Regulatory Perspective for Companion Diagnostics

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Food and Drug Administration (FDA)
Center for Devices and Radiological Health (CDRH)
Office of In Vitro Diagnostics and Radiological Health (OIR)
### Division of Immunology and Hematology Devices (DIHD)
- Hematology and coagulation tests
- Tests for immunological disease
- Flow cytometry

### Division of Chemistry and Toxicology Devices (DCTD)
- General and specialized chemistry tests (i.e., neonatal biochemical screening tests, endocrine tests, and tests for women's health)
- Drug of abuse tests
- Therapeutic drug monitoring tests

### Division of Microbiology Devices (DMD)
- Detection of microorganisms (bacteria, fungi, mycobacteria, viruses) by chemical, immunological, and nucleic acid amplification methods
- Biothreat agents
- New and emerging infectious diseases

### Division of Molecular Genetics and Pathology (DMGP)
- Oncology companion diagnostic tests
- Genetic disorder (heritable somatic mutations) tests
- Pathology and cytology

### Division of Radiological Health (DRH)
- Diagnostic radiology devices
- Radiation therapy devices
- Medical and non-medical electronic product radiation control (e.g. ultrasound products)

### Division of Mammography and Quality Standards (DMQS)
- Implements the Mammography Quality Program authorized by the Federal Mammography Quality Standards Act of 1992
Presentation Topics

• Background

• FDA Review of Companion Diagnostics (CoDx)

• Current Status and Recent Approvals

• Emerging Issues and Challenges
  – Follow-on CoDx
Personalized Medicine

• The success of personalized medicine depends on having accurate, reproducible and clinically useful companion diagnostic tests to identify patients who can benefit from targeted therapies.

• **Companion Diagnostics (CoDx)** are those tests that provides information that is essential for the safe and effective use of a corresponding drug or biological product.
FDA Expectation for CoDx

“Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices”

• Guidance finalized August 6, 2014
• Defines companion diagnostic device and various scenarios for use
• Describes FDA policies for approval and labeling
• Contemporaneous regulatory approvals of the device and therapeutic product

Drug Development Trend

• Dramatic increase in biomarker-targeted drug development programs
  – In the early 1990s, 5% of new drug approvals were for targeted therapies
  – In 2013, 45% were for targeted therapies

• Increase in use of tests to detect/measure biomarkers to identify the Intent-To-Treat (ITT) population
Why Companion Diagnostics

• Companion diagnostics segregate a patient population into two subsets: **marker-positive vs. marker-negative**
  – a qualitative result based on an underlying semi-quantitative / quantitative assessment to which a **clinical decision point or cut-off** is applied

• The safety and efficacy of the therapeutic product is evaluated in the population that is treated in the clinical trial, e.g., marker-positive study
  – marker-positive: enrolled, safety and efficacy evaluated
  – marker-negative: not enrolled, safety and efficacy not evaluated

• Leading to more focused therapies that offer better outcomes and less toxicity to patients
CoDx Policy

• Co-approval of a test and corresponding drug required when the test is essential for safe and effective use of the therapeutic product

• CoDx requirement
  – Decision made by drug review division
  – Device Center provides insight

• Labeling
  – Therapeutic label refers to “FDA approved Test”
  – Device label names the drug
Business Issues

• Therapeutic product sponsors are responsible for assuring that a companion diagnostic (CoDx) device will be brought forward

• Device sponsors are responsible for CoDx submission, performance, compliance with device regulations

• Therapeutic product and CoDx sponsors should carefully define expectations for each other
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FDA Review for CoDx

- Intended Use / Indications for Use
- Device Description (reagents, platform)
- Pre-analytical
- Analytical Performance
- Clinical Performance
- Instrumentation, Software validation (as applicable)
- Labeling (package insert)
Overview of CoDx Validation

• The test is used to select target population enrolled in the therapeutic clinical trial
  – In Vitro Companion Diagnostic Devices (IVD CoDx)
  – 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
Overview of CoDx Validation

- 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 results of the therapeutic clinical trial
When the CoDx is not the Clinical Trial Assay (CTA)

- Changing the test (e.g., technology platform) can change the results for a patient’s specimen, and potentially changes the patient population from what was selected in the therapeutic clinical trial.

