Companion Diagnostics
Points to Consider

FDA Medical Device Technology Innovation Partnerships
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Why are Companion Diagnostics Regulated?

• Drug usage depends on the biomarker/test results (if the test doesn’t work, the drug could be improperly administered)

• CoDx considered significant risk devices (Class III/PMA)
  – Used to make treatment decisions
  – Carry the same risk profile as the drug

• Co-development is a device and drug/biologic collaboration
  – Cross-labeling
  – concurrent FDA approval
What does FDA consider a Companion Diagnostic?

When therapeutic decisions are made or optimized on the basis of a test result.

--Or when the pivotal trial selected based on a test.

Examples include:

• Specific drug target (e.g., target molecules)
• Unique markers related to drug response or dosing
• Distinct populations have adverse events (e.g., HLA haplotypes)
Planning a CoDx: Example
cobas® 4800 BRAF V600 Mutation Test

Drug and Device FDA approved August 12, 2011

Device: Roche Molecular Systems, Inc.
Real-time PCR technology
Detects and amplifies wild type and mutant BRAF gene results in valine to glutamate at codon 600(V600E)

Drug: Hoffmann LaRoche Vemurafenib (Zelboraf)
Kinase inhibitor
A single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
cobas® 4800 BRAF V600 Mutation Test

Identify the Target Population

• The cobas® 4800 BRAF V600 Mutation Test is an in vitro diagnostic device intended for the qualitative detection of BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue.

• The cobas® 4800 BRAF V600 Mutation Test is a real-time PCR test on the cobas 4800 system, and is intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib.
Analytically Validate Your Assay Prior to Using in Trial

- Assay selects target population enrolled in the trial
- Safety and Efficacy of drug are determined in this population
- Recognize the analytical performance of the test determines who is selected and is not selected
- Drug is not evaluated in individuals excluded by test
- Must be able to demonstrate the same population can be identified after drug approval
- May impact drug claims
cobas® 4800 BRAF V600 Mutation Test

- Pre-analytic steps are part of assay
  - e.g., DNA extraction, melanin extraction, bisulfite modification, etc.
- Validation with each specimen type
- All steps should follow specific protocol (future labeling)
- Studies should demonstrate robustness at clinical cut-off, as needed
- Clinical samples from target population
cobas® 4800 BRAF V600 Mutation Test

Analytical Variables (Summary available on Web)

- Melanin Interference/melanin extraction
  - Used one method, validated method, validated dilution step for invalids that might be caused by high melanin.
- Analytical sensitivity – Cut-off for “test-positives”
  - Limit of Detection (% mutation detected in background of WT)
  - Minimum and maximum input DNA (recommend 125ng/25 μL)
  - Limit of Blank (demonstrates no false positives)
  - Minimum Tumor content (Recommendation to macrodissect at 50% tumor improves test performance)
- Accuracy /correlation to reference method
- Cross Reactivity (other V600 mutations)
  - Cross reacts with V600K and V600R
- Precision (repeatability and reproducibility)
Planning a CoDx Cont’d,

Clinical Validation

- With companion diagnostics, the clinical validity is supported by the drug trial.
- Training Set should be distinct from validation sample set
- Analytical validation precedes clinical validation
- Clinical decision points should be finalized prior to use in pivotal trial
- The test is typically validated in the phase III study
- May need representation of test negative and test positive in trial in the test for predictive claim: Randomization is stratified by marker
  - “Predictive” claims for companion diagnostics rely on understanding the effect of the drug in both biomarker positive and biomarker negative patients.
  - Targeted Design Enroll a subgroup defined by marker; Test is not studied for effectiveness. Test claim limited to ‘selection’.
POTENTIAL PITFALL: Design Changes

KEY ISSUE: When CoDx used to identify a distinct group of patients, the pharma sponsor needs to ensure that the same patient population can be identified after drug approval.

