

Understanding How the Critical Path Initiative (CPI) Will Impact Phase I Trials

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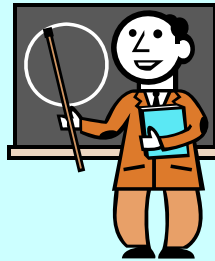
IIR 7th Annual Phase I Clinical Trials Conference
Las Vegas
October 11-13

Agenda

- The Why of CPI!



- What is CPI?



- Where are We Now?



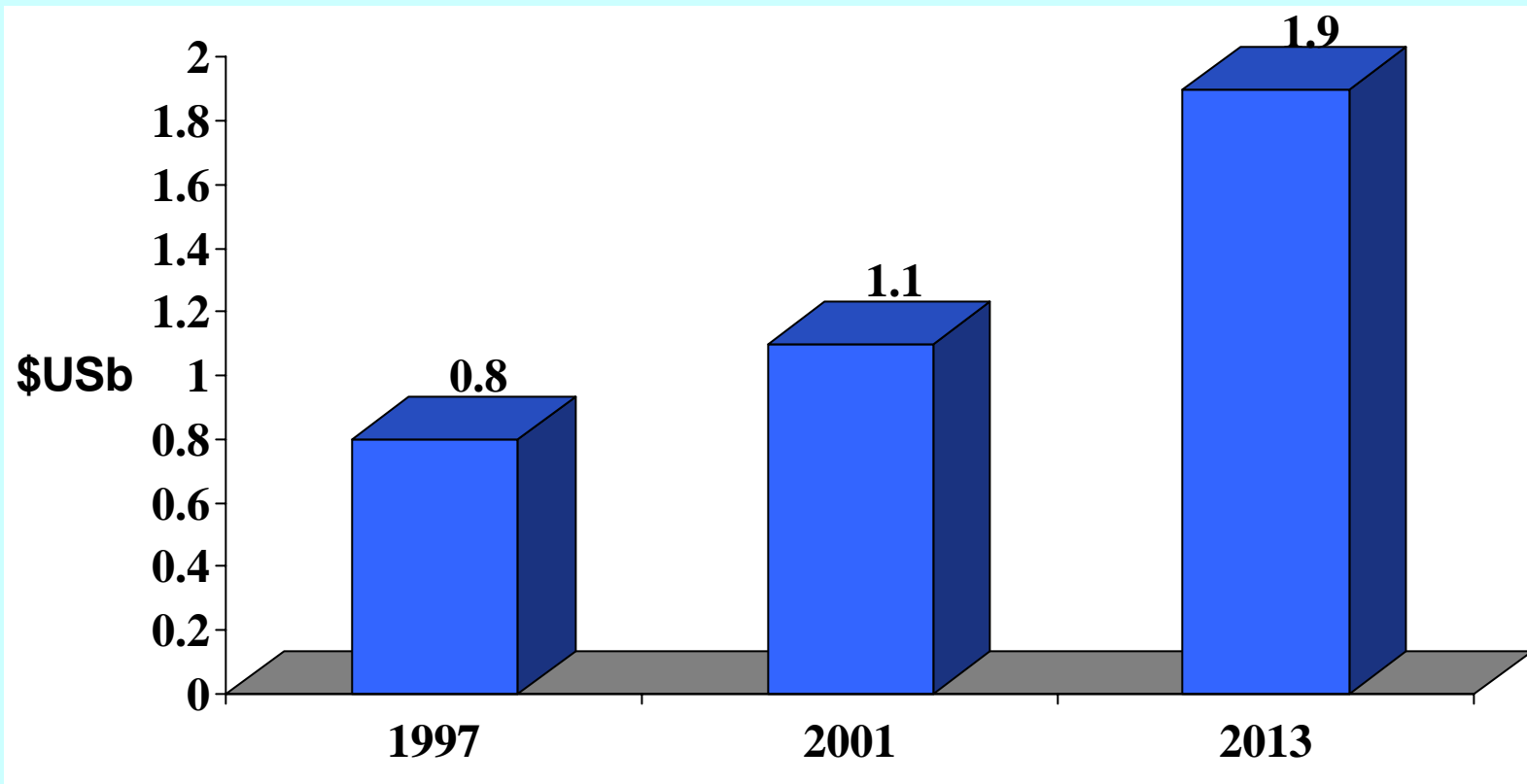
- Where are We Going and When?



The Why of CPI!



