

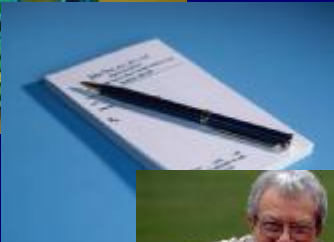
FDA Regulatory Hurdles: What is the Status Quo?

Institute of Medicine
Policy Issues in the Development of
Personalized Medicine in Oncology
Washington, June 8th -9th, 2009

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Office of *In Vitro* Diagnostic Devices
FDA

Personalized Medicine

The Right Dose of
The Right Therapy for
The Right Indication for
The Right Patient at
The Right Time.



Common Regulatory Themes

- Gaps in oversight (Task Force on Genetic Testing)
- Clinical validity (SACGT)
- Clinical utility (SACGHS)

(Cost issues – pay for performance, cost effectiveness, comparative effectiveness)

Medical Device Amendments of 1976

General Controls

- Register and list
- Follow good manufacturing practices
- Report device failures
- Inventory of tests on the market
- System for remedying device failures

Risk-Based Regulation

- Class I: common, low risk devices
 - s Most exempt from premarket submission
- Class II: more complex, higher risk
 - s Special controls
 - s Most require Premarket Notification [510(k)]
- Class III: most complex, highest risk
 - s All require Premarket Application [PMA]
 - s Require an inspection before approval

FDA Review

- Technology a factor but not determinative
- Intended use and indications for use
- Different administrative packages
- Same core – science

Elements of Review

- Analytical performance
 - Correctly detects analyte
- Clinical validity
 - Correctly identifies disease/condition
- Labeling

Analytical Performance

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

Clinical Validity

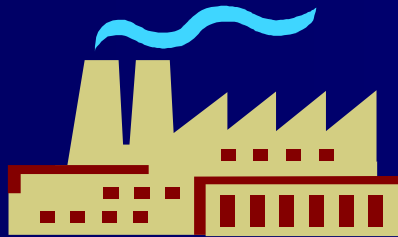
- Yardstick of truth – can signals can be turned in to clinical action
- Clinical sensitivity
- Clinical specificity
- Predictive values

Regulatory Flexibility

- Process is Malleable
- Review experience – focused claims
- Transparency – web posting of review templates
- Guidances

IVDs – Dual Regulatory Paths

MDTs



Distributed “Test kits” must undergo FDA review prior to marketing while lab developed tests enter the market without review



LDTs



CLIA, State, and local

Laboratory Developed Tests

- Wide variety of tests
- Common practice in laboratories
- Medical devices
- FDA enforcement discretion
- Recognition of CLIA's role

IVDs – Two Regulatory Paths

	CLIA	FDA
Research Phase	No	Yes
Analytical validation	Post hoc sampling	Yes
Clinical validation	No	Yes
Report Adverse Events	No requirement; no system	Yes
Transparent Results	No public information	Published review summary