Changes to test can change enrollment patterns
• Changing the cut-off, measuring range or any test parameter that could change the results for a patient sample, potentially changes who is enrolled.

What if:
• The relationship between drug efficacy and marker not well known.
• There is a correlation with other markers
• There is a dose-response relationship with the marker

Mid- and Post-trial test changes are problematic
Need to consider how post-trial discordance will be handled
Bridging Studies:

Test used in drug trials not the marketed version

- More than a method comparison
- Statistical Plan that takes into account discordance, missing samples and impact on drug efficacy.
- Retest 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.

Sponsor should 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
Bridging Studies:

- Need well annotated records for bridging studies (e.g., demographics, previous treatments and factors that affect the test such as %tumor content)
- Need to control for bias due to lost samples
- Need both screen negative and screen positive
- Ensure storage conditions don’t impact assay
- Need plan for sample acquisition, storage, and access for re-test analyses (SAVE both screen negative and screen positive)
- What if re-analysis using market test results provides different conclusions? Degree of discordance will be a review issue
- Will need to provide evidence of analytical performance between old and new test.
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Clinical Trial:

- Enrolled Test positives
- Used analytically validated final test in the trial
- Formalized melanin extraction method
- Employed macrodissection (avoided RUO devices)
- Narrowed specimen type
- Addressed prescreening
- Enrolled V600K due to cross-reactivity

Successes in Process:

- Engaged FDA (both CDRH and CDER) early and often
- Submitted modular Device application ahead of Drug application
Most Common Pitfalls, con’td

- Instability of analytes
- Lack of reproducibility
- Minor changes not minor
- May involve more than one test
- Lack of reproducibility
- Use of RUO instruments and reagents
- Pre-screening by enrollment sites (check prevalence at testing sites)
  - May eliminate difficult cases, Inflates test performance, Drug study may not get test borderlines
CoDx Dilemmas:

• Multiple tests used to accrue patients to trial
  – substantial variation between tests
  – the clinical impact of false negative results are not known
- uncertainty about performance of original testing and selection methods (e.g., alleles, cut-offs).

• Adding new analytes (e.g., mutations) to test/Expanding claimed mutations to test
  ➢ not enrolled in clinical trial

• Practice of medicine ahead of clinical validated tests;
  continuous discoveries and changes to treatment regimens
Summary

• **Plan to ensure** market tests will select same patients as in the trial following drug approval (Drug efficacy is tied to performance of the test.)

• **Plan early.** Timing is critical in the co-approval process

• **Avoid changes to test prior to validation.**

• **Have a sample aquisition plan.** Consider a test may be needed – Store clinical trial samples and get informed consent (sufficient patient sample should be collected and appropriately stored; this is critical when beginning phase III trial without the test intended for market)
Companion Diagnostics

Modular PMA review process: analytical, manufacturing, and clinical performance submitted in modules - useful for companion diagnostics.

– Guidance document “Premarket Approval Application Modular Review”
Companion Diagnostic
Regulatory Oversight During Trial:

- CDER /CBER identify CoDx – will request CDRH consults for device aspect
- Options for regulatory oversight during test validation:
  - Submit an IDE for the device
  - Submit the device information in the IND
- Very important to consider timing:
  - Don’t want IND to be held up by outstanding device issues
  - Will you be seeking accelerated approval?
  - Co-Approval timelines on track?
- Obtain CDRH feedback using the pre-IDE process early on
  (Non-binding, confidential, interactive and flexible process for obtaining CDRH feedback about protocols)
Regulatory Oversight cont’d:

Pre-IDE
- Non-binding, confidential, interactive and flexible process for obtaining CDRH feedback about protocols

IDE (Investigational Device Exemption)
- Significant risk / patient management
- Tests are labeled Investigational Use Only (IUO)
- Permits use to collect data to support submission
- Demonstrates device safety, reliability around the cut-off

Best to submit in advance of the therapeutic submission.
Allow adequate time to ensure device review criteria are met.