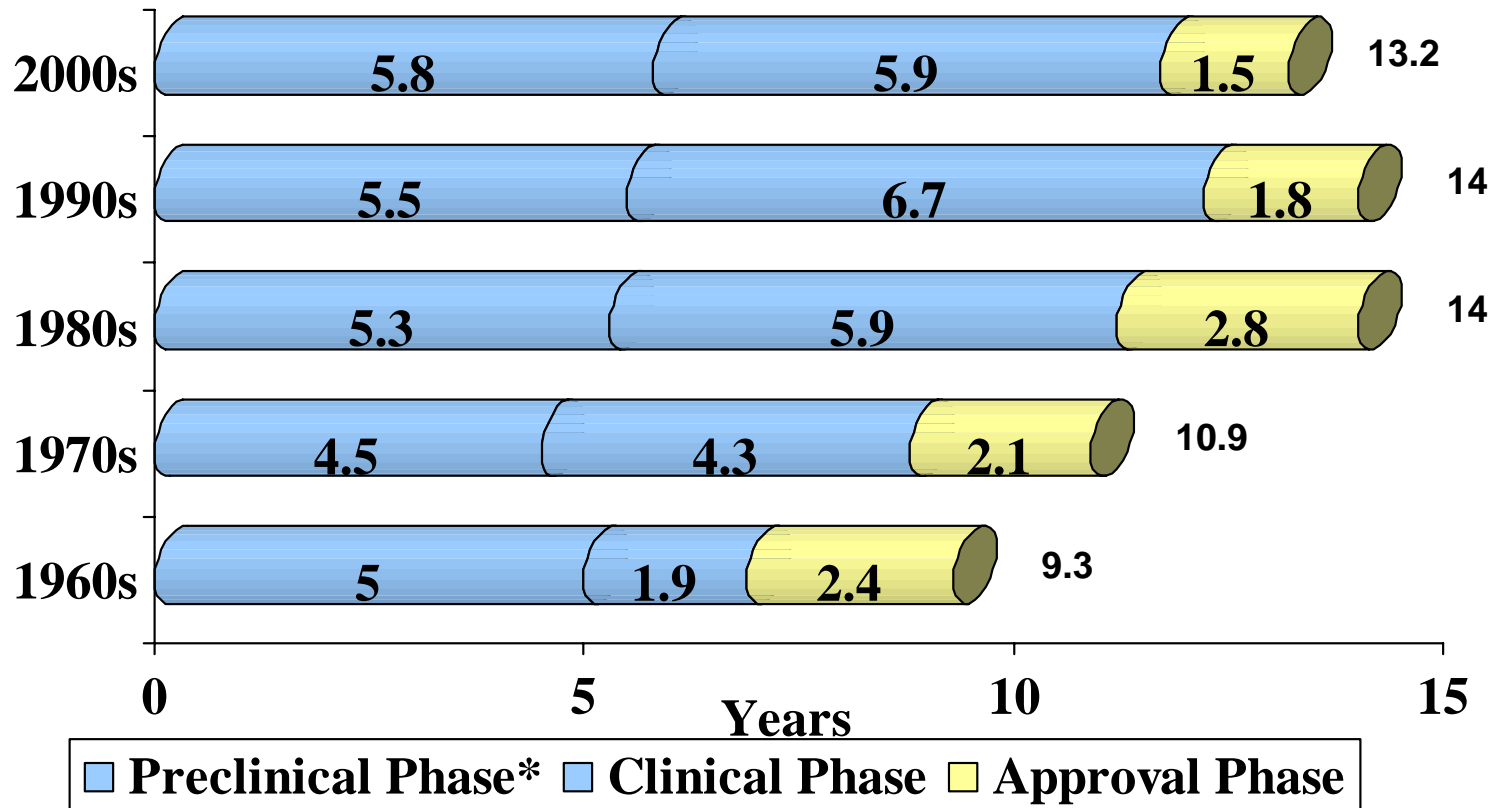
Basic Challenges Remain: Cost of New Drug Development



