulation (21 CFR 312)

Will an IDE be required?



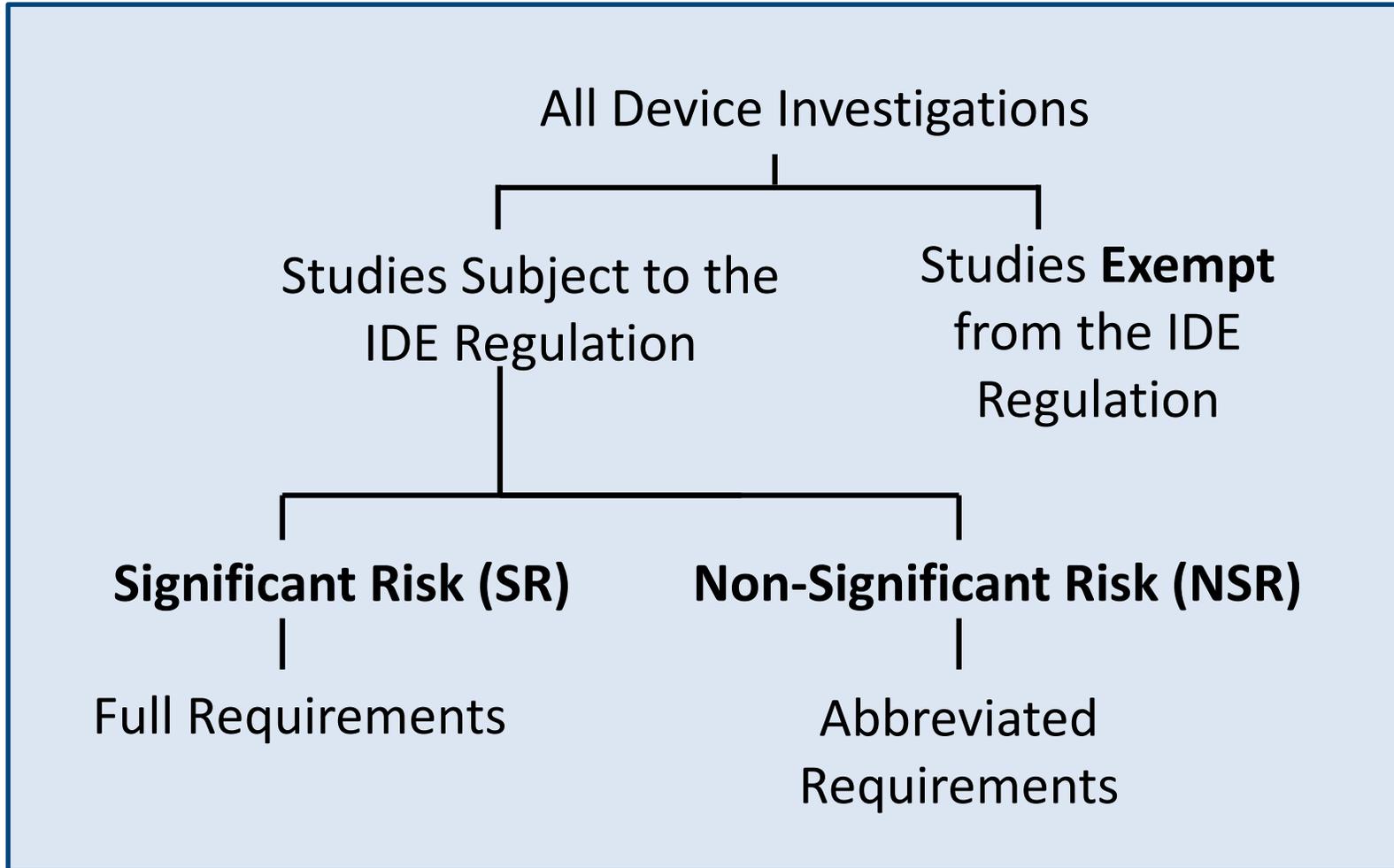
- If an IVD is used to identify a biomarker in a drug trial, then an IDE may be needed (if the IVD is not already FDA cleared or approved for the intended use).
- Need for an approved IDE based on the risk to patients
- Irrespective of trial phase or number of patients
- Testing sites should comply with IDE requirements when in the US or testing US patients (i.e. does not apply for foreign testing of foreign patients)
- A test for patient enrollment should be analytically validated (minimum validation, assay fully specified, and locked down) whether it is used in an SR or NSR study

Factors to consider in making a risk determination*

- Will use of the results from an investigational IVD lead to some study **subjects foregoing or delaying a treatment** that is known to be effective?
- Will use of the results from an investigational IVD expose study subjects to safety risks (e.g., adverse events from the investigational therapeutic product) that **exceed the risks** encountered with the control arm therapy or non-trial standard of care?
- Is it likely, based on existing knowledge about the relationship between the biomarker and the investigational therapeutic product, that **incorrect results** from the investigational IVD would present a potential for serious risk to study subjects?
- Does use of the investigational IVD require **invasive sampling** that is not part of standard of care?

