

Issues in Clinical Trial Design for Companion Diagnostic Devices

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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

Premarket Risk Based Regulation

- **Class I: common, low risk devices**
 - **e.g., mass spectrometer for clinical use**
 - *Most exempt from premarket submission*
 - *General controls*
- **Class II: more complex, moderate risk**
 - **e.g., prognosis, monitoring in already diagnosed cancer patients**
 - *Premarket Notification [510(k)]*
 - *General & Special controls*
- **Class III: most complex, high risk**
 - **e.g., cancer diagnosis or screening, most companion diagnostics**
 - *Premarket Application [PMA]*
 - ***Safety, effectiveness***

Basis of Premarket Device Review: Safety and Effectiveness



- **Safety**

- *Are there reasonable assurances, based on **valid scientific evidence** that probable benefits to health from use of the device outweigh any probable risks? [860.7(d)(1)]*

- **Effectiveness**

- *Is there reasonable assurance based on **valid scientific evidence** that the use of the device in the target population will provide clinically significant results? [860.7(e)(1)]*

FDA Review:

Basic Components of IVD Submission

- Intended use/indications for use
- Device description (platform, software)
- Pre-analytical performance
- Analytical performance
- Clinical performance
- Instrumentation, software validation (as applicable)
- Labeling (package insert)
- Manufacturing, BIMO



Drug/Device Codevelopment: 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?
- Will a bridging study be required?



Drug/Device Codevelopment: Key Regulatory Questions



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Investigational Device Exemption

**Guidance for Sponsors,
Investigators, and Institutional
Review Boards**

**Questions and Answers on
Informed Consent Elements,
21 CFR § 50.25(c)**

**Guidance for Industry and FDA
Staff**

**In Vitro Diagnostic (IVD) Device
Studies -Frequently Asked
Questions**

**Guidance for IRBs, Clinical
Investigators, and Sponsors**

**IRB Responsibilities for Reviewing
the Qualifications of Investigators,
Adequacy of Research Sites, and the
Determination of Whether an
IND/IDE is Needed**

**Information Sheet Guidance For
IRBs, Clinical Investigators, and
Sponsors**

**Significant Risk and Nonsignificant Risk
Medical Device Studies**

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

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)

Key Regulatory Questions: Is an IDE needed?



- **If a diagnostic is used to identify a biomarker in a drug trial**, then an Investigational Device Exemption (IDE) may be needed (if the diagnostic is not already FDA cleared or approved for the intended use).
- FDA approval of IDE application exempts device from premarket clearance/approval requirement when used in the investigational setting.
- IDE requirement is based on risk to patients – does the use of the test result pose a *significant risk* or a *non-significant risk*?
- Submit risk assessment pre-submission to CDRH to determine if an IDE is needed for your diagnostic.

DRAFT!

**Investigational In Vitro
Diagnostics in Oncology Trials:
Streamlined Submission Process
for Study Risk Determination
Guidance for Industry**

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Assessing Risk

1. Will use of the investigational test results lead to some trial subjects foregoing or delaying a treatment that is known to be effective?
2. 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?
3. 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?
4. Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?

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



Drug/Device Codevelopment: Key Regulatory Questions



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Key Regulatory Questions: 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 companion diagnostic 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.
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>