Source: DiMasi et al, Journal of Health Economics, 2003 March

New Drug Development Times in US Spanning Five Decades

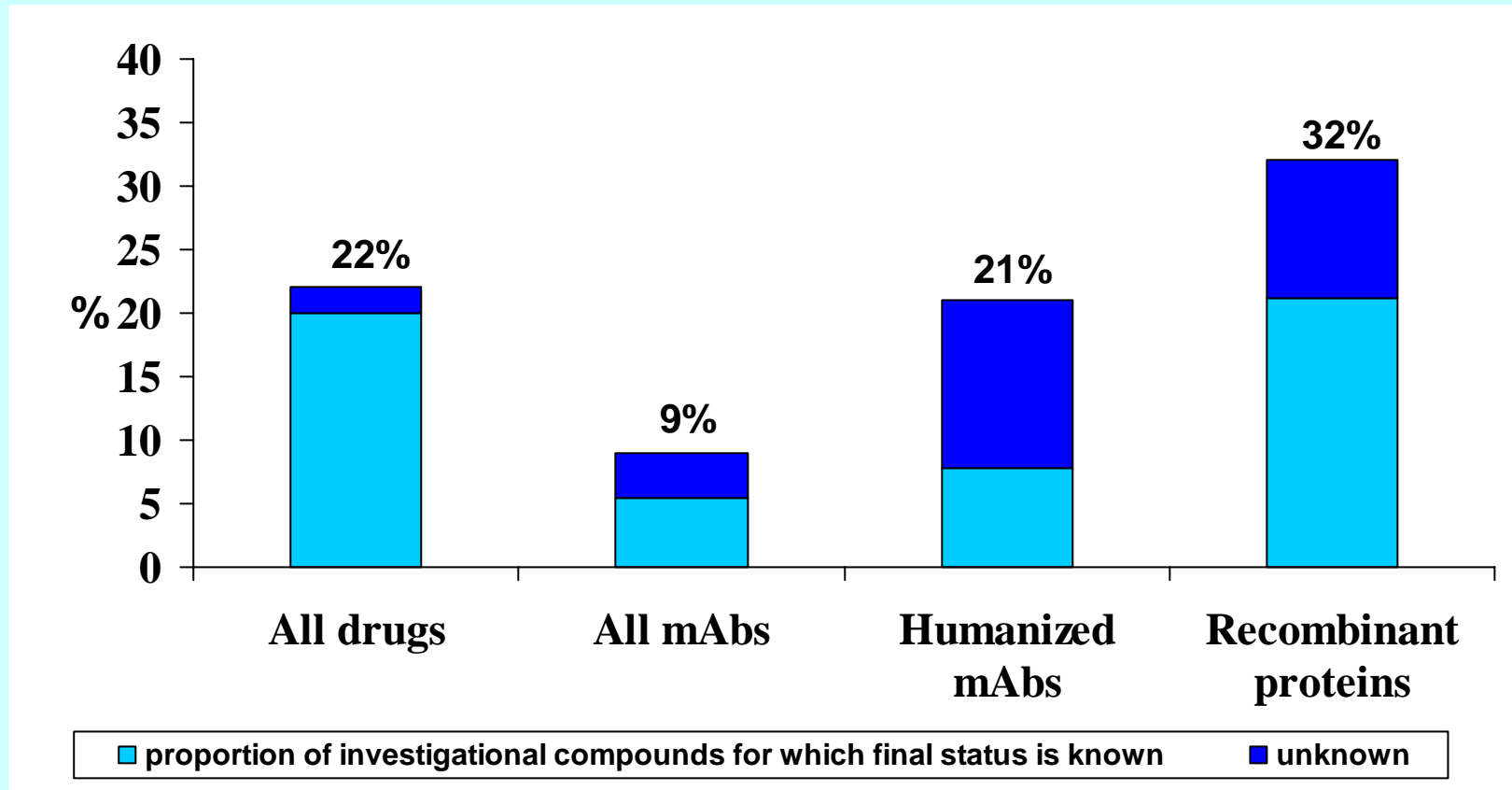
1963-2005



*Preclinical phase=synthesis to IND filing

Source: Tufts CSDD, 2005

US Success Rates for “New” Drugs & Biologicals



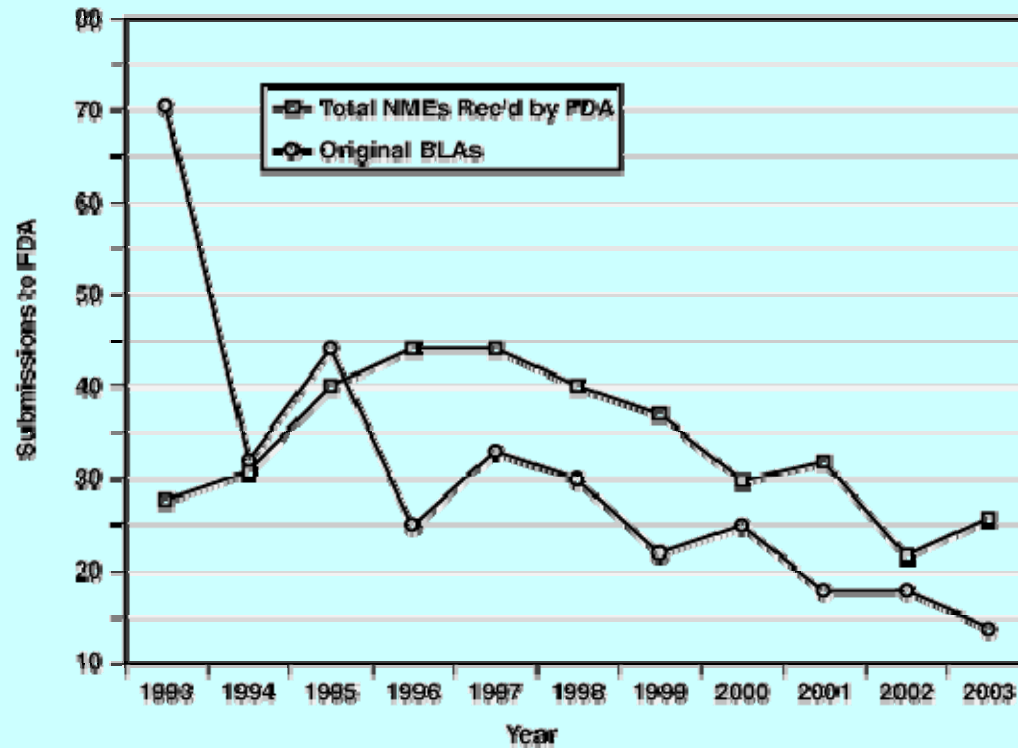
Source: Tufts CSDD, 2002

Ideal versus Real: What Do the Metrics Tell Us!

	\$100 million	\$200 million
Time reduction	18.9%	41.3%
Clinical success rate	25.2%-25.6%	30.4%-31.7%
Out-of-pocket preclinical cost reduction	29.8%	59.6%

FDA: Innovation or Stagnation

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA



The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

Productivity: Output

- There is clearly a dip or plateau in the new drugs pipeline
- Cause is multifactorial
 - Genomics & other new science not at full potential (10-15 yrs)
 - Mergers and other business arrangements have decreased candidates
 - Easy targets taken/chronic disease harder to study
 - Failure rate has not improved
 - Rapidly escalating costs & complexity decrease willingness/ability to bring many candidates forward into the clinic

