Companion Diagnostic Regulatory Update from the Pharmaceutical Perspective

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Disclaimer

- The regulatory analysis given in this presentation reflects my own personal views and not that of my employer, GlaxoSmithKline.
Discussion Topics

- CDx regulatory issues specific to Next Generation Sequencing (NGS)
- FDA laboratory-developed test regulation (LDT) update
- Roche KRAS Test Model for Follow on Companion Diagnostic Test Validation
- General Companion Diagnostic regulatory considerations

IVD = *in vitro diagnostic*
FDA Pre-market IVD Review Elements

- **Analytical validation**
  - Correctly identifies analyte
  - Accuracy relative to a reference standard
  - Measurement Precision
  - Limits of detection
  - Interfering substances

- **Clinical validation**
  - Correctly identifies disease/condition
  - Clinical sensitivity, clinical specificity, predictive values

- **Diagnostic Product Labeling**
  - Clear and accurate test information available to the physician
NGS-based CDx Test Regulatory Challenges

- FDA will need to employ a “new approach” towards NGS Regulation
  - NGS provides information about multiple NSCLC CDx targets simultaneously from a single sample. This requires a FDA regulatory paradigm shift from the current “One drug/One test” CDx PMA submission model.

- Analytical Validation Standards
  - Full analytical validation for rare markers will not be feasible. This requires guidelines for representative “non-biased” sampling of DNA sequences.
  - Development of acceptance criteria for “controlled” clinical variant databases to permit use as a NGS analytical reference method.

- Clinical Data Interpretation
  - Analytes of Undetermined Clinical Significance – NGS provides unprecedented ability to detect new or rare genetic variants. This will likely cause biomarker discovery to outpace the understanding of the biomarker’s clinical utility.
  - Clear and accurate communication of complex NGS test results to physicians and patients
Scalable NGS CDx Test Labeling Framework

Scalable labeling framework is key to industry’s decision to pursue development and registration of multiplex/NGS platforms

<table>
<thead>
<tr>
<th></th>
<th>Biomarker A</th>
<th>Biomarker Z (Analyte of Unknown Significance)</th>
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<tbody>
<tr>
<td>Type of Claim</td>
<td>Predictive</td>
<td>Analytical</td>
</tr>
<tr>
<td>Intended To Be Used</td>
<td>Yes</td>
<td>No (not outside clinical trials)</td>
</tr>
<tr>
<td>for Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection</td>
<td></td>
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<tr>
<td>Subject to FDA</td>
<td>PMA (Quality,</td>
<td>Yes (Quality, Analytical)</td>
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<tr>
<td>Review</td>
<td>Analytical,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical)</td>
<td></td>
</tr>
<tr>
<td>Clinical Utility</td>
<td>Yes</td>
<td>Not at present</td>
</tr>
<tr>
<td>Data</td>
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</table>

Biomarker Z (AoUS) could be “upgraded” to an FDA-approved Predictive Claim after submission of additional clinical utility data and PMA review/approval

Adapted from the Erling Donnelly from Pfizer Presentation at “World CDx Regulation 2015” on April 29, 2015
Re-classification of NGS Analyzers to Class II 510(k) exempt Medical Devices

<table>
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<th>PRODUCT</th>
<th>DATE</th>
<th>510(K) NUMBER</th>
<th>Class</th>
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Reclassified as Class I per FDA:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm

Background:

- Centers for Medicare & Medicaid Services (CMS) regulates laboratory testing in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA).

- IVD test kits made by a traditional device manufacturer are subject to FDA pre-market review of test safety and effectiveness.

- FDA exercises enforcement discretion on LDTs. LDTs developed by a clinical laboratory for use at its own facilities can be sold without FDA premarket review.

- FDA is concerned that CLIA regulations alone DO NOT ensure diagnostic devices are safe and effective as required by the FD&C Act.
• What is the distance from sample collection to laboratory?
• How many discrete items does the test analyze?
• What instrumentation is necessary to perform the test?
FDA/CDCR H/OIR Concerns with LDTs

- Past industry practice to leverage FDA LDT enforcement discretion through adoption of “IVD testing services” in the place of “IVD test kits” that require FDA pre-market clearance/approval.

- Proliferation of genetic LDTs with some labs adopting aggressive direct to consumer marketing outside FDA pre-market review.

- Complex genetic LDTs based on complex “black box” data analysis algorithms not verifiable by an independent third party.

- Potential health risk of LDTs due to use of “non-GMP” Research Use Only (RUO) reagents, software and instrumentation. i.e., RUO LDT components not developed under a Quality System to ensure batch to batch consistency in LDT performance.