*See Draft Guidance: Investigational IVDs Used in Clinical Investigations of Therapeutic Products (Dec. 2017)

Investigational Device Exemption



<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm162453.htm>

Do I need an IDE for my study?

- **Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination**
 - Final issued October 2019
 - The streamlined submission process can ONLY be used for new INDs.
 - IND sponsor may choose to submit SRD request in an IND
 - Alternatively (as current practice), submit a SRD Q-sub to CDRH
 - CDRH/CDER/CBER make SRD at an IND safety meeting
 - Safe-to-proceed letter will include study risk determination
- **Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program**
 - Issued May 2019
 - Can use to request a Study Risk Determination
 - Goal 21 day decision

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



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Key Regulatory Question: Is my test a CDx?

- **Will the test for the biomarker result in a companion diagnostic device?**
- Companion diagnostic requirement decision made by drug/biologic review division – [CDER/CBER]; device review center (CDRH) provides insight
- *Is there adequate evidence of clinical activity of the drug in the biomarker positive population identified by the companion diagnostic?*
- *Is the IVD essential for the safe and effective use of the corresponding therapeutic product?*

IVDs: Companion Diagnostics

- Companion diagnostics are a subset 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.
 - *If the safe and effective use of the therapeutic product requires a particular test result, that test is a companion diagnostic.*
- Drugs and their companion tests refer to each other in their labels.
- Guidance on In Vitro Companion Diagnostic Devices.
<https://www.fda.gov/media/81309/download>

Is the test essential for S&E use of the therapeutic?

- Companion Diagnostics vs. Complementary Diagnostics
 - Companion Dx: A test that provides information that is essential for the **safe and effective** use of a corresponding therapeutic product.
 - Complementary Dx (**DRAFT DEFINITION**): A test that identifies a subgroup(s) of the indicated population that has a **different benefit-risk profile than the broader population** for whom the corresponding therapeutic product is indicated. [e.g., enhanced overall survival)

- Whether Companion / Complementary
 - Decision made by drug review division, typically during the review of the therapeutic submission
 - Device Center provides insight
 - An IVD can be both a CDx and a Complementary Dx depending on the therapeutic and patient population identified (e.g., PD-L1)
 - Companion Dx I.U refer to aid in the identification of patients for the therapeutic product
 - Complementary Dx I.U refer to the observed outcome in a subset