**Source: FDA, 2004*

Productivity: Input

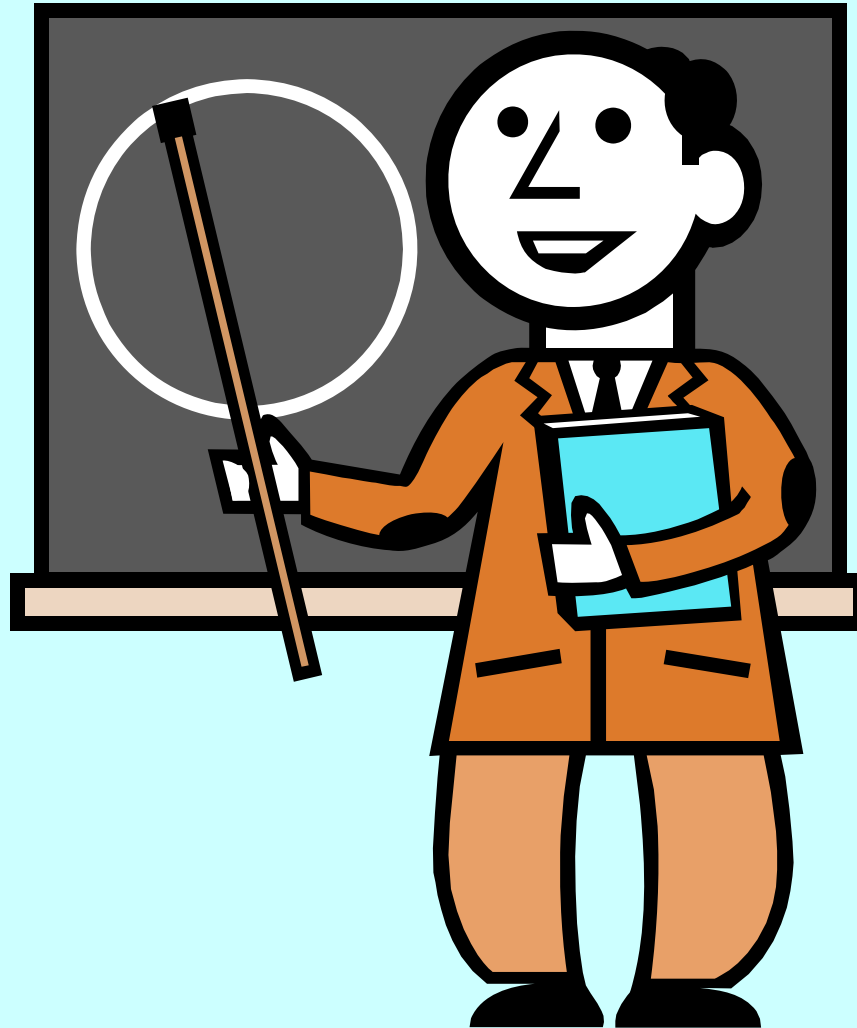
- Basic research- What's druggable
- Discovery- Validate targets + biomarkers
- Pre-clinical- Animal versus modeling
- Clinical- New trial design (e.g. Adaptive CTs, exploratory INDs, dosing, attrition)
- Manufacturing- Technology turnover
- Regulatory Review- Pre vs Post approval safety

Central “Critical Path” Thesis

- Societal investment in R&D to improve the drug development process – that is inextricably intertwined with FDA standards – has been lacking
- Huge public & private basic research & specific product development investment
- Minor investment in development tools & public standards
 - Academia not funded
 - Not conceptualized as FDA’s role
 - Efforts in private sector not generalizable or are proprietary

**Source: FDA, 2004*

What is CPI?

