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

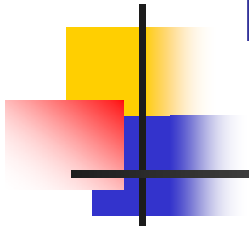
Analytical Performance

- Accuracy
- Precision
- Analytical specificity
- Analytical sensitivity

Clinical Performance

- Signals can be turned in to clinical action
- Diagnostic sensitivity
- Diagnostic specificity
- Predictive value or positive or negative results

Labeling -- 809.10(b)



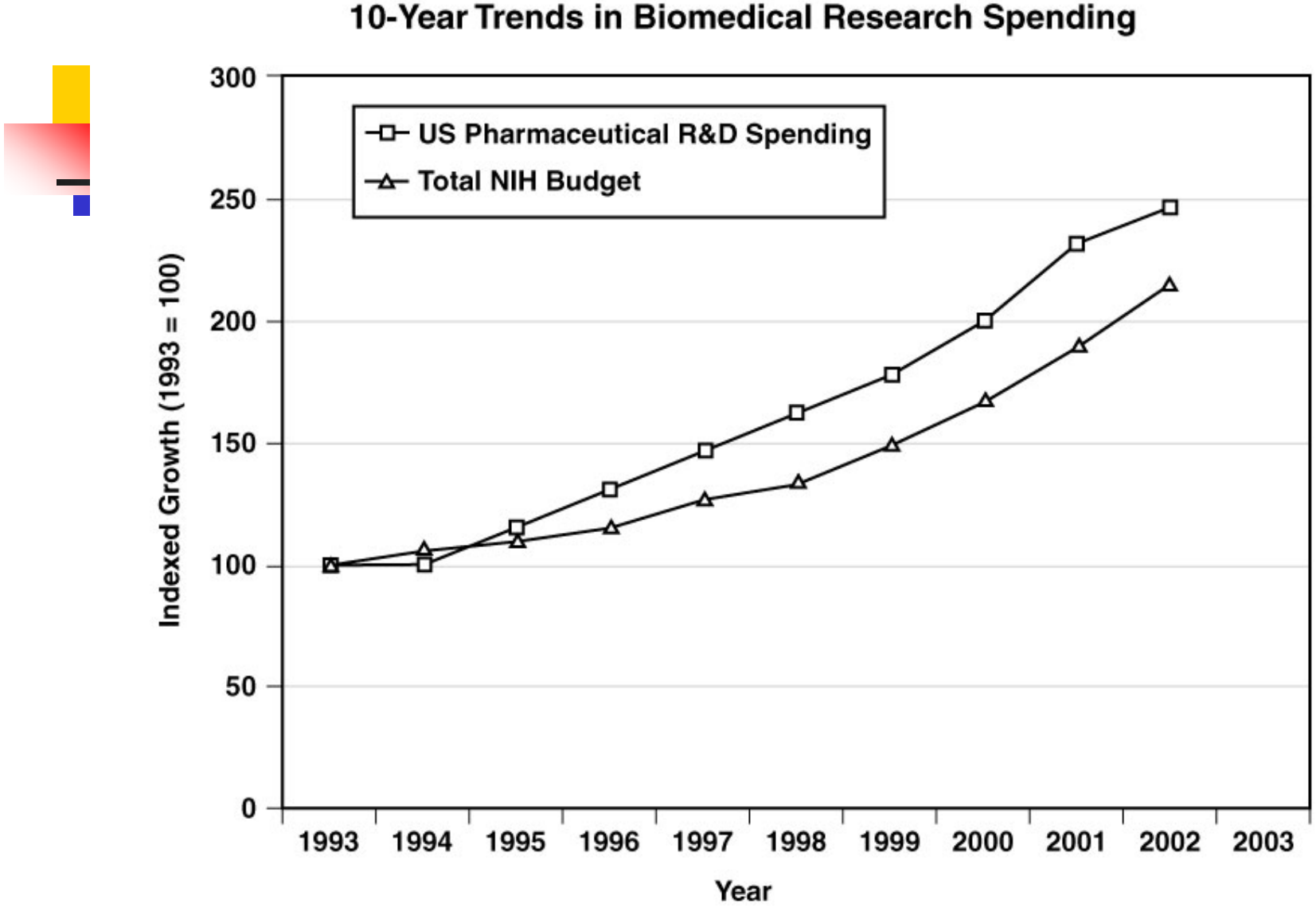
- Intended use
- Performance characteristics
- Limitations

