How FDA, CMS, and Other Federal Agencies Are Responding to Rapid Changes in the Laboratories

Alberto Gutierrez
Partner

Executive War College
May 2, 2018
New Orleans, Louisiana
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
Change!

- FDA Medical Device Amendments 1976
- CLIA 1988
Regulation

- Law
- Regulations
- Guidances
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
Safety

“There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.”

21 CFR 860.7
Effectiveness

“There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

21 CFR 860.7
Valid Scientific Evidence

- Well controlled investigations
- Partially controlled studies
- Studies and objective trials without matched controls
- Well-documented case histories conducted by qualified experts, and
- Reports of significant human experience with a marketed device from which it can be fairly and responsibly concluded by qualified experts that there is a reasonable assurance of safety and effectiveness

21 CFR 860.7
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
Elements of Review

- **Analytical validity**
  Correctly detects analyte

- **Clinical validity**
  Correctly identifies disease/condition

- **Labeling**
  Intended Use
Does It make sense?

- Broad range of tests
- Needs to cover from sample collection to result report
- Needs to cover tests where user expertise and variance is crucial to test performance
Types of Claims

• Specific
• Tools or General Claims
Rely on CLIA

- Expertise of laboratorians
- Proficiency testing
- Laboratory quality systems
Current Regulatory Reality

1) Commercially Distributed Test Pathway:

Test designed, manufactured, and used in a single lab

“test kit” manufactured for distribution to multiple labs

FDA approval

“Test kits” distributed to patients, hospital, or clinical lab

Patient

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

Patient
New Reality

• January 2017 FDA issues a White Paper
• FDA will wait for congress to address the LDT issue through law
• FDA continues working with the clinical community, laboratories, CMS (CLIA and payment issues), CDC, CLIA certifiers and IVD manufacturers to address regulatory issues
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
Least Burdensome

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
Special Issues with NGS

• Lack of specific intended use
• Ability to detected multiple analytes
• Can’t predefine what the test will detect
• Unprecedented ability to detect rare variants
• Dependence on software pipelines and big data
• Rapidly evolving technology
• High throughput allows discovery to outpace clinical knowledge
FDA, CMS and CDC collaboration

- FDA guidance on analytical validity
- FDA guidance on data bases
- FDA Precision Medicine
- NIST Standards
- CDC facilitated first consensus guidance
- CLIAC NGS workgroup
  - Challenges of existing regulatory framework
Summary

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

• Laboratories 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.