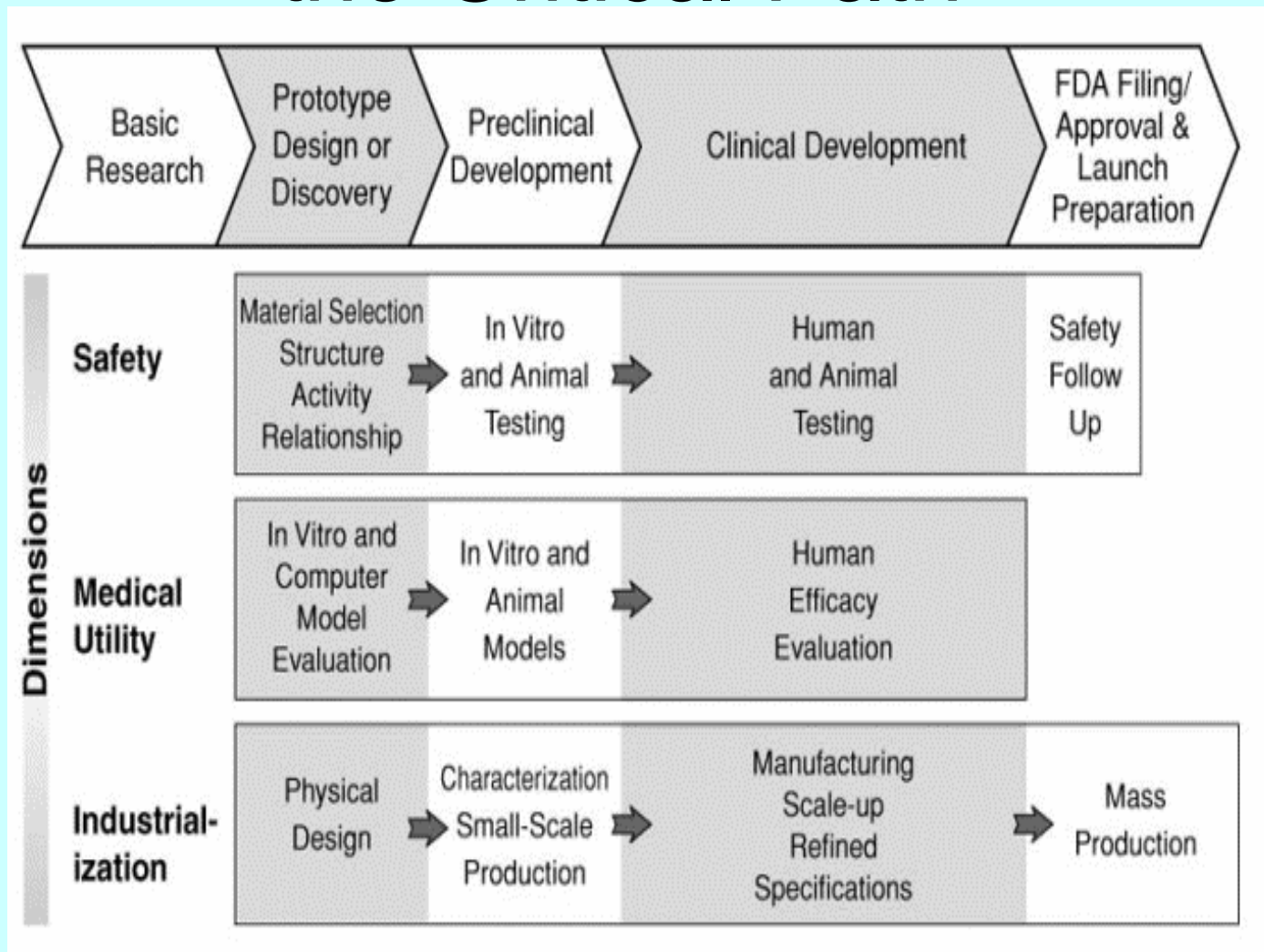


Three Dimensions of the Critical Path

- Assessment of Safety – how to predict if a potential product will be harmful?
- Proof of Efficacy – how to determine if a potential product will have medical benefit?
- Industrialization – how to manufacture a product at commercial scale with consistently high quality?

**Source: FDA, 2004*

Working in Three Dimensions on the Critical Path



**Source: FDA, 2004*

FDA and the Critical Path

- Applied science not keeping pace with discovery
- Translational medicine
- Biomarkers are key; PGx is next
- Design and conduct of clinical trials

Bench to Bedside

- The feedback loop
- The bridge
- FDA's "super office" of translational science

FDA and Biomarkers

- Common for internal use, uncommon to have validated ones
- Agency assessing endpoints already in use.
- Priorities include: proteomics, imaging, immune response, liver toxicity, and QT prolongation

FDA: PGx is Now

- Move from population-based model to targeted approach
- Voluntary Genomic Data Submission program encourages sponsor to submit PGx data if not regulatory
- Agency wants to expand science base, instill public confidence, and improve regulatory decision-making

Exploratory INDs

- Address cost, time, and attrition rate challenges with “early into man” guidance
- Lessen amount of data required before phase 1 and better characterize compounds to narrow down the number brought forward
- One approach involved microdosing volunteers with pharmacologically inactive doses to assess PK and do imaging

Where are We Now?



Critical Path Opportunities List

March 2006

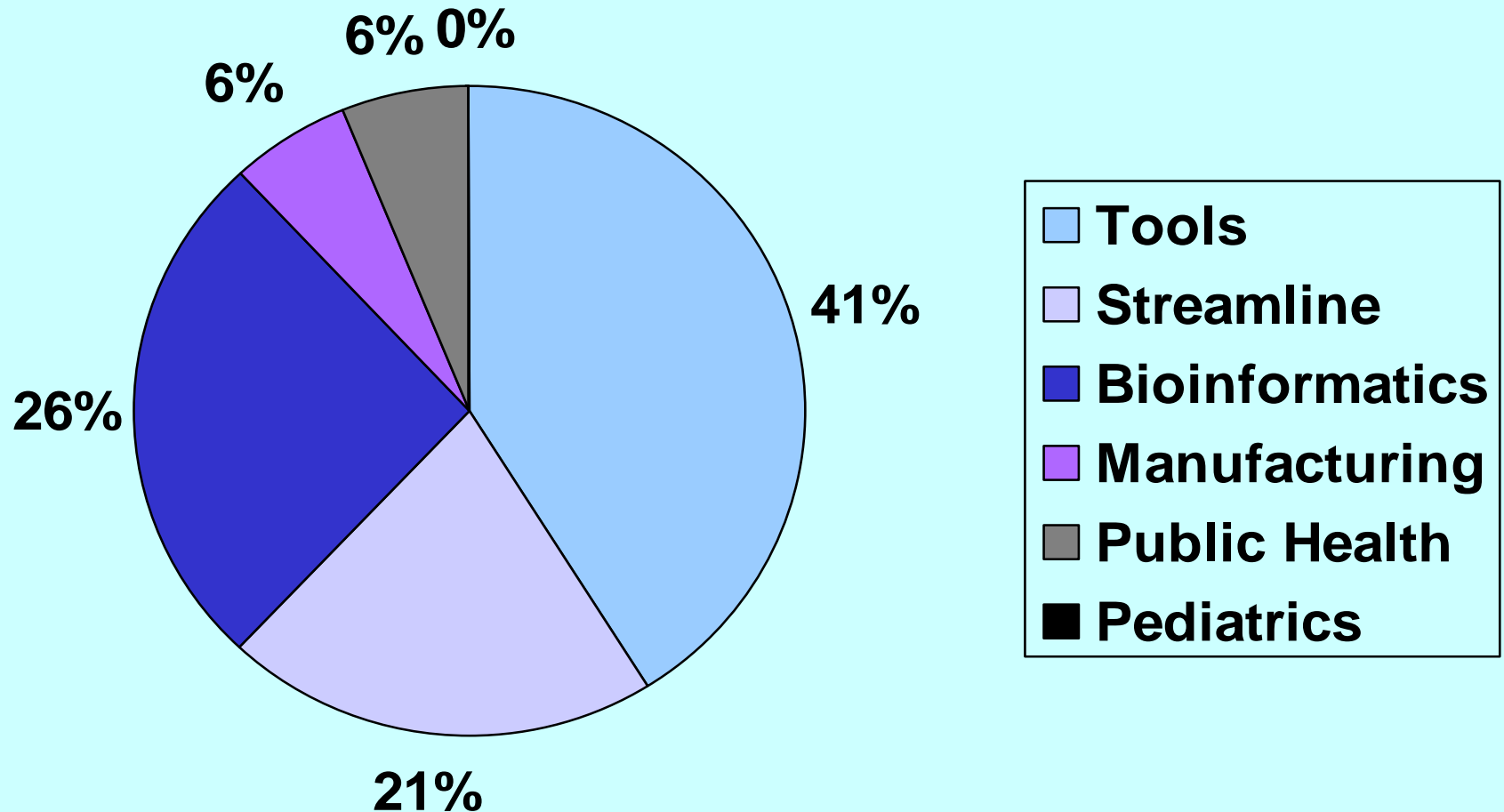
- Topic 1: Better Evaluation Tools
 - Developing new biomarkers and disease models to improve clinical trials and medical therapy*
- Topic 2: Streamlining Clinical Trials
 - Creating innovative and efficient clinical trials and improved clinical endpoints*
- Topic 3: Harnessing Bioinformatics
 - Data pooling and simulation models*

