U.S. FOOD & DRUG ADMINISTRATION

Planning for Co-development of Companion Diagnostics

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SBIA: Pivotal Steps and Avoiding Pitfalls for Start-ups – March 31, 2021

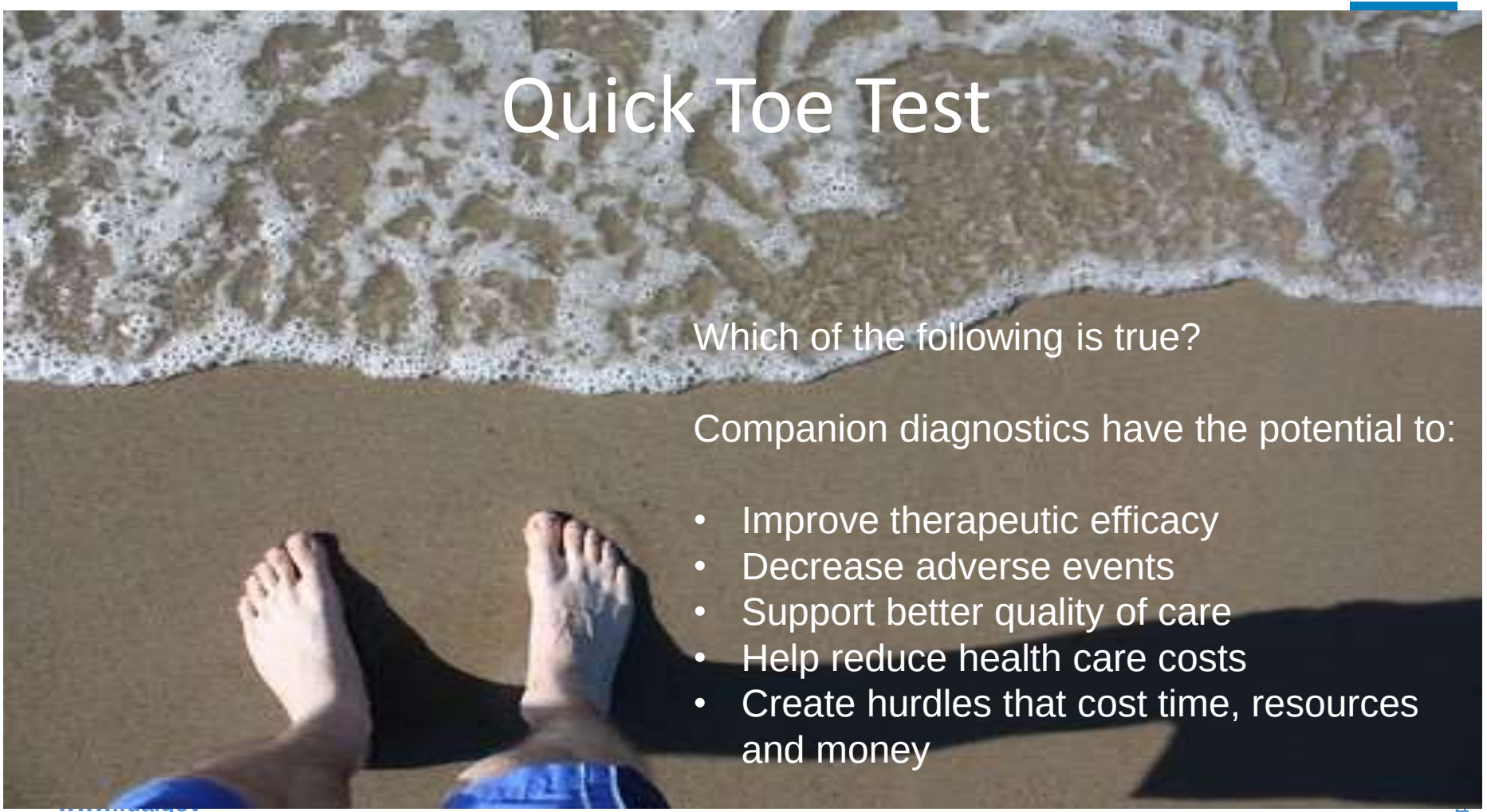
Overview

- Points to consider when using a diagnostic in a trial
- Planning for successful companion diagnostic
- Regulatory processes

Why do I need a companion diagnostic (CDx)?

