FDA Overview of Molecular Diagnostics and the Critical Path Initiative

Steven Gutman, MD, MBA
Director, Office of In Vitro Diagnostics
Medical Device Amendments of 1976

- General controls
- Registration and listing
- Good manufacturing practices
- Post market reporting
Premarket Review

- 510(k)s
- PMA
- Administrative differences
- Common scientific base
Analytical Performance

- Accuracy
- Precision
- Analytical specificity
- Analytical sensitivity
Clinical Performance

- Signals can be turned into clinical action
- Diagnostic sensitivity
- Diagnostic specificity
- Predictive value or positive or negative results
Labeling -- 809.10(b)

- Intended use
- Performance characteristics
- Limitations
Life Cycle

- Analytical performance
- Feasibility *
- Clinical performance
- FDA approval – market access
---------------------
- Real world use
The Real World of Regulation

- FDA
- CMS (CLIA)
- CMS and others (third party pay)
10-Year Trends in Major Drug and Biological Product Submissions to FDA

- □ Total NMEs Rec'd by FDA
- ○ Original BLAs

Year

Submissions to FDA

Critical Path Initiative

- Biomarkers appear in two contexts
- Diagnosis
- Drug discovery
- Concept of personalized medicine grounded in genomic map but not bounded by this
Critical Path Initiative

- Infrastructure
- Opportunities list
- Pilot programs
Bad News

- Cutting edge new technology -- multiplex, bioinformatics, nanotechnology
- Paucity of material or method standards
- Biological and clinical nuances
- Financial uncertainties
Bad News

- Scientific limitations are clear
- Spectrum bias
- Verification bias
- Impact of missing data points
- Discrepancy
Good News

- Regulatory trail is well lit
- Literature
- Standards
- Guidances
Principle Road Maps

- STARD Initiative
- ReMARK Initiative
Growing Literature on Co-Development

- Simon and Wang, 2006
- Pennello and Vishnuvajjala, 2005
- Sargent et al, 2005
- Pustzai and Hess, 2004
Growing FDA Guidance

- Voluntary Genomic Data Submissions guidance
- Concept paper on co-development
- Statistical guidance on IVD labeling
- Guidance on pharmacogenetic and heritable genetic tests
- Bayesian statistics
Good News

- Broad menu of regulatory tools
- Mandate to be least burdensome
- New scientific resources -- MDUFMA
- New regulatory programs -- FDA data template, critical path
Flexible Regulatory Tools

- Pre-IDE
- Expedited reviews
- Real time reviews
- De novo classification
Review Successes

- Cystic Fibrosis test – 109 days
- Avian flu – 14 days
- UGT1A1 – 9 days
Co-Development

- If predictive diagnostic determines drug choice
- Safety and effectiveness of drug becomes hostage to diagnostic
- Need to understand system as a whole
Predictive Marker

- Identify patients by biomarker status; randomize therapy across all patients
- Identify patients by biomarker status; randomize therapy in subsets
- Randomize by treatment; look back at biomarkers
Predictive Marker

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Positive test</th>
<th>Positive test</th>
<th>Neg test</th>
<th>Neg test</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (response)</td>
<td>B (non-response)</td>
<td>C (response)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td>D (non-response)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>E (response)</td>
<td>F (non-response)</td>
<td>G (response)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>H (non-response)</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>Positive test</td>
<td>Positive test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A</strong> (response)</td>
<td><strong>B</strong> (non-response)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Positive test</th>
<th>Positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E</strong> (response)</td>
<td><strong>F</strong> (non-response)</td>
<td></td>
</tr>
</tbody>
</table>
FDA Mission

- Promote public health
- Protect public health
- Tension in objectives
Good Science