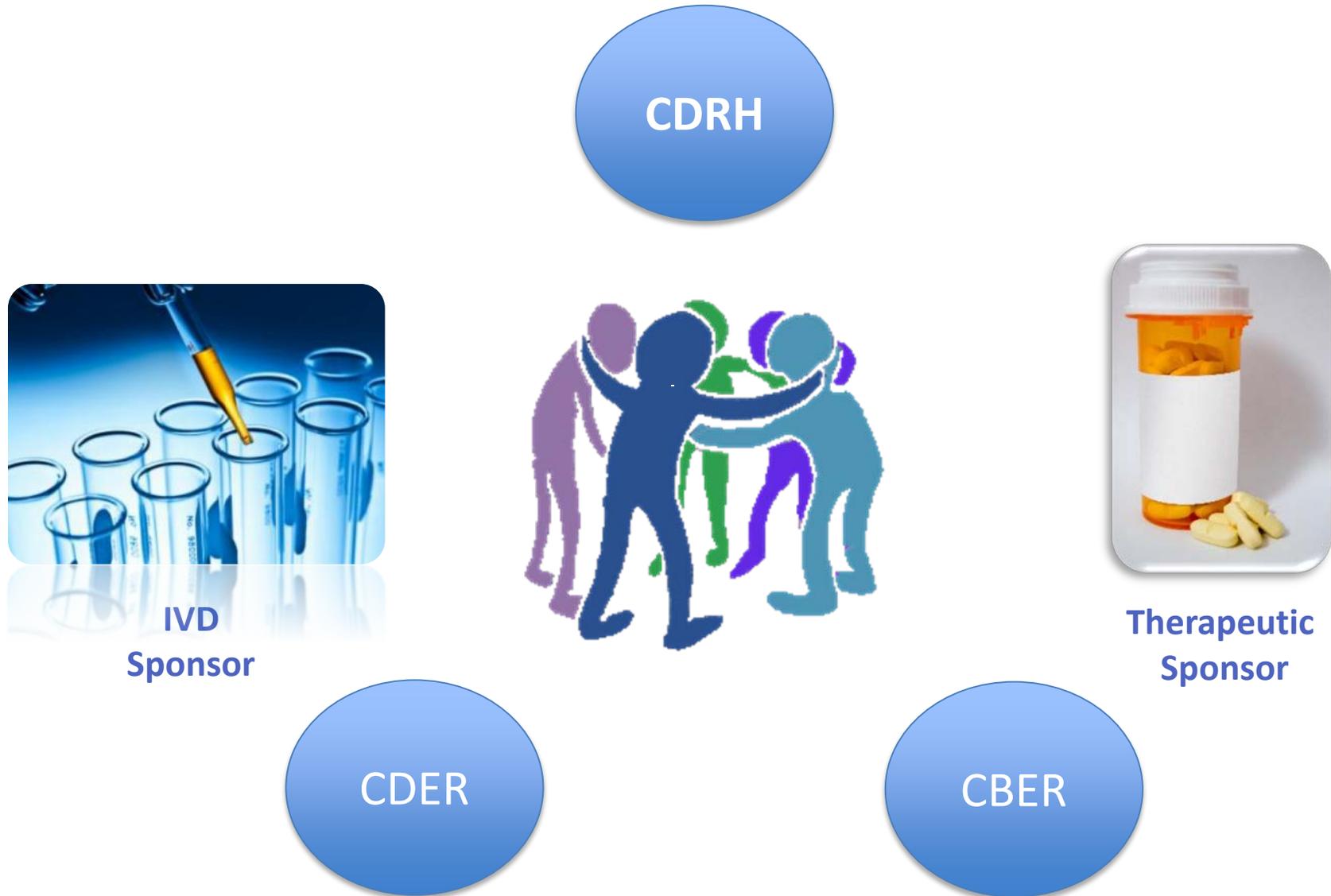


Companion Diagnostics



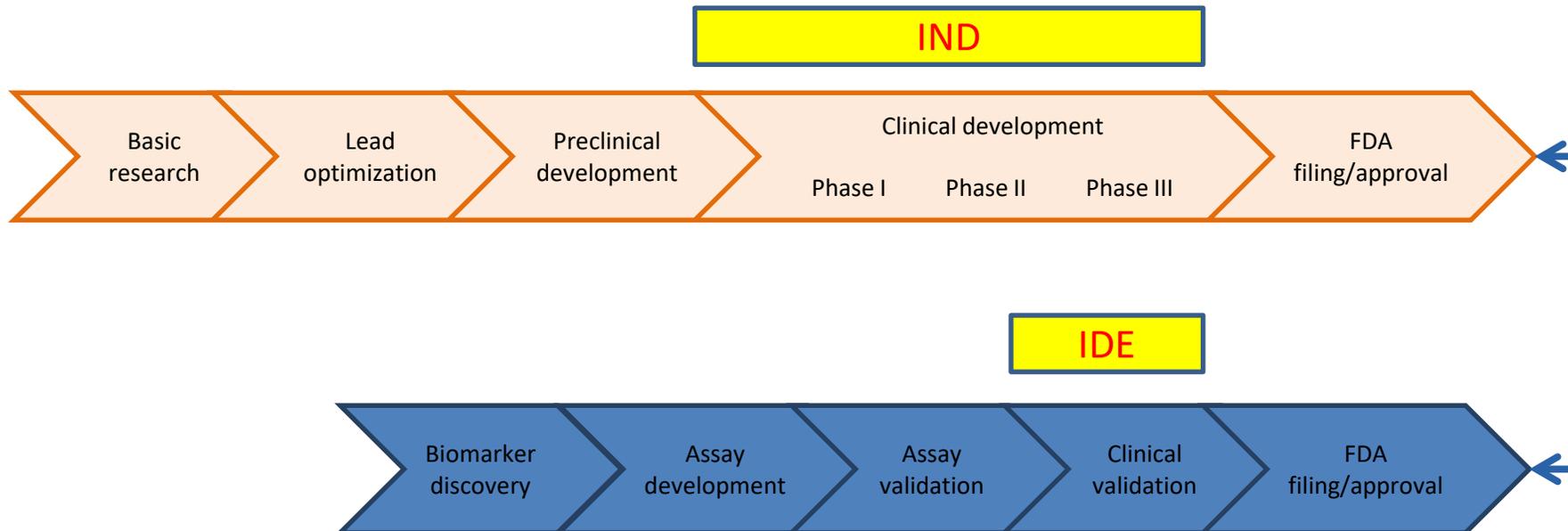
- Tests required to determine whether a specific drug should or should not be administered to a patient
- Test used for patient selection into therapeutic trial
- Clinical validation of test comes from a successful drug trial
- Problems can arise when the final test intended for marketing is not the one(s) used to screen patients for the trial
 - Pre-screening
 - Test changes
 - Missing outcome data in clinical trial assay (CTA) negative population