Critical Path Opportunities List

March 2006

- Topic 4: Moving Manufacturing into the 21st Century
 - Manufacturing, scale-up, and quality management*
- Topic 5: Developing Products to Address Urgent Public Health Needs
- Topic 6: Specific At-Risk Populations: Pediatrics
 - Unlocking innovation in pediatric populations*

Meeting the Opportunities List



*34 projects were initiated under the Critical Path Initiative between 2004-2006

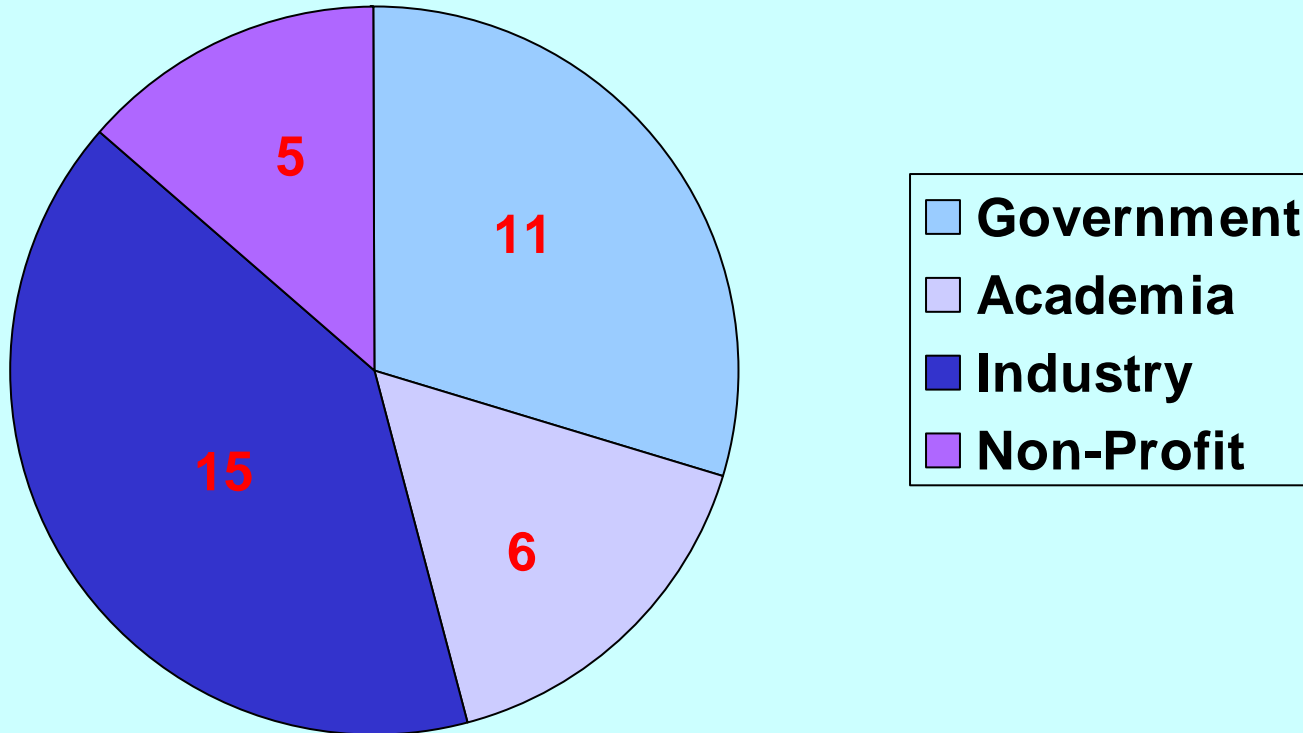
Opportunities List: Examples

- Better Evaluation Tools
 - 2005: *Liver Toxicology Biomarker Study, FDA & BG Medicine*
- Streamlining Clinical Trials
 - 2004: *Digital Mammography for Breast Cancer Screening, FDA, NCI & Industry*
- Harnessing Bioinformatics
 - 2005: *Orphan Disease Registry, C-Path & C-DISC*