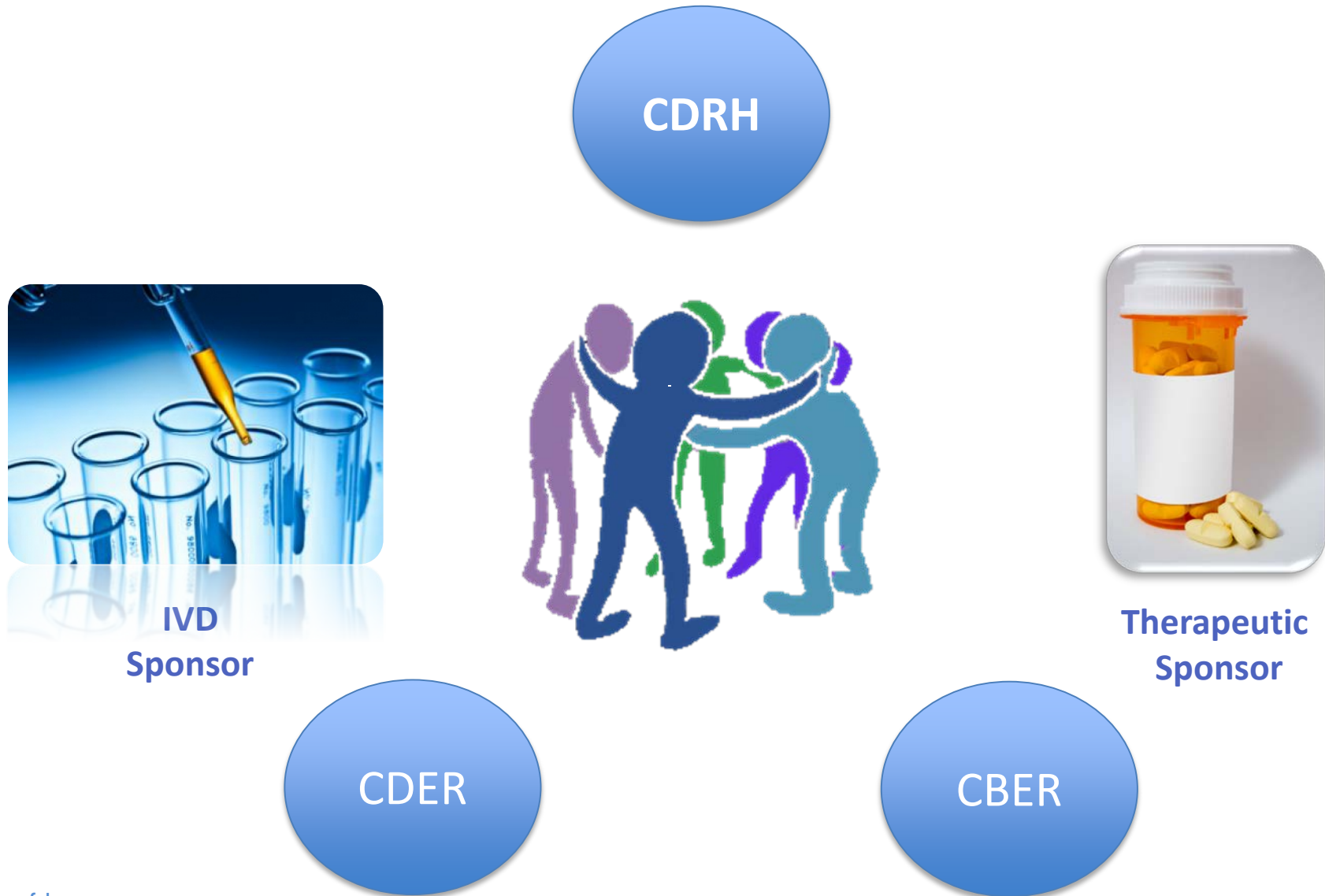


Companion Diagnostics



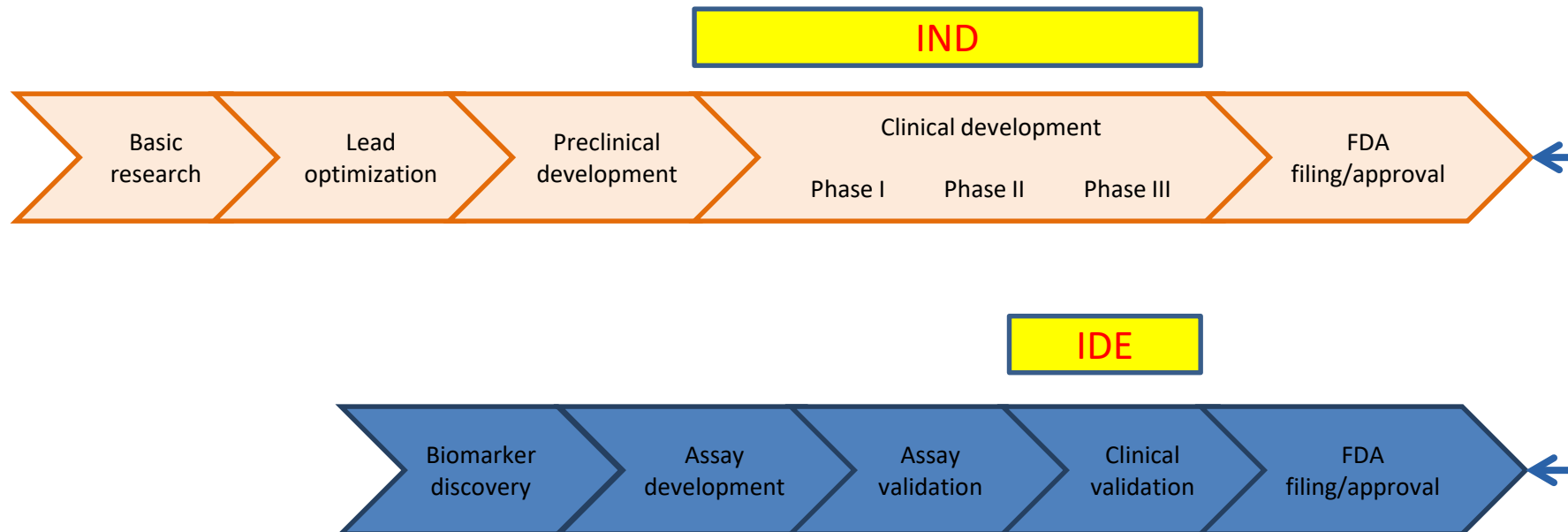
- Tests required to determine whether a specific drug should or should not be administered to a patient
- Test used for patient selection into therapeutic trial
- Clinical validation of test comes from a successful drug trial
- Problems can arise when the final test intended for marketing is not the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

Codevelopment: Therapeutic + IVD



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



*Contains Nonbinding Recommendations
Draft - Not for Implementation*

DRAFT!

1 **Principles for Codevelopment of an**
2 **In Vitro Companion Diagnostic**
3 **Device with a Therapeutic Product**

4
5
6 **Draft Guidance for Industry and**
7 **Food and Drug Administration Staff**

8
9 ***DRAFT GUIDANCE***

10 **This guidance document is being distributed for comment purposes only.**

11 **Document issued on: July 15, 2016**

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<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm510824.pdf>

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



Drug/Device Codevelopment: 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?
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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

Components of the Intended Use

What assay measures, how to use results



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 ≤ 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 Intended Use claims;
Less dependent on the technology or assay format

Scientific Review : IVD Performance

- **Analytical** Performance Characteristics
 - Reliability and accuracy of analyte measurements
 - Studies specific to the assay technology such as accuracy for molecular assays, inter-reader agreement for IHC assays, etc.
- **Clinical** Performance Characteristics