Life Cycle

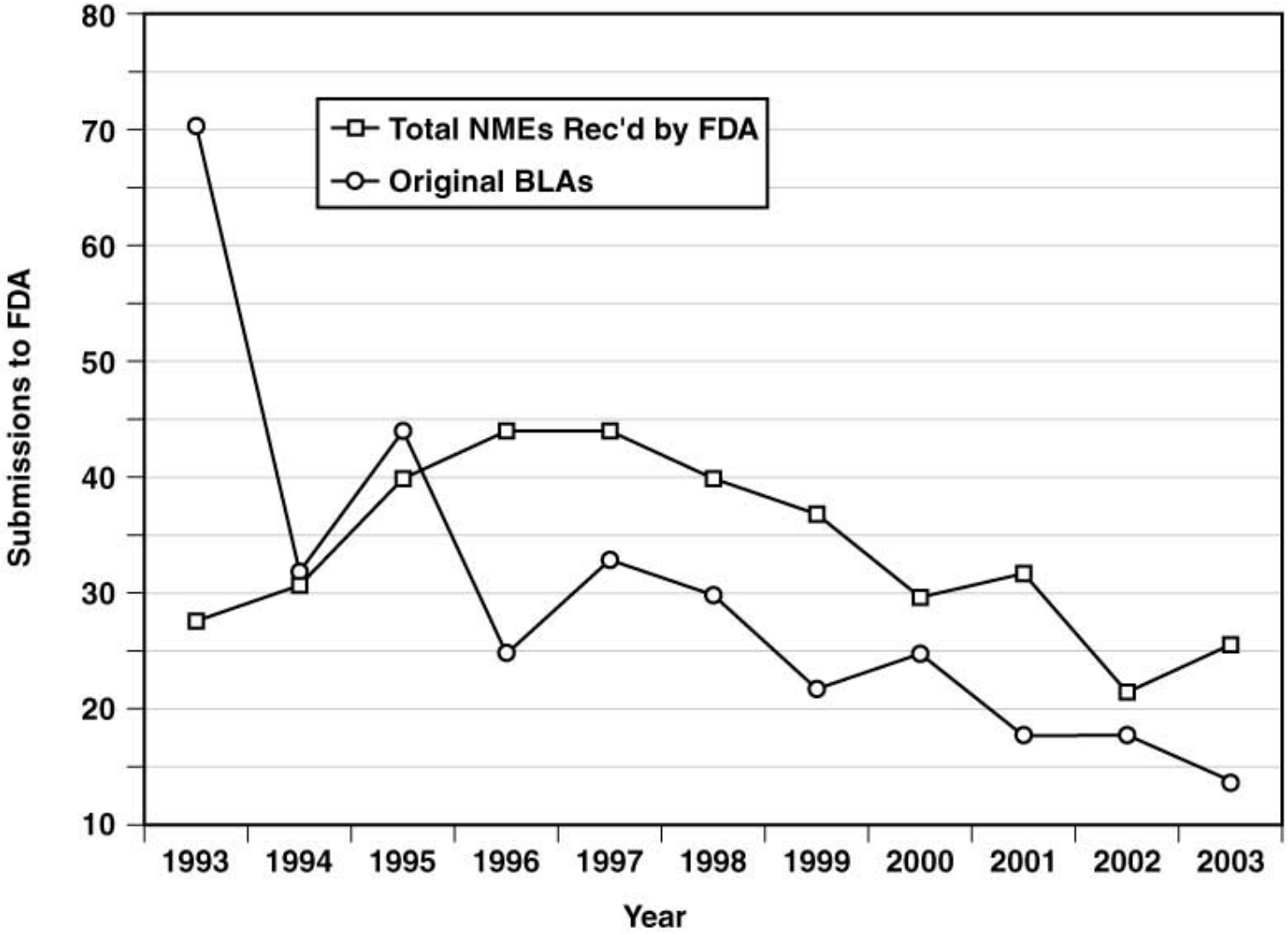
- Analytical performance
- Feasibility *
- Clinical performance
- FDA approval – market access
- ----------
- Real world use

The Real World of Regulation

- FDA
- CMS (CLIA)
- CMS and others (third party pay)


10-Year Trends in Biomedical Research Spending
US Pharmaceutical R&D Spending
Total NIH Budget
Indexed Growth (1993 = 100)
300
250
200
150
100
50
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Year

10-Year Trends in Major Drug and Biological Product 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

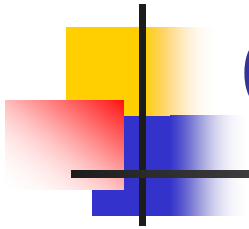
	Positive test	Positive test	Neg test	Neg test
Therapy	A (response)	B (non-response)	C (response)	D (non-response)
Placebo	E (response)	F (non-response)	G (response)	H (non-response)

Predictive Marker

	Positive test	Positive test		
Therapy	A (response)	B (non-response)		
Placebo	E (response)	F (non-response)		

FDA Mission

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



Good Science