FDA intends to extend the same patient health risk-based regulatory approach used for IVD test kits to LDTs.
## Risk-Based, Phased-In Enforcement

<table>
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<tr>
<th>Category</th>
<th>Notification</th>
<th>MDRs</th>
<th>Premarket Review</th>
<th>QSRs</th>
<th>R&amp;L</th>
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</thead>
<tbody>
<tr>
<td><strong>Highest risk</strong></td>
<td>6m</td>
<td>6m</td>
<td>1y</td>
<td>Upon PMA submission</td>
<td>Upon PMA approval</td>
</tr>
<tr>
<td>LDTs already on market</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LDTs with same intended use as cleared/approved companion diagnostics</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>LDTs with same intended use as approved Class III medical devices</td>
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<td></td>
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<td></td>
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<tr>
<td>Certain LDTs for determining safety and effectiveness of blood or blood products</td>
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<tr>
<td><strong>Subsequent high risk</strong></td>
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<td>6m</td>
<td>2-5y</td>
<td>Upon PMA submission</td>
<td>Upon PMA approval</td>
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<td><strong>Moderate risk</strong></td>
<td>6m</td>
<td>6m</td>
<td>5-9y</td>
<td>Upon 510k clearance</td>
<td>Upon 510k clearance</td>
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<tr>
<td>categories in priority order determined by public process</td>
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FDA Objective for LDT Regulation

Innovation

Safety & Efficacy

The Patient
LDT Case Study – OvaSure™ Test Timeline

May 2005
Initial biomarker panel results in PNAS showing high PPV

February 2006
Labcorp licenses prognostic panel as an IVD from Yale

February 2008
Visintin et al. confirmatory study in Clinical Cancer Research showing high PPV

June 23, 2008
LabCorp announces OvaSure test availability

2005

2006

2007

2008

September 29, 2008
FDA Warning Letter to LabCorp

October 24, 2008
LabCorp OvaSure Voluntary Withdrawal

November 2008
Serious concerns with statistical methodology for Visintin et al. study published as Letters to Editor
Opposed to Proposed FDA LDT Regulatory Framework

Academic Labs, Clinical Labs and Pathology Groups

- American Clinical Laboratory Association (ACLA) challenges FDA LDT jurisdiction on the grounds that FDA should not regulate the “Practice of Medicine”

- Regulatory Implementation by FDA Guidance vs. a formal “Comment and Rule-making Process”

- Modernize existing CLIA regulations instead of imposing the existing FDA Medical Device Regulatory Framework
Comparison of FDA IVD Test and CLIA LDT Regulation

<table>
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<tr>
<th>Regulations</th>
<th>FDA</th>
<th>CLIA (CMS)</th>
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<tbody>
<tr>
<td>Analytical Validity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical Validity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reagent Quality Management System</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>On-Going Proficiency Testing (CAP)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pre-Market Data Review</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Product Labeling Requirements</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Post Market Adverse Event Reporting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lab Personnel Qualifications</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical Test Performance Data Transparency</td>
<td>Yes</td>
<td>No</td>
</tr>
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</table>
Support Proposed FDA LDT Regulatory Framework with Concerns

Pharmaceutical Industry:

- GSK, PhRMA and Pfizer representative examples

- Patient Safety drives the Need for FDA LDT Regulation

- Concerns about decreased access to medicines due to the smaller number of labs offering companion diagnostic testing as a consequence of Clinical Lab industry consolidation.

- Requests “enforcement discretion” for investigational companion diagnostic tests used in early stage non-pivotal clinical studies.

www.regulations.gov Public Docket FDA-2011-D-0360
“Follow on” CDx Test Validation

- KRAS, BRAF and EGFR LDTs are in “bullseye” for FDA regulation based on FDA approved CDx Test Kit alternatives
- FDA expected to issue a “Follow on” CDx Test Validation Guidance in the near future
- FDA recently approved the Roche cobas® KRAS Mutation Test on May 7, 2015 (P140023). This is the first example of a “Follow on” CDx Test PMA Approval.
- Roche KRAS Test Indications for Use identical to the first “FDA approved” QIAGEN therascreen® KRAS RGQ PCR Kit
  - No KRAS mutation detected test result makes CRC patients eligible for Erbitux® (cetuximab) or
  - No KRAS mutation detected test result makes CRC patients eligible for Vectibix® (panitumumab).
Novel CDx Test Validation Approach used for the Roche cobas® KRAS Mutation Test