 - Clinical sensitivity and specificity
 - Positive and negative predictive values
- **Labeling**
 - Intended use, device design, directions for use, warnings/limitations, result interpretation, performance

Analytical Performance

- For tests that detect multiple possible genetic changes, e.g., multiple mutations within a gene, should be analytically validated for each change to be detected
- Establishing analytical validity creates unique challenges for new and emerging technologies, i.e. next-generation sequencing (NGS)
 - Multiplex assays often require complex validation
 - Representative approach for gene sequencing tests
- When performing analytical validation, consideration should be made of the ultimate specimen source to be used once drug is on the market, e.g., FFPE tissue, blood, CSF, etc.

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)

- 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
 - 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

Drug/Device Codevelopment: Key Regulatory Questions



- Will an IDE be required?
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Key Regulatory Questions:

Will I need to perform a bridging study?

- **Is the clinical trial assay (CTA) the same device as the market ready assay (MRA) that is the subject of a PMA application?**
 - *Various issues may arise due to the clinical trial study design and enrollment procedures*
 - *A bridging study may help resolve the issues*
- A **bridging study** is needed to show equivalency between CTA and the intended MRA (i.e., CDx)
 - Re-test patient specimens (include CTA positive and negative) with new/revised test to support safety and efficacy of the therapeutic product
 - 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
- Mid-trial changes to device such as change in cut-offs, etc.
- 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).