Co-development: Therapeutic + IVD



Co-development

- 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 are typically demonstrated in the same clinical trial.
- From a regulatory perspective, the goal is simultaneous approval of the drug and diagnostic.



Codevelopment: Benefits & Challenges

Benefits

- For pharmaceutical companies:
 - Potential for optimum patient population and smaller future trials
 - Improved drug effect if marker effective
- For diagnostic companies:
 - New type of diagnostic claim
 - Well characterized subjects
 - Extensive follow-up

Challenges

- May not be adequate data early on to determine the best biomarker to measure; whether test needed
- Appropriate statistics (may allow for e.g., adaptive trial design if drug not effective in the general population)
- Test used in drug trials not the marketed version (platform change)
- Appropriate storage of clinical trial samples; IRB, IC



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Key Regulatory Questions:

Is my device performance adequate?



Does the companion diagnostic device have adequate performance data to be approved contemporaneously with the drug?

Analytical Performance Validation

- Performed using procured specimens from the intended use population (exception for rare mutations)
- Critical performance characteristics should be assessed **before** using test in trial
- Test should be fully specified and locked down prior to use in the trial
- Important to assess analytical performance at the clinical decision point (cut-off)

Clinical Performance Validation

- Supported by the results of the drug trial when companion diagnostic device is used to test specimens and identify patients eligible for the trial

Intended Use of the IVD

“Intended Use”-driving force of the scientific review

- **Understanding:**

Integration of disease(s)/condition(s).

Integration of patient clinical management and public health (surveillance)

- **Who** will be tested, where and when: outpatients, inpatients, pediatrics, adults, acutely ill, etc.
- **What** are the appropriate specimens and analytes: type, timing, handling
- **How** test result(s) may be used: patient management

Scientific Review : IVD Validation

- Assay selects the target population enrolled in a clinical trial
 - A specific test is identified for detecting the marker
 - A specific protocol is used with the test
 - A clinical decision point (cut-off) is selected
 - A specific specimen type is identified for testing
- Analytical validation (e.g., accuracy, reproducibility, specificity, stability) is obtained with attention to the clinical decision point
- Clinical validation of the device is supported by the results of the therapeutic clinical trial
- Labeling
 - Intended use, device design, directions for use, warnings/limitations, result interpretation, performance

CDx Challenges - Specimens

- Each claimed specimen requires analytical validation
 - Tissue type (e.g., blood, bone marrow, tumor, urine),
 - Tissue collection (e.g., tissue block, FNA, whole blood spot cards, special collection devices) and stability
 - Tissue collection/preparation reagents (frozen vs. FFPE; anticoagulants; preservatives, regulatory status)

- Inability to re-test specimens
 - Informed consent issues
 - Poor quality sample, lack of sample, missing sample



Solutions - Specimens

- Select one specimen type
 - Specify the specimen type in the trial
 - Specify the processing steps as well as volume, cell/tumor proportion, etc. so that validation requirement is limited to these specifics
 - Estimate amount of specimen needed to meet clinical validation requirements
 - Capture protocol deviations
 - Consider whether it is possible to get paired specimens at time of collection

- Bank samples from all patients evaluated for enrollment – (test negative and test positive)
 - Obtain adequate sample volumes for retesting
 - Consider policies in foreign countries
 - Ensure Informed consent documents cover the testing



Clinical Performance



- Determine how the device will be used in clinical setting and ensure study design is appropriate
- Study design should support the Intended Use
- Pre-specified clinical and statistical analysis plan (including acceptance criteria)
- Establish clinical performance of device compared to an endpoint or appropriate surrogate
- Analytical validation precedes clinical validation

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Key Regulatory Questions: Will a bridging study be required?