- Analytical validation studies employed procured CRC tissue specimens and Sanger Bi-directional DNA Sequencing as the Reference
- The CRC clinical validation tissue specimen set was obtained from another Roche CRC drug study that did not include the prospective use of Erbitux® or Vectibix®
- The Clinical Validation CRC FFPE Tissue Specimens were retrospectively tested with the investigational Roche KRAS Test, the FDA approved QIAGEN KRAS Test and Sanger Bi-directional DNA sequencing
- Clinical performance of the Roche cobas® KRAS Mutation Test with Erbitux® and Vectibix® were imputed based on the Percent Positive and Percent Negative Result Agreement rates relative to the QIAGEN therascreen® KRAS RGQ PCR Kit Reference
Companion Diagnostic Development
CDx and Drug Regulatory Inter-Dependencies

Drug Candidate
Pre-Clinical Development
Feasibility Studies Using LDT Test
Investigational Use Only (IUO) Clinical Trial Assay (CTA)
Investigational Device Exemption (IDE)
Companion Diagnostic Test Validation
CDx PMA Documentation:
• Manufacturing/Quality
• Analytical Testing
• Clinical Data
Design Lock for CDx Assay
CDx PMA Approval

Submit IND
Phase I
Phase II
Phase III
Phase IV
Drugs NDA Approval
Best Practices for Effective Partnering with Dx

- Develop **Product Requirements** and **Regulatory Strategy** Documentation in collaboration with Dx Partner as soon as possible
- **Meet early with FDA** (CDER and CDRH) as a joint Rx/Dx Team
- Share pertinent regulatory correspondence with Dx partner especially related to clinical development strategy
- Obtain feedback from Dx partner during preparation of pertinent Rx regulatory submissions
- Regular joint meetings with Dx Partner to discuss project activities and synchronize timelines
- CDx Partner contract needs to include post-market support activities following NDA/PMA approval
CDx LDT Pre-screening and FDA CDx Bridging Study Design

- Bridging Study required to show comparability of “provisional” Clinical Trial Assay with “final” FDA Approved CDx Test Version
- Bridging requires retrospective testing of clinical trial samples with Final CDx Test Version
- Sample pre-screening with local site LDTs may lead to sampling bias for inclusion in the bridging study for FDA submission purposes:
  - Requires samples from both “randomized” patients (CDx positives receiving study drug) and non-randomized CDx test negative screened patients
  - Need to design Informed Consent to permit retrospective testing for CDx screen negative patients
Thank You

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NGS Discussion Topic #1

What is the appropriate role for FDA in the regulation of NGS-based companion diagnostic tests given the non-applicability of the One test/One Drug CDx regulatory paradigm?

Options include:

1. FDA continues to utilize a risk-based pre-market review of all NGS-based CDx tests.

2. FDA sets analytical validation standards and makes all NGS diagnostic tests exempt from pre-market review.

3. Highest risk NGS CDx tests (utilizing a black box algorithm) undergo FDA pre-market review and while “follow on” CDx tests are subject to technical review by a FDA accredited third party.
NGS Discussion Topic #2

What would be an appropriate level of “representative” NGS analytical validation for CDx tests?

- Considering that full analytical validation for rare markers will not be feasible, what elements should be considered during development of guidelines for “non-biased” partial sampling of DNA sequences?

- What parameters should be considered during development of acceptance criteria for “controlled” clinical variant databases to permit use as a NGS analytical reference method?
Rationale: NGS provides unprecedented ability to detect new or rare genetic variants. This will likely cause biomarker discovery to outpace the understanding of the biomarker’s clinical utility.

- Should information about “Analytes of Undetermined Clinical Significance” be reported to physicians and patients?
Discussion: Lab Modification of FDA Approved Companion Diagnostic Tests

- The FDA approved EGFR CDx Tests are indicated for FFPE Tissue use. Lab modifies a FDA BRAF test to allow use of Fine Needle Aspirates that constitute about 50% of NSCLC clinical specimens.

- The FDA approved BRAF drug/companion diagnostic test pairs are indicated for metastatic melanoma treatment. Lab modifies the FDA approved BRAF test to determine BRAF status of thyroid tumor tissue and physician prescribes a BRAF inhibitor for treatment on the basis of this information.

How will FDA regulate lab modification of FDA approved tests to address an unmet medical need? Responsible party for test adverse event reporting?

Roche FDA HPV: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394773.htm
LDT Framework Discussion

Should FDA “carve out” Investigational CDx Tests used in early phase, non-pivotal drug studies?

- FDA IDE regulations have the objective to show “patient safety” of the IVD test
- The level of IDE documentation varies depending on the specific intended use of the test:
  - Blood screening test for HIV or Hepatitis – Stringent IDE documentation standard
  - IUO CDx Test to support a Pivotal Oncology Phase 3 Study – moderate IDE documentation standard based on risk profile for inaccurate test results
  - IHC Biomarker Investigational CDx Tests used to support early stage “non-pivotal” drug studies- Technical report attached to IND file