- In Vitro Diagnostic (IVD) [21 CFR 809.3] Risk-based regulation – what are the risks if the test result is wrong
- CDx are essential for the safety and/or efficacy of the therapeutic.
- Patient population must be identifiable after approval
- Comply with regulations when used to support drug approval
  - Performance is critical
  - Drug label – refers to an FDA approved test

Quick Toe Test



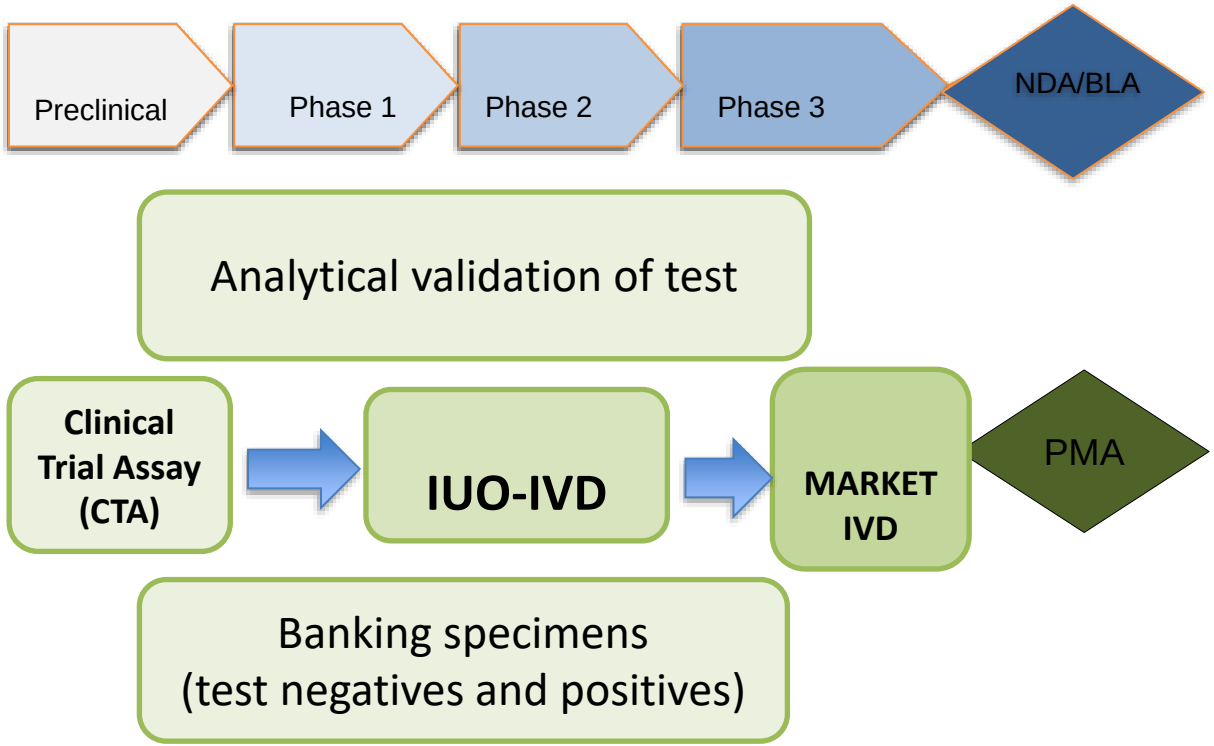
Which of the following is true?

Companion diagnostics have the potential to:

- Improve therapeutic efficacy
- Decrease adverse events
- Support better quality of care
- Help reduce health care costs
- Create hurdles that cost time, resources and money

Co-development – Idealized scenario

PLAN EARLY!

