Companion Diagnostics Update and Co-Development

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Jennifer Shen, Ph.D., RAC
Food and Drug Administration (FDA)
Center for Devices and Radiological Health (CDRH)
Office of In Vitro Diagnostics and Radiological Health (OIR)

Overview

- **Companion Diagnostic (CDx) Test Performance Evaluation (analytical and clinical)**
- **Review Issues and Challenges in CDx**
- **What Does It Take To Create A Good Submission**

FDA Review for CDx

- **Intended Use / Indications for Use**
- **Device Description (platform, software)**
- **Pre-analytical**
- **Analytical Performance**
- **Clinical Performance**
- **Instrumentation, Software validation (as applicable)**
- **Labeling (package insert)**

Molecular Test – Analyte Source

Specimens Types

- Whole blood
- Plasma
- Buccal swab
- Tumor Tissue
- Urine

Unique Challenges for Each Specimen Types

- Stability
- Sources of interference
- Intra-biological variability

Test Performance Evaluation

Analytical Performance

- Does my test measure the analyte I think it does? Correctly? How reliably?

Clinical Performance

- Does my test result correlate with target condition of interest in a clinically significant way?

Analytical Performance: Goals

- **Test = Specimen ⟶ Result (validate all steps)**
- **Pre-analytic steps are part of assay**
  - e.g., DNA/RNA extraction, bisulfite modification
- **Validation with each specimen type**
- **All studies should follow protocol in labeling**
- **Studies should demonstrate robustness at clinical cut-off, as needed**

Clinical Performance: Goals

- **Determine how the device will be used in clinical setting and ensure study design is appropriate**
- **Study design should support the Intended Use**
- **Consider possible confounding co-variables**
- **Pre-specified clinical and statistical analysis plan**
- **Establish clinical performance of device compared to an endpoint or appropriate surrogate**
- **Analytical validation precedes clinical validation**

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CDx Test Performance*	Issues and Challenges
Accuracy	
Precision: Repeatability, Reproducibility	
Sample Preparation: Pre-analytical	
Performance Around the Cut-off	
Stability	
Clinical	

*not a comprehensive list

CDx Test Performance*	Issues and Challenges
Accuracy	No comparators No **specimens** for rare alleles
Precision: Repeatability, Reproducibility	Not enough **specimens**
Sample Preparation: Pre-analytical	Lots of variability
Performance Around the Cut-off	Difficult to get **specimens**
Stability	**Specimens** may lack stability
Clinical	**Clinical Trial Assay (CTA)** Extremely low prevalence

*not a comprehensive list

CDx Challenges - Specimens

Each claimed specimen requires analytical validation

- Tissue type (e.g., blood, bone marrow, tumor, urine)
- Tissue collection (e.g., tissue block, fine needle aspiration, special collection devices)
- Tissue collection reagents (frozen vs. FFPE; anticoagulants; preservatives)

Inability to re-test specimens

- Informed consent issues
- Poor quality samples, insufficient samples, missing samples

Solutions - Specimens

Select one specimen type

- Specify the specimen type in the trial
- Specify the processing steps as well as volume, cell/tumor proportion, 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
- Collection devices needed to be labeled for IVD use, or bring them in with the PMA submission

Solutions - Specimens

Bank samples from all patients evaluated for trial enrollment

- Test negative and test positive
- Obtain adequate sample volumes for retesting
- Consider policies in foreign countries
- Ensure Informed consent documents cover the testing
- Consider impact of storage on analytes
- Plan ahead to conduct stability testing of the samples by comparing different time points to baseline results

CDx Challenges - Clinical Trial Assays (CTA)

- CTA is not the final CDx intended for marketing
- Multiple tests used in registrational trial
- Pre-screening at local testing sites
- Mid-trial changes
- Missing outcome in CTA negative population

Clinical Trial	CTA	CDx	
Not Enrolled	Negative	Negative	
	Negative	Positive	→ **Missing outcome**
Enrolled	Positive	Negative	
	Positive	Positive	

Solution - Bridging Studies

- Statistical Plan that takes into account discordance, missing samples and impact on drug efficacy
- Re-test population should be representative of the intended use population for the device
- Re-analysis of the trial for effectiveness of device is potentially biased if subset not representative

Solution - Bridging Studies

- Plan to analyze worse case scenario for missing data with sensitivity analysis

- Plan to assess available sample representativeness and incorporate into an analysis plan
  - ✓ Identify variables that have effects on the test result
  - ✓ Identify variables that can impact therapeutic outcomes

- Predictive claims: the device should demonstrate a differential therapeutic treatment effect on clinical outcome(s) (e.g., overall survival)

Other Approaches to CDx Challenges

- Intended Use that limit risks
- Use of cell lines to supplement analytical studies
- Allow composite comparators for accuracy
- Unique statistical approaches
- Limitations in labeling / package insert

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Strategy For A Good Submission

- **Guidance Documents**
- **FDA CDx and PMA Databases**
- **The Pre-submission Program**

- Excellent Organization
- Defensible Intended Uses
- Thorough Explanations of the Technology
- Adequate Description of the Studies
- Completeness of the Validation Studies

Guidance Documents

In Vitro Companion Diagnostic Devices
http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm

Design Considerations for Pivotal Clinical Investigations for Medical Devices
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm

Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm

OIR Guidance
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm

FDA CDx & PMA Databases

Summaries of Validation Studies for FDA Approved CDx Devices are Publicly Available

- **CDx and Drug Co-approvals**
  http://www.fda.gov/CompanionDiagnostics

- **PMA Summary of Safety and Effectiveness (SSED) and Labeling (Package Insert)**
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

The Pre-Submission Program

Provides free feedback on your submission protocols and clinical study

- A mechanism to obtain FDA feedback on future submissions, e.g., 510(k), PMA, HDE, IDE
- A formal written request from a sponsor for FDA feedback
- An opportunity to ask questions and conduct discussions prior to pre-market submissions
  - Regulatory pathway
  - Clinical or analytical study protocol review

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Sponsors Deserve Recognition

- Excellent Organization
- Fast and Timely Responses
- Willingness to Explore New Statistical Strategies
- Open Dialogue on Assay Performance
- Interactive Labeling Discussions
- Patience

Thank you!

Questions?
Jennifer.Shen@fda.hhs.gov

Feel Free to Contact Us

Office of In Vitro Diagnostics and Radiological Health (OIR)

- **Division of Immunology and Hematology (DIHD)**
- **Division of Microbiology (DMD)**
- **Division of Chemistry and Toxicology Devices (DCTD)**
- **Division of Radiological Health and Mammography Quality Standards**
- **Personalized Medicine Staff**
- **http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhoffices/ucm115904.htm**