- Requires Bridging Studies
  - A bridging study is not just a method comparison
  - To show that the revised test (IVD CoDx) supports safety and efficacy of the therapeutic product.
Bridging Studies

- Re-test patient specimens (CTA negative and positive) with new/revised test to support safety and efficacy of the therapeutic product

- Re-test population is representative of the intended use population for the device

- **Statistical Analysis Plan** should consider discordance, missing samples, address bias and impact on therapeutic product efficacy
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CoDx Current Status

To date: 21 different approved drug/diagnostic combinations

– All (except one) are for oncology indications
– Many are HER-2 specific
– Others are novel agents/new tests

http://www.fda.gov/CompanionDiagnostics
# Recent CoDx Approvals

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>IVD Device</th>
<th>Device Manufacturer</th>
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<tbody>
<tr>
<td>Erbitux (cetuximab) Vectibix (panitumumab)</td>
<td>cobas KRAS Mutation Test</td>
<td>Roche Molecular Systems, Inc.</td>
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<tr>
<td>Lynparza (olaparib)</td>
<td>BRACAnalysis CDx</td>
<td>Myriad Genetic Laboratories, Inc.</td>
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<tr>
<td>Gilotrif (afatinib)</td>
<td><em>therascreen</em> EGFR RGQ PCR Kit</td>
<td>Qiagen Manchester, Ltd.</td>
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<td>Tarceva (erlotinib)</td>
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<td>Xalkori (crizotinib)</td>
<td>VYSIS ALK Break Apart FISH Probe Kit</td>
<td>Abbott Molecular Inc.</td>
</tr>
<tr>
<td>Mekinist (tramatenib) Tafinlar (dabrafenib)</td>
<td>THxID BRAF Kit</td>
<td>bioMérieux Inc.</td>
</tr>
<tr>
<td>Zelboraf (vemurafenib)</td>
<td>cobas 4800 BRAF V600 Mutation Test</td>
<td>Roche Molecular Systems, Inc.</td>
</tr>
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CoDx Approvals in 2014

• QIAGEN *therascreen* KRAS RGQ PCR kit: aid in the identification of colorectal cancer patients for treatment with erbitux (cetuximab) and vectibix (panitumumab) based on a KRAS no mutation detected test result.

• Myriad BRACAnalysis CDx™: aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib). To be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108
BRACAnalysis CDx

Device includes the following:
- Sample collection kit
- BRACAnalysis CDx Sanger sequencing test
- BRACAnalysis CDx Large Rearrangement Test (BART CDx)
- Alternate Primer Sequencing (APS)
- Confirmatory PCR Analysis (CPA)
- Defined variant classification process

• The test is intended to be performed at a single laboratory site
Regulatory Breakthroughs

• First LDT approved as CoDx

• First CoDx approved without a list of specified variants. Instead, variant classification process approved as part of the test.
  – Types of variants are included in the labeling

• First CoDx approved with conditions
  – Perform additional analytical testing
  – Report results from ongoing confirmatory trials
  – Provide updates on variant classification process
  – Monitor and report on robustness of classification process\(^1\)
BRACAnalysis CDx – Case Study

• FDA and Sponsors’ Collaborative Efforts

• Accelerating Anticancer Agent Development and Validation Workshop (AAADV)
  – May 6 - 8, 2015, Bethesda, MD
  – http://www.acceleratingworkshop.org/2015-program/

• DIA Meeting on Companion Diagnostics
  – September 30 – October 1, 2015, Bethesda, MD
  – http://DIAGlobal.org/CD
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CoDx Complexities

One Indication, One Drug, One Test, One Allele
• NSCLC, Abbott VYSIS ALK Break Apart FISH Probe Kit for Xalkori® (crizotinib)

