FDA's Precision Medicine Initiative: Achievements and Challenges

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Companion Diagnostic Forum
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Disclosures

- Consulting with several diagnostic companies, laboratories, patient groups and professional groups on FDA regulation, and LDT landscape
- I no longer speak for the FDA
FDA Medical Device Regulations - 1976

- Provided definition of ‘medical device’
- Defined the standard to be used
  - Safe and Effective
- Provided Regulatory Paradigm
  - Risk-Based regulation of medical devices
Regulatory Standard

Safety

• There is reasonable assurance … that the probable benefits … outweigh any probable risks. [21CFR860.7(d)(1)]

Effectiveness

• There is reasonable assurance that … the use of the device … will provide clinically significant results. [21CFR860.7(e)(1)]
Risk-Based Classification

• Class I: common, low risk devices
  • Most exempt from premarket submission
  • General controls

• Class II: more complex, higher risk
  • Most require Premarket Notification [510(k)]
  • Special controls

• Class III: most complex, highest risk
  • Premarket Application [PMA] or HDE
  • Safety, effectiveness
Applied to Commercial Kits

- Not directed at laboratory developed devices (also known as in house tests, laboratory test services, “home brew tests”)
- Enforcement discretion
Current Regulatory Reality

1) Commercially Distributed Test Pathway:

   - "test kit" manufactured for distribution to multiple labs
   - FDA approval
   - "Test kits" distributed to patients, hospital, or clinical lab

2) Lab Developed Test (LDT) Pathway:

   - Test designed, manufactured, and used in a single lab
   - FDA "enforcement discretion"
   - LDTs (lab developed tests) enter the market without review
Companion Diagnostics

- HER-2/neu – to measure expression of HER-2/neu as an aid in the assessment of breast cancer patients for whom Herceptin® treatment is considered.

- EGFR - to identify EGFR expression as an aid in identifying colorectal cancer patients eligible for treatment with Erbitux (cetuximab).
Companion Diagnostics

- Identify patients who are most likely to benefit from a particular therapeutic product;
- Identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- Monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.
Regulatory Issues for Companion Diagnostics

• Association of biomarker with therapy
  – Regulation of therapeutic product plus regulation of diagnostic product to produce a useful clinical pair

• How to accomplish both
  – Different manufacturers
  – Different regulations
  – Different review timelines
  – Different exclusivity rules
  – Different life cycles for the products
FDA Personalized Medicine Staff

• Formed June-August 2009
• Purpose: Address personalized medicine issues that affect policy and regulations for diagnostic devices
Omapro and T315I Testing

NDA 022-374

OMAPRO (omacetaxine mepesuccinate) for injection [ODAC, March 2010]

• Accrual using multiple independently developed laboratory tests
• Gaps, discordances with central labs’ testing
• “VOTE: Should a well characterized in vitro diagnostic to identify patients with the T315I mutation be required and reviewed by the FDA and correlated to clinical trial results prior to approval of omacetaxine for the proposed indication?”

RESULT: Yes=7, No=1, Abstain=0
Companion Diagnostic Guidances

- Draft July 14, 2011
- Final August 6, 2014
Codevelopment Guidance

• Draft July 15, 2016
Many successful CDx examples

<table>
<thead>
<tr>
<th>Companion Diagnostics in Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>36</strong> Approved IVD Companion Diagnostic-Therapeutic Product Pairs</td>
</tr>
<tr>
<td><strong>26</strong> Approved IVD Companion Diagnostics</td>
</tr>
<tr>
<td><strong>17</strong> Approved Cancer Therapeutic Products</td>
</tr>
<tr>
<td><strong>11</strong> Molecular markers</td>
</tr>
<tr>
<td>ALK, BRCA, BRAF, C-KIT, EGFR, HER-2/NEU, KIT, KRAS, PDGFRB, PD-L1, 17p deletion</td>
</tr>
</tbody>
</table>

(as of Feb 2017)

Updated list at [www.fda.gov/companiondiagnostics](http://www.fda.gov/companiondiagnostics)
Companion Diagnostic Challenges

- One drug one test paradigm
- Wide use of LDTs
- Clinical evidence needed for follow-on diagnostics
- Limited sample size
- Multiplexing
- Biomarker information that may be useful
Oncomine Dx Target Test

• The Oncomine™ Dx Target Test is a qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System.