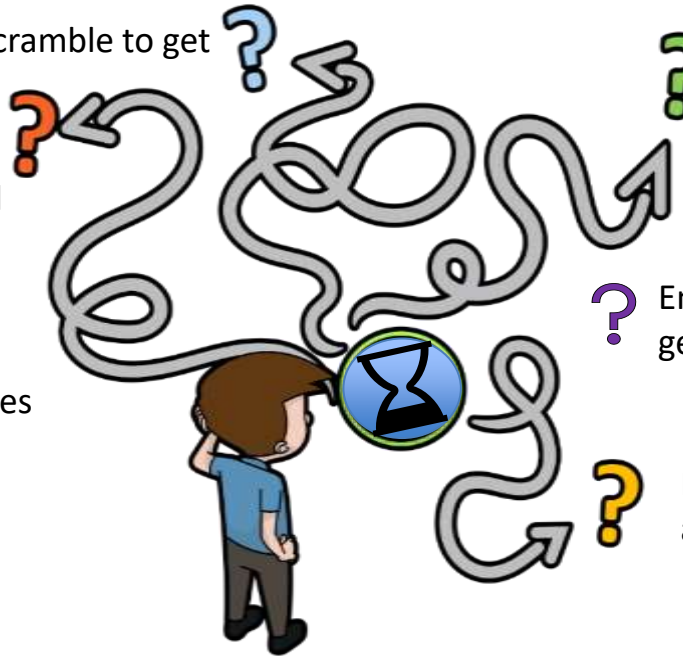


More realistic scenario:
Need to bridge a CDx to clinical trial assay(s)

Early phase data
used to support the Rx - Scramble to get specimens

Variety of LDTs used to enroll patients; Absence of screen negatives

Mid-trial test changes



Post-hoc, retrospective analyses points to a better cut-off or safety concerns

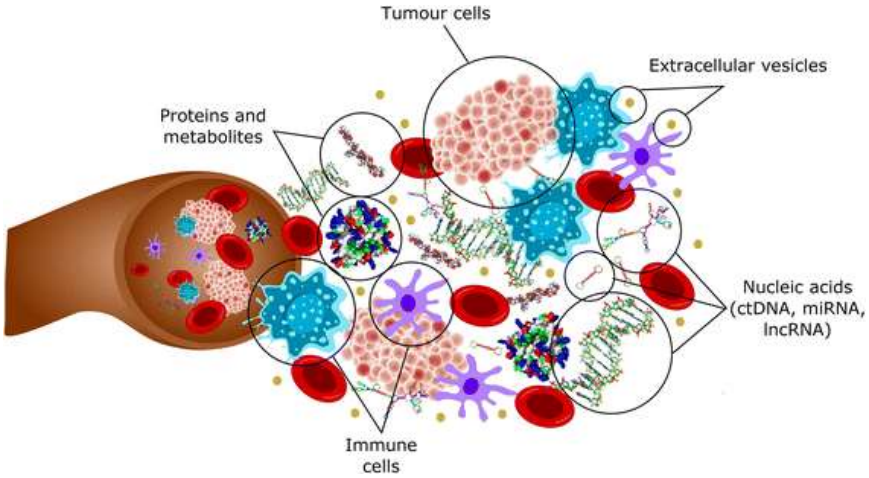
Enrollment lead to variety of unexpected genetic variants

Dx brought in late – inability to meet anticipated timelines

Where to Start -Define the Biomarker

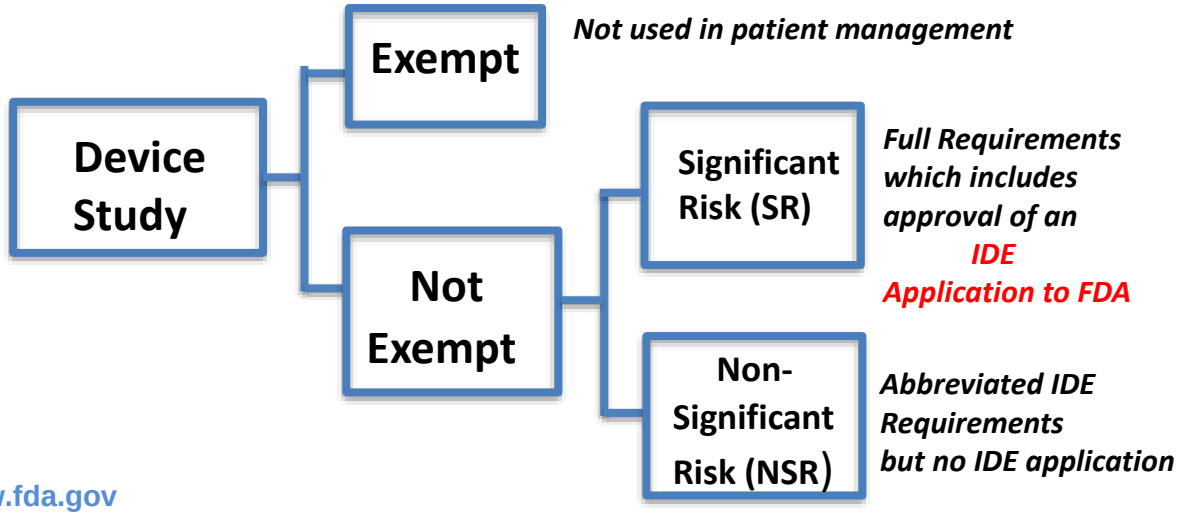
Biomarker definition and test parameters determine eligibility and success of the trial