One Indication, More Than One Drug, One Test, Same Alleles
• CRC, QIAGEN therascreen KRAS RGQ PCR Kit for two therapeutics: Erbitux® (cetuximab) and Vectibix® (panitumumab)

Originally One Indication, One Drug
• Breast cancer, HER2 and Herceptin, Tests: Dako IHC / Vysis PathVysion FISH
• Expanded the indication to gastric cancer
• Other drugs for the same analyte – Perjeta, Kadcyla
CoDx Complexities

One Indication, More Than One Drug, Two Tests, Same Gene but Different Allele Representation

- BRAFV600 mutation in melanoma
  - Roche cobas BRAF V600 Mutations Test for Zelboraf® (vemurafenib)
  - BioMérieux THxID BRAF Kit for Tafinlar® (dabrafenib) and Mekinist® (trametinib)

- EGFR Activating Mutations in NSCLC
  - Roche cobas EGFR Mutation Test for Tarceva® (erlotinib)
  - Qiagen *therascreen* EGFR RGQ PCR Kit for Gilotrif® (afatinib)
Emerging Issues and Challenges

• The Case of PD-L1
  – Multiple disease indications, biologics products, IHC tests, molecular targets
    – [Link](http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm436716.htm)

• Next-Generation Sequencing (NGS) as CoDx
  – Oncopanel: One Test, Multiple Indications, Multiple Drugs, Different Genes, Multiple Variants/Allele Representation

• Follow-on CoDx
“Follow-on” CoDx

- Defining “Follow-on” CoDx

  - the same intended use and therapeutic indication as the originally-approved CoDx on the market (e.g., an indication for use with Herceptin)

  - Other considerations: biomarker, analyte type, specimen type, methodology, improvement of sensitivity
"Follow-On" CoDx

- "Follow-on" CoDx should consistently and accurately select the same intended use patient population as the originally-approved companion diagnostic devices for the indicated therapeutic drug.

- "Follow-on" CoDx should demonstrate the same or comparable level of analytical and clinical performance for specific mutations in the originally-approved companion diagnostic device.
# Follow-on CoDx Approval

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<th>QIAGEN</th>
<th>Roche Molecular System</th>
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## Intended Use (IU)

The *therascreen* 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 *therascreen* KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with **Erbitux** (cetuximab) and **Vectibix** (panitumumab) based on a KRAS no mutation detected test result.

The *cobas* KRAS Mutation Test, for use with the *cobas* 4800 System, is a real-time **PCR** test for the detection of **seven somatic mutations** in codons 12 and 13 of the KRAS gene in DNA derived from **formalin-fixed paraffin-embedded human colorectal cancer (CRC)** tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with **Erbitux** (cetuximab) or with **Vectibix** (panitumumab) may be indicated based on a no mutation detected result.
“Follow-On” CoDx – Studies

• Analytical Studies
  – should be comparable to the original CoDx approval
  – accuracy, LoD, reproducibility, etc.

• Agreement Study
  – comparison to a reference method, and/or
  – comparison to the originally-approved CoDx

• Clinical Performance
  – predictive values of follow-on CoDx
  – clinical specimens with outcome data
  – procured specimens without outcome data
"Follow-on" CoDx – Challenges

• Follow-on CoDx in NGS panel test

• Agreement analysis: clinical sample set should be similar to the target patient population

• Dilemma in determining impact of discordance
  – Is discordance random?
  – Is there bias impacting device performance?
Marketing Submissions for CoDx

• Most CoDx will require a PMA

• Modular PMA approach is highly preferred over traditional
  – Can begin CoDx review early
  – Final clinical module coincides with BLA/NDA filing

• CoDx review, in practice, follows therapeutic review timeline
CoDx Approvals: Lessons Learned

• Think outside the box, use all possible regulatory mechanisms to create pathways that work

• Inter-center communication now highly effective and review staff working well together
  – Co-attendance at meetings
  – Questions/consults transmitted in timely manner
  – Approvals and press well-coordinated

• Encourage early interaction of CoDx sponsors with FDA/CDRH through pre-submission process
Questions?

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