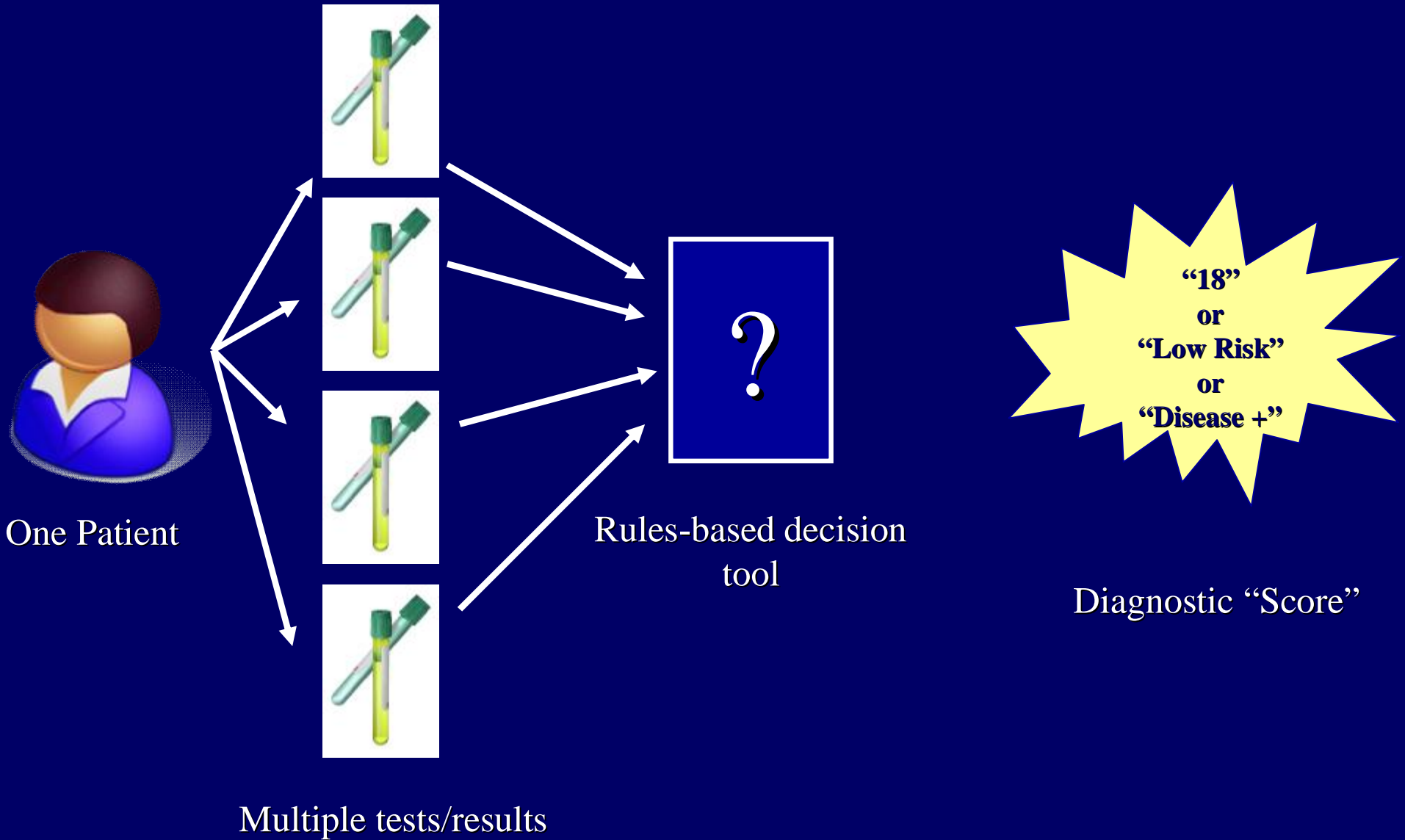
FDA Initiative: ASRs

- ASR rule – 1997
- Intent was not a safe harbor
- Misunderstanding (inadvertent or deliberate) of spirit and letter of law
- “Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions” (Sept 2007)

FDA Initiative: IVDMIAAs

- In Vitro Diagnostic Multivariate Index Assay – integrative interpretative diagnostic model first identified in 2004

IVDMIA_s



IVDMIA Validation

- Training Set(s)
 - Develop classifier
 - Cross Validation
 - Lock down classifier
 - Independent Validation
- Confirmatory studies w/Protocols

FDA Initiative: IVDMIAAs

- Compliance letters
- Guidance
- Not viewed by FDA as new authority (dissentions noted) but clearly new application of authority

FDA Initiative: Co-Development

- White paper
- If predictive diagnostic determines drug choice/dose, safety and effectiveness of drug becomes hostage to diagnostic

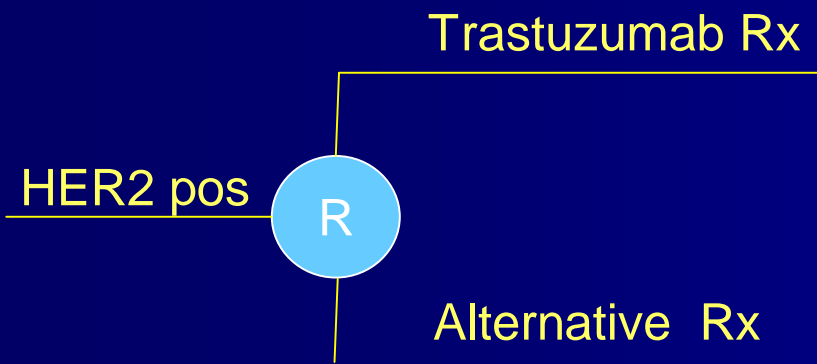
Co-Development – Good News

- Collaborative models in FDA (HER2/neu the best)
- Parallel reviews
- Parallel panel meetings
- Cross labeling in real time

Challenges

- Life cycle of drug vs device
- IP issues
- IVD vs Pharma
- Regulatory Culture

Market Positive Drug Trial



- Effectiveness of the drug in the marker-positive population was assessed.
- No information about dependence of drug's effectiveness on test result.

What Was Learned About the Test?

- $PPV = A/(A+B)$
- $NPV = ??/??$
- $Sens = A/(A+??)$
- $Spec = ??/(??+B)$

	Drug Response	No Drug Response
Test Positive	A	B
Test Negative	??	??

FDA Initiatives

- Hold laboratories accountable for models that do not fit LTD – example OvaSure
- Companion Diagnostics
- RUO

Regulation of Laboratory Developed Test

- Industry - Parity between IVDs and LDTs
- Consumer advocates - more comprehensive regulatory assurances
- Commercial Laboratories – predictability
- Congress concerned with issues
 - Kennedy, Obama bills
 - GAO DTC testing report

Regulation of Laboratory Developed Test

- WLF petition under review
- Genentech Petition under review
 - Several comments con and pro
- Problem is clear
- No easy answers

Common Regulatory Concerns

- Workload
- Iterative development
- Chilling of new technology

Common Regulatory Concerns

- Conflicts between CLIA/QSRs
- Appropriate review thresholds
- Off label use
- Public health

Disparate Solutions

- 21st Personalized Medicine Coalition – registry with comment
- ACLA – registry with CMS/FDA collaborative regulation
- AdvaMed – regulation based on risk not business model

Disparate Solutions

- Caveat: No free lunch – to do this right (whoever gets short straw has a day job)

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RAND Health Study (2003)

- Incorrect use of lab tests
- Theophylline – 62%
- Potassium – 22%
- FOBT – 72%
- HBA1C – 42%
- Lipid tests – 42%