

Impact of FDA Regulation on Oncology Drug Research and Development

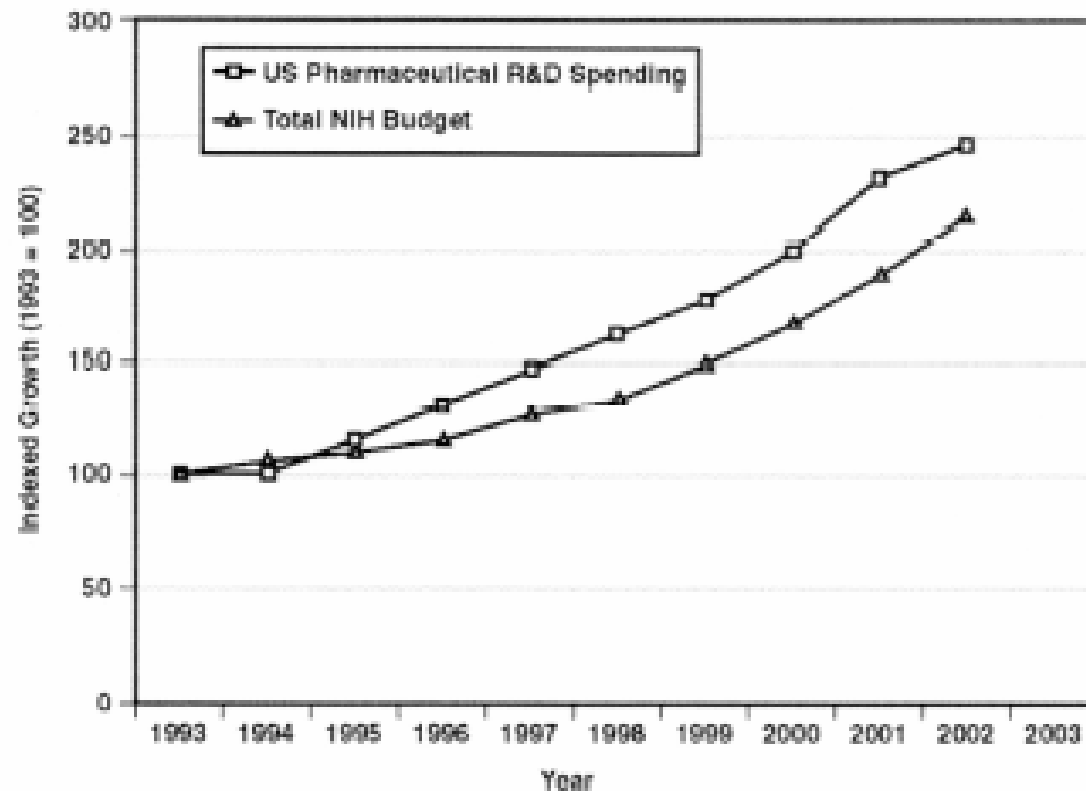
March 13, 2008

Cancer Statistics in the U.S.

- ▶ Estimated 559,650 deaths in 2007
- ▶ Most common cause of death for people <85 yrs.
- ▶ Mortality rates declining by 1% per year since 1990
 - Results skewed by breast, colorectal and prostate
- ▶ Cancer is many different diseases

Trends in Biomedical Research Spending

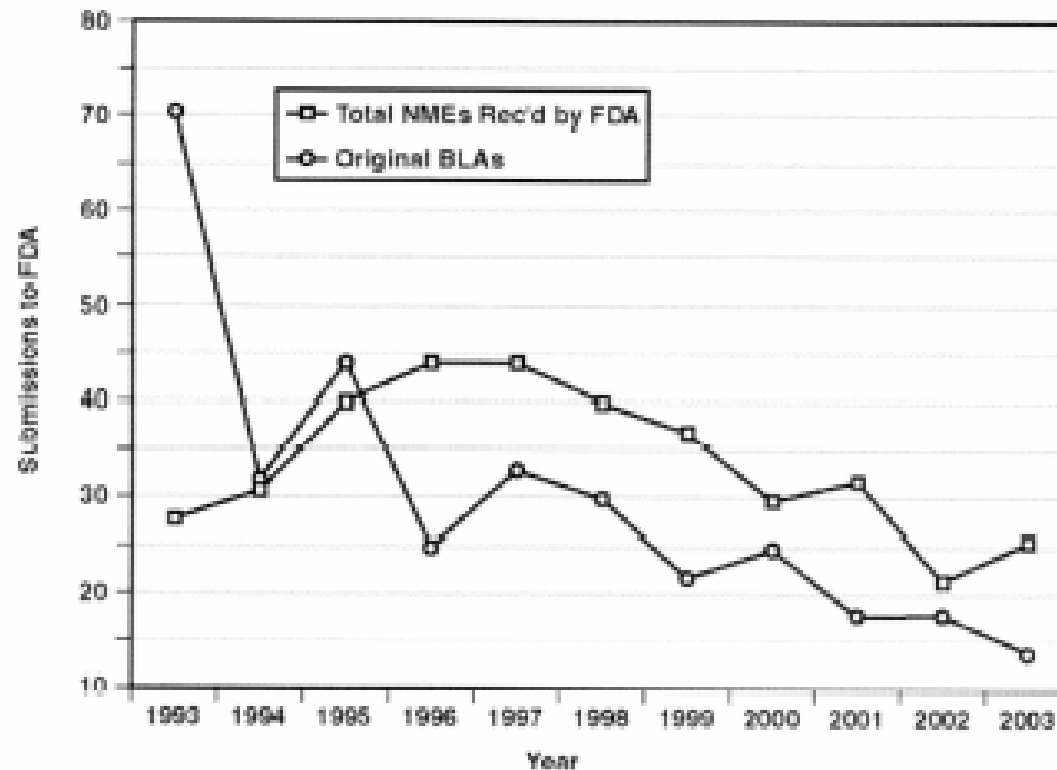
Figure 1: 10-Year Trends in Biomedical Research Spending