• The test is indicated to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

June 2017
Table 1

List of variants for therapeutic use

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>BRAF V600E</td>
<td>TAFINLAR®(dabrafenib) in combination with MEKINIST® (trametinib)</td>
</tr>
<tr>
<td>EGFR</td>
<td>L858R, Exon 19 deletions</td>
<td>IRESSA® (gefitinib)</td>
</tr>
<tr>
<td>ROS1</td>
<td>ROS1 fusions</td>
<td>XALKORI® (crizotinib)</td>
</tr>
</tbody>
</table>

- The first CDx that simultaneously assesses a patient’s eligibility for treatment with multiple NSCLC therapies.
Table 2

List of variants for genetic profiling

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant ID</th>
<th>Nucleotide change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>COSM754</td>
<td>c.1035T&gt;A</td>
</tr>
<tr>
<td>MET</td>
<td>COSM707</td>
<td>c.3029C&gt;T</td>
</tr>
<tr>
<td>KRAS</td>
<td>COSM512</td>
<td>c.34_35delGGinsTT</td>
</tr>
<tr>
<td>KRAS</td>
<td>COSM516</td>
<td>c.34G&gt;T</td>
</tr>
</tbody>
</table>

• Analytical performance using NSCLC specimens has been established for the variants listed in Table 2.

• The test is not indicated to be used for standalone diagnostic purposes, screening, monitoring, risk assessment, or prognosis.
Authorization of MSK-IMPACT through the De Novo pathway creates a Class II regulatory pathway for oncopanels that meet the following:

- Can meet general and special controls described in the authorization
- Do not make companion diagnostic claims
- Subsequent oncopanels of that type now eligible to use the 510(k) pathway
- Can choose to submit 510(k) to FDA directly or elect to use an accredited FDA third-party reviewer
Use of Third Party Reviewers

- FDA developing a strong third party review program for IVDs that is also meant to attract and make it possible for laboratories to have their LDTs reviewed
- Currently there are 7 accredited parties

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/accredit.cfm
Three Tiered Approach

Level 1: Companion Diagnostics
Prescriptive for a specific therapeutic
Clinical study or clinical concordance to previous CDx

Level 2: Cancer Mutations with Evidence of Clinical Significance
For use in accordance with professional guidelines
Publicly available clinical evidence

Level 3: Cancer Mutations with Potential Clinical Significance
Informational, use for clinical trial enrollment
Clinical or mechanistic rationale for inclusion in panel
As clinical evidence develops, mutations/biomarkers may move from table 3 to table 2 provided the new claim is reviewed via a submission to the FDA or a third party reviewer.
FoundationOne CDx

- Parallel review
- On FDA approval CMS issued a proposed national coverage determination
- FDA and CMS coordinated to set rational framework for approving/clearing and paying for cancer tests.
CMS proposed NCD for NGS

• In line with FDA’s scheme
• Coverage of Table 1 claims
• Coverage with evidence development of Table 2 and Table 3 claims
  – Registries for Table 2 claims
  – Clinical Trial enrollment for Table 3 claims
CMS final NCD for NGS

- Coverage for tests that FDA approved with table 1 claims
- No coverage with evidence development for tests cleared for tumor profiling
Summary

• Government bodies need to continue tackling issues as innovation changes tests and testing.

• Laboratories, manufacturers and professional bodies need to partner with governmental bodies to assure that innovation can continue to flourish but that regulatory gaps do not leave patients at risk.

• Patients should be engaged since patients preferences and needs are best understood by them.