- ✓ Define the analyte
- ✓ Select the specimen
- ✓ Select the technology
- ✓ Select the Cut-off/Clinical decision



Do I need an Investigational Device exemption (IDE)?

- IDE enables use of an investigational test
- Tests used to select patients for investigational Rx are investigational
- Irrespective of phase or number of patients
- IDE requirements are also based on risks to patients.



How do I determine if I have an SR investigational device?

- IRB can make this decision (FDA can determine otherwise)
- Submit a Study Risk Determination Risk request to CDRH, or in the IND
- Describe why you believe the test is NSR based on 4 criteria
  1. Are patients foregoing effective treatments
  2. A priori information about safety or efficacy in the biomarker subset
  3. Are patients exposed to adverse events
  4. Significant risk procedures for obtaining the specimen

Submitting an IDE Application to FDA

If SR –

- **use a single clinical trial assay,** but if that is not possible,
- consider a central reference lab to **confirm the results of the specimens** sent forward by the other local testing sites.

IDEs are reviewed for safety –

- Demonstrate device reliability around the cut-off
- Informed consent should indicate that the test is investigational for this purpose and the risks

Example Case

- First in human trial to explore drug benefit in patients whose tumor tissues express elevated levels of a protein biomarker.
- Immunohistochemistry test; scoring based on intensity 0, 1+, 2+ and 3+
- Two-arm trial; 0+/1+ vs 2+/3+
- Archived specimens will be tested
- Second line indication (there are other therapeutic options)

- All-comer study = Non-significant risk

Multiple Clinical Trial Assays –Sources of bias

- Not a novel biomarker (labs already adopted their own testing)
- Multiple tests used - discordance between tests
- Prescreening
- Missing outcome date in CTA negative population

General Population

….Select the green apples

Bridging Study Basics

Test used in drug trial not the version intended for marketing:

- Retest all screen positive – have a plan to obtain negatives
- Concordance at cut-off critical
- Assess agreement between CTA and CDx
- Account for discordance, missing samples and impact on drug efficacy
- Retest population should be representative of the target population.

Clinical Trial Assay	IVD-CDx	Availability
CTA neg	IVD neg	Not needed
CTA neg	IVD pos	Missing Outcome
CTA pos	IVD neg	✓ Available
CTA pos	IVD pos	✓ Available

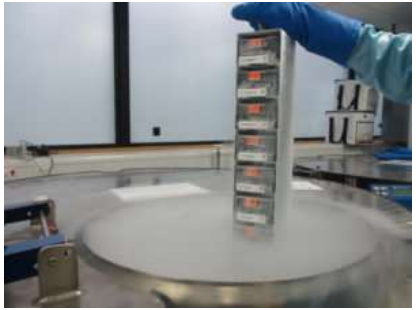
What if re-analysis using market test results provides different conclusions?

Degree of discordance will be a review issue

The prevalence of the biomarker is extremely low… What if I have multiple Clinical Trial Assay(s)?

- Short of having a single clinical trial assay or distributed reagents:
  - Include a central testing lab as a designated screening site (this will enable a large proportion of the testing at a single site and provide some test negatives)
  - Attempt to use sites that use the same technology
  - Qualify the labs meet a threshold of performance
  - Collect information about local testing method (technology/reagents, cut-off, test LoD, prevalence of the biomarker(s) in that lab
- Attempt to obtain * test negatives from the labs
- *Pre-plan the number of negatives needed for a bridging study

Develop a Specimen Acquisition Plan



- Bank specimens from patients evaluated for enrollment (test negative and test positive)
  - Request sufficient specimen from investigational sites for additional tests
  - Have a plan to obtain representative negatives
- Consider obtaining paired specimens liquid biopsy/tumor or blood/bone marrow
- Consider impact of storing specimens
- Single uniform method is employed for specimen handling, including preanalytical steps
- Consider pre-planning specimen stability studies
- Consider policies in foreign countries
- Appropriate informed consents for test validation
- Collect adequate annotation (tumor characteristics, patient characteristics, testing)

Companion Diagnostic – Clinical Validation

- Assay should be fully specified /locked down assay

- Plan to ensure instruments, software, and reagents will be legally marketed (i.e., not RUO)
- Collection devices and preanalytical reagents need to be legally marketed

For CoDx, the clinical validity is supported by the drug trial.