Challenge Question 1

In a clinical study, the efficacy of an investigational therapeutic is based on a specific biomarker which was used to enroll patients into the study. A companion diagnostic would be required if...

- A. The study meets its clinical endpoint.
- B. Detection of the biomarker in patients is necessary to identify patients for treatment.
- C. Only a specific technology can identify the biomarker.
- D. Only if the biomarker was used to enroll patients into the study.

Challenge Question 1

In a clinical study, the efficacy of an investigational therapeutic is based on a specific biomarker which was used to enroll patients into the study. A companion diagnostic would be required only if...

- A. The study meets its clinical endpoint.
- B. Detection of the biomarker in patients is necessary to identify patients for treatment.**
- C. A specific technology can identify the biomarker.
- D. The biomarker was used to enroll patients into the study.

Challenge Question 2



A clinical study investigating the efficacy of a drug which has been approved in gastric cancer in patients with Stage IV colon cancer who have progressed on standard first line therapy. Patients, who have been randomized 1:1 between the investigative arm and the control arm, are tested with the investigational drug's CDx to determine the presence of a biomarker suspected to be associated with a resistance to the investigational drug which the CDx also detects.

Based on this information, would an approved IDE be required?

Challenge Question 2



A clinical study investigating the efficacy of a drug which has been **approved in gastric cancer** in patients with Stage IV colon cancer who have progressed on standard first line therapy. Patients, who have been randomized 1:1 between the investigative arm and the control arm, **are tested with the investigational drug's CDx** to determine the presence of a biomarker suspected to be associated with a resistance to the investigational drug which the CDx also detects.

Based on this information, would an approved IDE be required?

Answer: Yes

Challenge Question 3



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

Challenge Question 3



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- c) Use of CTA without adequate analytical validation
- d) Discordant results identified between the patient medical record and the CTA
- e) Pre-screening

Presentation Overview

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



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

- Medical Devices Standards Database
 - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm>

- Clinical Laboratory Standards Institute (CLSI)
 - Develop global consensus standards and guidelines for healthcare testing (industry, government, professional)
 - Evaluation Protocols (EP) for study design/analysis
 - EP5-A2, EP6-A, EP9-A2, EP12-A2, EP17-A, EP21-A
 - www.clsi.org

- ISO (International Standards Organization)
 - Standards for estimating bias and imprecision of test methods



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>
- Find other guidances at
<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>

FDA Approved Companion Diagnostics

www.fda.gov/companiondiagnostics



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Products and Medical Procedures

- In Vitro Diagnostics**
- Proposed Pilot Triage Program
- Drugs of Abuse Tests
- Blood Glucose Monitoring Devices
- Home Use Tests
- Lab Tests

Companion Diagnostic Devices: In vitro and Imaging Tools

A *companion diagnostic device* can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

	Drug Trade Name (Generic Name)	Device Trade Name	PMA	Device Manufacturer	Intended Use (IU)/ Indications for Use (IFU)
1	Erbix (cetuximab)	therascreen KRAS RGQ PCR Kit	P110030	Qiagen Manchester, Ltd.	The <i>therascreen</i> KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human KRAS oncogene, using DNA extracted from formalin fixed paraffin-embedded (FFPE) colorectal cancer (CRC) tissue. The <i>therascreen</i> KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbix (cetuximab) based on a KRAS no mutation detected test result.
2	Erbix (cetuximab); Vectibix (panitumumab)	DAKO EGFR PharmDx Kit	P030044 S001-S002	Dako North America, Inc.	The EGFR pharmDx™ assay is a qualitative immunohistochemical (IHC) kit system to identify epidermal growth factor receptor (EGFR) expression in normal and neoplastic tissues routinely-fixed for histological evaluation EGFR pharmDx specifically detects the EGFR (HER1) protein in EGFR-expressing cells. EGFR pharmDx is indicated as an aid in identifying colorectal cancer patients eligible for treatment with Erbix (cetuximab) or Vectibix (panitumumab).



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