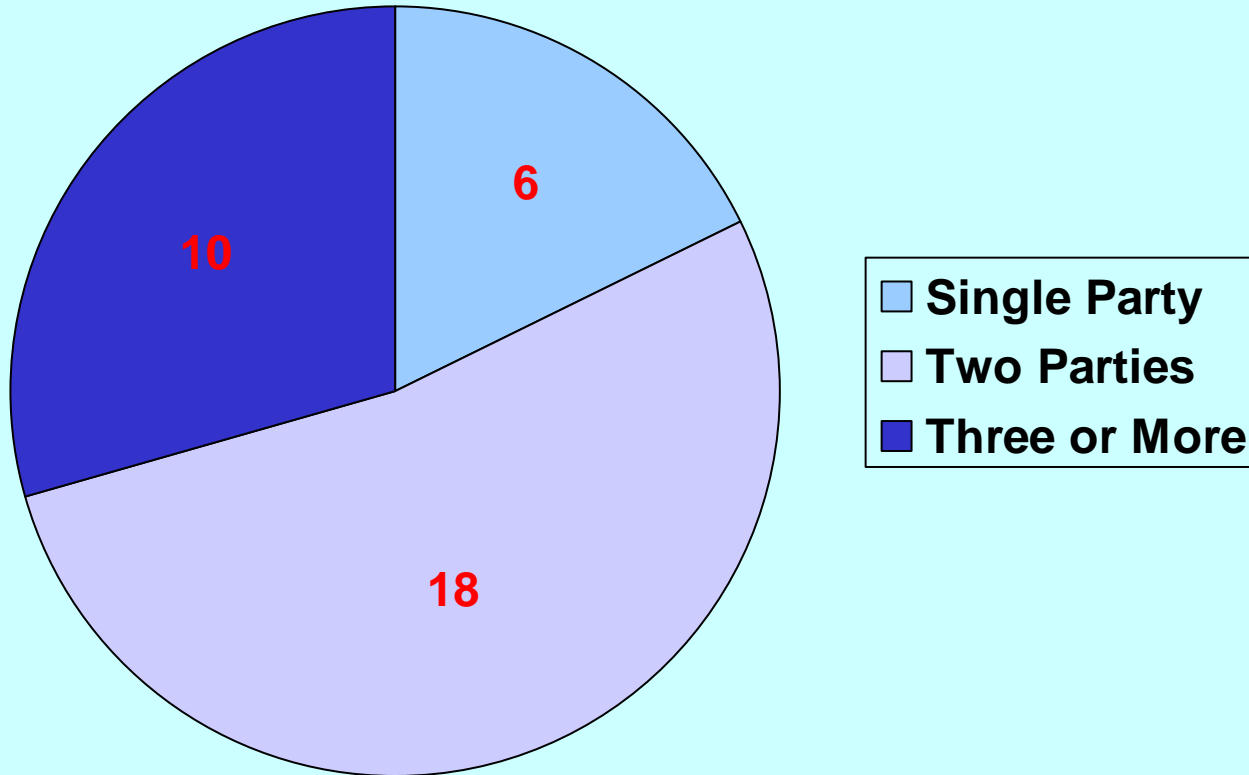
Opportunities List: Examples

- Moving Manufacturing into the 21st Century
 - 2004: *Vaccines for Meningococcal Disease in Africa, FDA, WHO & PATH*
- Developing Products to Address Urgent Public Health Needs
 - 2006: *Distinguishing Potential Hoax Materials from Bioterror Agents, FDA & Industry*
- Specific At-Risk Populations: Pediatrics
 - No CP projects initiated*

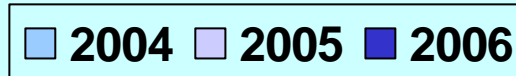
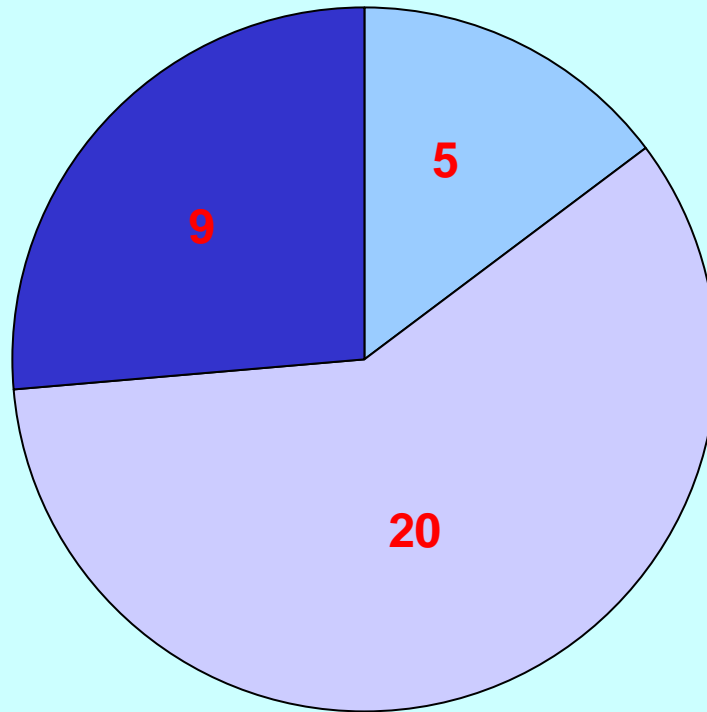
Who is Involved?



