Medical Device Amendments of 1976

- General controls
- Registration and listing
- Good manufacturing practices
- Adverse event reporting
Medical Device Amendments of 1976

- Premarket review – risk based – intended use
- Different administrative practices
- Common core scientific process
Standardized Road Map for Evaluation

- Analytical performance
- Clinical performance
- Labeling
Analytical Performance

- Accuracy
- Precision
- Specificity
- Limits of detection/measurement
Clinical Performance

- Yardstick of truth
- Clinical sensitivity
- Clinical specificity
- Predictive values
- Payment/penalty for weaker surrogates
Labeling

- 809.10(b)
- Intended use
- Performance
- Limitations
Laboratory Developed Tests

- Tests developed at single site for use at that site
- Long rich history of use
- Broad menu
- FDA considers these medical devices
- Enforcement discretion
Laboratory Developed Tests

☐ Subject to CLIA +
☐ Analytical performance
☐ Quality system
Laboratory Developed Tests

- No threshold between research and clinical use
- No specific premarket review (sampling)
- No clinical validation
- No reporting requirements
ASR Rule -- 1997

- Incremental increase regulation
- Down-classification
- Deliberate effort to create safe harbor
Active ingredients of building blocks of laboratory developed tests

Antibodies, specific receptor proteins, nucleic acid sequences, and similar biological reagents which through chemical binding or reaction with substances in specimen are intended for identification and quantification of an individual chemical substance or ligand in biological specimens
ASR: Impact on Manufacturers

- Required to register and list
- Required to meet good manufacturing practices
- Required to report adverse events
- Restricted distribution, use, and labeling
ASR: Impact on Laboratories

- Restricted to high complexity laboratories
- CLIA requirements
- Report disclaimers
Disclaimers

- Mandatory language
- Discretionary explanation
Laboratory Developed Tests

- Least burdensome path to market
- Most common path for genetic tests, including DTC genetic tests
- Source of inadvertent or deliberate abuse
Status of FDA Initiatives

- ASR Guidance – Questions and Answers
- In Vitro Diagnostic Multivariate Index Assays
- FDA is currently not regulating laboratory developed tests
Status of FDA Initiatives

- Watching with interest growing arena of DTC genomics
- Following with interest progress of SACGHS report issued May 1, 2008
- Following with interest multiple additional proposals
Critical Path Initiative – epiphany #1

- Biomarkers for diagnostic use
- Biomarkers for drug development
- If diagnostic drives drug treatment than the drug becomes hostage to the diagnostic and FDA cares
Predictive Marker

- Simon and Wang, 2006
- Pennello and Vishnuvajjala, 2005
- Sargent et al, 2005
- Pustzai and Hess, 2004
## Predictive Marker

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Positive Test</th>
<th>Negative Test</th>
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<tbody>
<tr>
<td><strong>Therapy</strong></td>
<td>A (response)</td>
<td>B (non-response)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>E (response)</td>
<td>F (non-response)</td>
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IVD Life Cycle – epiphany #2

- Analytical Validity
- Clinical Validity
- Labeling
- Transparency
- Third party payers
- Users
Good Science

- Dual mission to protect and promote public health
- Valuable role in translational process of new diagnostic tests – [www.fda.gov/cdrh/oivd](http://www.fda.gov/cdrh/oivd)
- Not last stop on the train
- Science not regulation
Dover Beach -- Arnold

...Let us be true
To one another! for the world, which seems
To lie before us like a land of dreams,
So various, so beautiful, so new,
Hath really neither joy, nor love, nor light,
Nor certitude, nor peace, nor help for pain;
And we are here as on a darkling plain
Swept with confused alarms of struggle and flight,
Where ignorant armies clash by night.