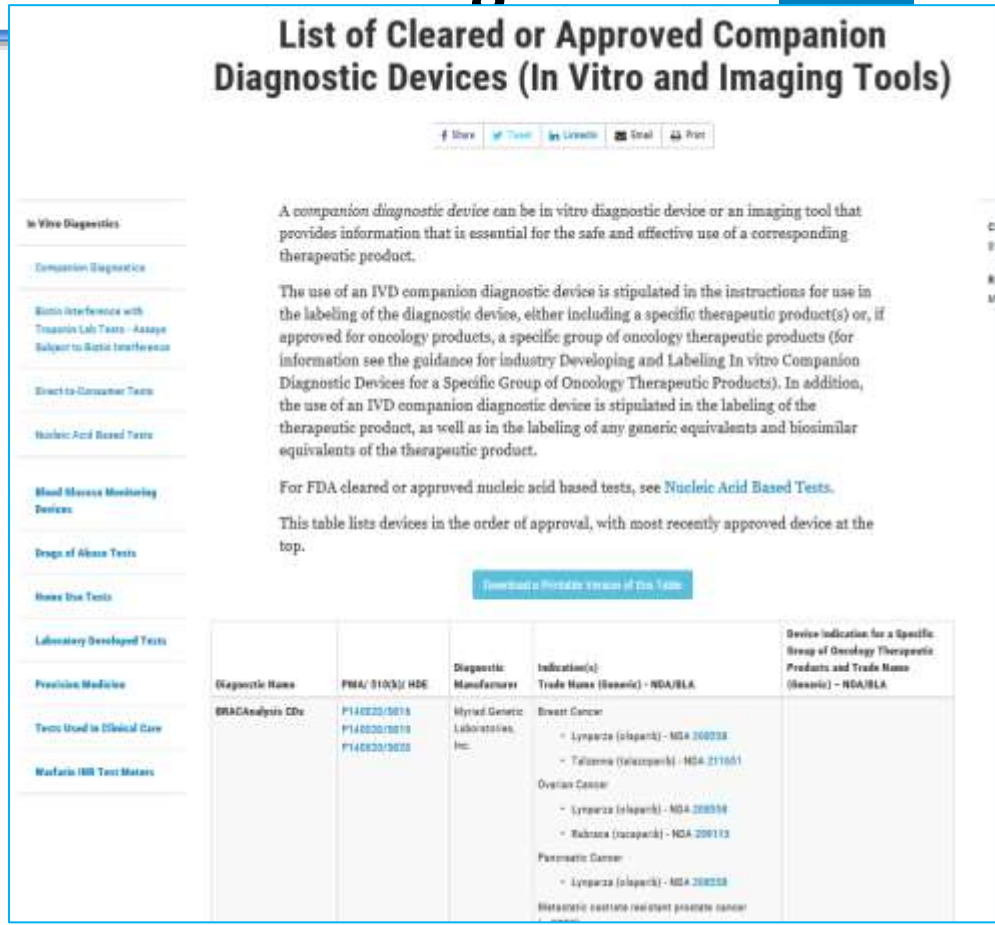
- Avoid turning your validation set into your training set
  - If you optimize your CDx based on results of your pivotal trial, you have turned that specimen set into a “training set” which can no longer be considered the “clinical validation set”

Complementary Diagnostics

- Identifies populations for which use of a therapeutic product has different benefit-risk profiles (definition under development)
- Test is not essential for safe and effective use of the therapeutic product but are in the Drug labeling
- Changes from CDx to CompDx during review and vice versa
- Development path similar to CDx
- Centers are working on a guidance document

Novel CDx Requiring Unique Review Strategies

- Tumor agnostic biomarkers
  - (pan tumor indications)
  - MSI/dMMR
  - TMB
  - NTRK
- Structural rearrangements and novel variants
  - (rules for interpretation)
- Liquid Biopsy
  - (Paired with resected specimens when possible)
- PD-L1 Immunohistochemistry/TMB
  - Harmonization efforts