A Collaborative Effort



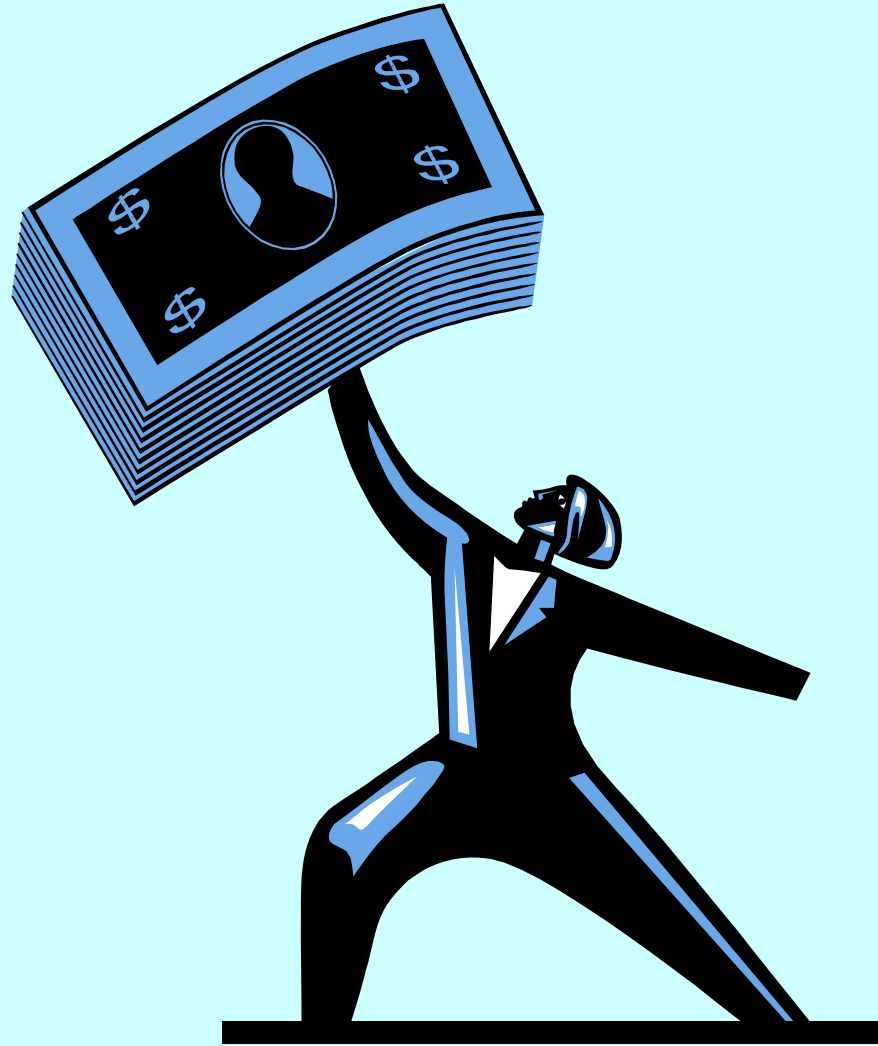
Project Initiation by Year



Where are We Going and When?



Show Me the Money!



FDA's Budget 2004-2006

	FY 2005 (estimate)	FY 2006* (enacted)	FY 2007 Increase
\$	-	\$0	\$5,940,000
FTE	-	-	6

“[One of the] Remaining Barriers [is that the] FDA does not have funding for the Critical Path [and there is] a lack of staffing for [these] projects.”

-Dr. Janet Woodcock, Acting Deputy Commissioner for FDA Operations

May 2005

**Table taken from the FDA website, 2006*

So, Who is Funding this Initiative?

- Private Sector
 - *Vaccines for Meningococcal Disease in Africa*
\$70 M from Bill & Melinda Gates
- Outside Agencies
 - *Digital Mammography for Breast Cancer Screening*
\$26.5 M from the NCI
- In-House Funding
 - *Cardiovascular Drug Safety & Biomarker Research Program (OBQI)*
\$675,000 from FDA

Phase I Facts & CPI Future

- PK accounts for 40% of exits from phase I
- 75% of cost of development spent on failure at early stages
- Rate at which new drugs entered clinical testing increased 52% from 1998-02 to 2003-05
- CPI provides tools that improve characterization of molecules entering phase I

FDA Facts & CPI Future

- Woodcock says validated biomarkers excluding patients at risk for AEs will be first target
- FDA needs funding, but also staff to set up projects and work with consortia
- Que vadis? Phase 0 and biological!
- Leavitt of the 1,000 days says personalized meds are his goal

CPI Milestones on the Road Less Traveled

