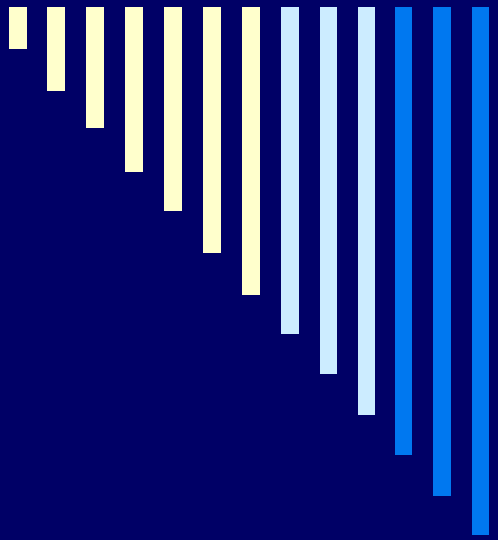

FDA Regulation of Genetic Tests

Steven Gutman, M.D.

Office of In Vitro Diagnostics

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

Analyte Specific Reagents

- 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

- Wang, O'Neill, Hung, 2007
- Simon and Wang, 2006
- Pennello and Vishnuvajjala, 2005
- Sargent et al, 2005
- Pustzai and Hess, 2004

Predictive Marker

	Positive Test		Negative Test	
Therapy	A (response)	B (non-response)	C (response)	D (non-response)
Placebo	E (response)	F (non-response)	G (response)	H (non-response)

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
- 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.