List of Cleared or Approved 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 is stipulated in the instructions for use in the labeling of the diagnostic device, either including a specific therapeutic product(s) or, if approved for oncology products, a specific group of oncology therapeutic products (for information see the guidance for industry Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products). In addition, the use of an IVD companion diagnostic device is stipulated in the labeling of the therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

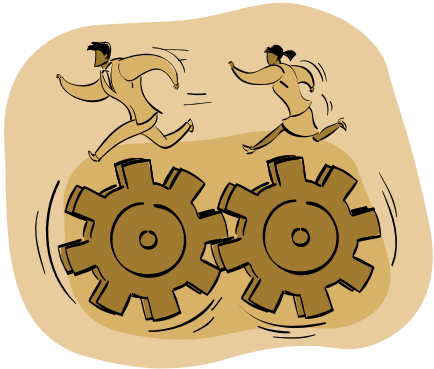
For FDA cleared or approved nucleic acid based tests, see Nucleic Acid Based Tests.

This table lists devices in the order of approval, with most recently approved device at the top.

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Indication(s) Trade Name (Generic) - NDA/BLA	Device Indication for a Specific Group of Oncology Therapeutic Products and Trade Name (Generic) – NDA/BLA
BRACAnalysis CDx	P140020/S015 P140020/S019 P140020/S020	Myriad Genetic Laboratories, Inc.	Breast Cancer - Lynparza (olaparib) - NDA 208558 - Talzenna (talazoparib) - NDA 211651 Ovarian Cancer - Lynparza (olaparib) - NDA 208558 - Rubraca (rucaparib) - NDA 209115 Pancreatic Cancer - Lynparza (olaparib) - NDA 208558 Metastatic castrate-resistant prostate cancer	

Submission Planning: Aligning Reviews

- Laboratory developed test (single site) vs Distributed kit
- Co-ordinate timing: Use the Modular PMA Process
- Consider Humanitarian Device Exemption (HDE)
  - Rare disease
  - Under 8000 tests per year
- Plan to allow time for manufacturing and BIMO inspections
- Plan for letters of cross-reference
- Master Device Files – useful when Rx wants to keep data confidential



Pre-submission Meetings

- Sponsors can meet with the FDA for nonbinding discussions and advice:
  - *before* conducting studies on protocols, statistical analysis plans
  - opportunity to address scientific and regulatory issues.
- *Can obtain a formal risk determination during risk determination Q-submissions*
- Guidance on the pre-submission process http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf
- General Content: Device description, Intended Use statement and specific questions with background supporting information

Breakthrough Devices

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program

- Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.
- More frequent and faster interactions
- Prioritized review of submissions
- Possible reimbursement advantages?

Summary

- Identify your biomarker and technology
- Define your clinical trial assay test strategy
- Ensure adequate specimen collection for validation studies
- Coordinate submission timing

If you do just one thing…

Engage CDRH Early.

Resources – Companion Diagnostics

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools
https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Draft Guidance on Principles of Codevelopment of Companion Diagnostic Devices with therapeutic product.
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM510824.pdf

Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
https://www.fda.gov/media/71147/download

Meijuan Li. **Statistical consideration and challenges in bridging study of personalized medicine.**
Jour of Biopharm Stat 2015; 25(3):1–11

Resources - IDEs

FDA Decisions for Investigational Device Exemption Clinical Investigations (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf), Food and Drug Administration, August 2014.

Study Risk Determinations: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (https://www.fda.gov/media/114034/download) Food and Drug Administration, January 6, 2021

Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-vitro-diagnostics-oncology-trials-streamlined-submission-process-study-risk)
Food and Drug Administration, October 2019

In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf), Food and Drug Administration, June 2010.

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), Food and Drug Administration, August 2013.

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), Food and Drug Administration, April 2006.

And More Resources…

- **Parallel Review Program & Payor Communication Task Force** https://www.fda.gov/about-fda/cdrh-innovation/payor-communication-task-force
- **Investigational Devices** https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm
- **Medical Device Databases** http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm
- **Device Advice** http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm
- **CDRH Learn** http://www.fda.gov/Training/CDRHLearn/default.htm

Thank you!

Questions?

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