- **When the final to-be-marketed test is not the Clinical Trial Assay (CTA).**
 - *Various issues may arise due to the clinical trial study design and enrollment procedures*
 - *Change in the test (e.g., technology/platform)*
 - *Can change the results for a patient specimen and potentially change the patient population selected in the trial.*
 - *A bridging study may help resolve the issues*
- A **bridging study** is needed to show equivalency between CTA and the intended CDx
 - Re-test patient specimens (include CTA positive and random subset of CTA negatives) with new/revised test
 - Determine effectiveness based on concordance between CTA and MRA to establish drug efficacy maintained



Issues – Clinical Trial Assays



- CTA typically not the final test intended for marketing
- Use of more than one CTA to enroll patients into the trial (e.g., local tests) or mid-trial changes to the device (e.g., cut-offs, etc.)
 - Can result in selection of different patient populations
- Use of CTA without adequate analytical validation
- Differences between CTA and MRA can lead to discordant results for a patient's specimen
- Pre-screening
- Sample ascertainment (i.e., missing samples)
- Stability of stored specimens
- Missing outcome data



Solution – Bridging Studies



- Statistical Plan should take into account discordance, missing samples and impact on drug efficacy.
- Retest population should be representative of the intended use population for the device – Beware of bias!
 - Assess available sample representativeness
 - Identify variables that have effects on the test result
 - Identify variables that can impact therapeutic outcomes
- **Plan to analyze worse case scenario for missing data with sensitivity analysis using range of hazard ratios in trials**
- Predictive claims: the device should demonstrate a differential therapeutic treatment effect on clinical outcome(s) (e.g., overall survival).

Other CDx Challenges

- Submission timelines
 - Need to account for time required to perform CDx analytical and clinical validation/bridging study
- Meeting other regulatory requirements for the CDx
 - Quality System Regulations (21 CFR 820)
 - IRB – analytical and clinical validation
- Understanding individual responsibilities
 - Co-development

Co-development Responsibilities

- Therapeutic product sponsors are responsible for assuring that a device will be brought forward for **contemporaneous review & approval**
- Device sponsors are responsible for Assay pre-market submission, performance, compliance with device regulations
- Therapeutic product and Device sponsors should carefully define expectations for each other
- Pre-market submissions review follows therapeutic review timeline



Useful Tips



- Establish biomarker testing strategy early
- Alert lead FDA center that therapy application includes a diagnostic device
- The pre-submission process is critical for new development programs/companion diagnostic programs
 - Schedule pre-sub meetings with CDRH as soon as test identified to discuss design of clinical studies, etc. Helpful if both diagnostic and pharmaceutical reps. present
 - Early interaction with Agency encouraged!

Useful Tools & Solutions



- **Modular PMA applications**
 - Allows for PMA to be reviewed as separate discrete sections (modules)
 - GMP/Manufacturing
 - Analytical / Non-clinical Validation
 - Instrumentation & Software
 - Clinical Validation

Premarket Approval Application Modular Review – <https://www.fda.gov/media/73513/download>
- **Medical Devices Standards Database**
 - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm>
- **Clinical Laboratory Standards Institute (CLSI) – <http://www.clsi.org>**
 - Develop global consensus standards and guidelines for healthcare testing (industry, government, professional)
 - Evaluation Protocols (EP) for study design/analysis
 - EP5-A3, EP6-A, EP7-A3, EP9-A2, EP12-A2, EP17-A2, EP21-A, EP37
- **ISO (International Standards Organization)**
 - Standards for estimating bias and imprecision of test methods



Challenge Question



The inclusion criteria for a Phase 3 study for a new drug in patients with prostate cancer who are known to be positive for BRCA1/BRCA2 mutations. Based on results from their Phase 2 study, a companion diagnostic will likely be needed to identify patients who will most likely benefit from treatment with the new drug. Therefore, the study investigators choose a BRCA1/BRCA2 CDx test for a different prostate cancer drug, as the study CTA to confirm the biomarker status after enrollment using the patients' most recent biopsy specimen. Which of the following are potential issues which may affect their study?

- a) Use of more than one CTA to enroll patients into the trial
- b) Sample ascertainment
- c) Use of CTA without adequate analytical validation
- d) Discordant results identified between the patient medical record and the CTA
- e) Pre-screening

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Useful Guidances



- In Vitro Diagnostic (IVD) Device Studies- Frequently Asked Questions:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf>
- 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>
- Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf>
- Significant Risk and Nonsignificant Risk Medical Device Studies:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf>
- Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices - Guidance for Industry and Food and Drug Administration Staff
<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM077295.pdf>
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