The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993-2003) and by pharmaceutical companies' research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2002/2003).

Trends in Major Drug and Biological Product Submissions to FDA

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.

Biomedical Funding for Clinical Research

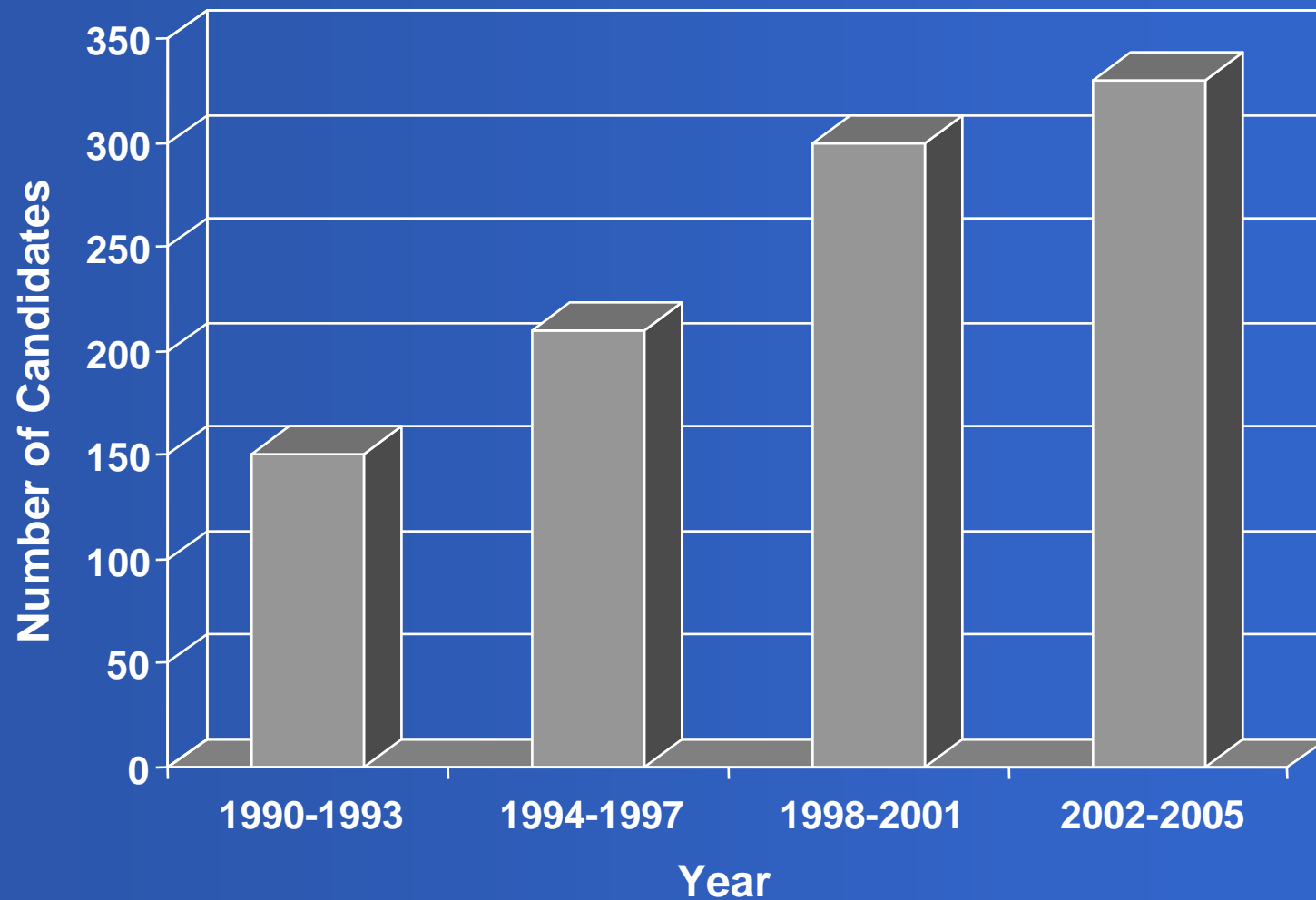
Category	Percent of Funding	
	1994	2003
Industry		
- Phase 1-3	28	41
- Phase 4	5	11
NIH	43	45

Moses et al. JAMA 2005; 294:1333-1342

Industry funding in '94, '03 was \$26.8 and \$54.1 billion

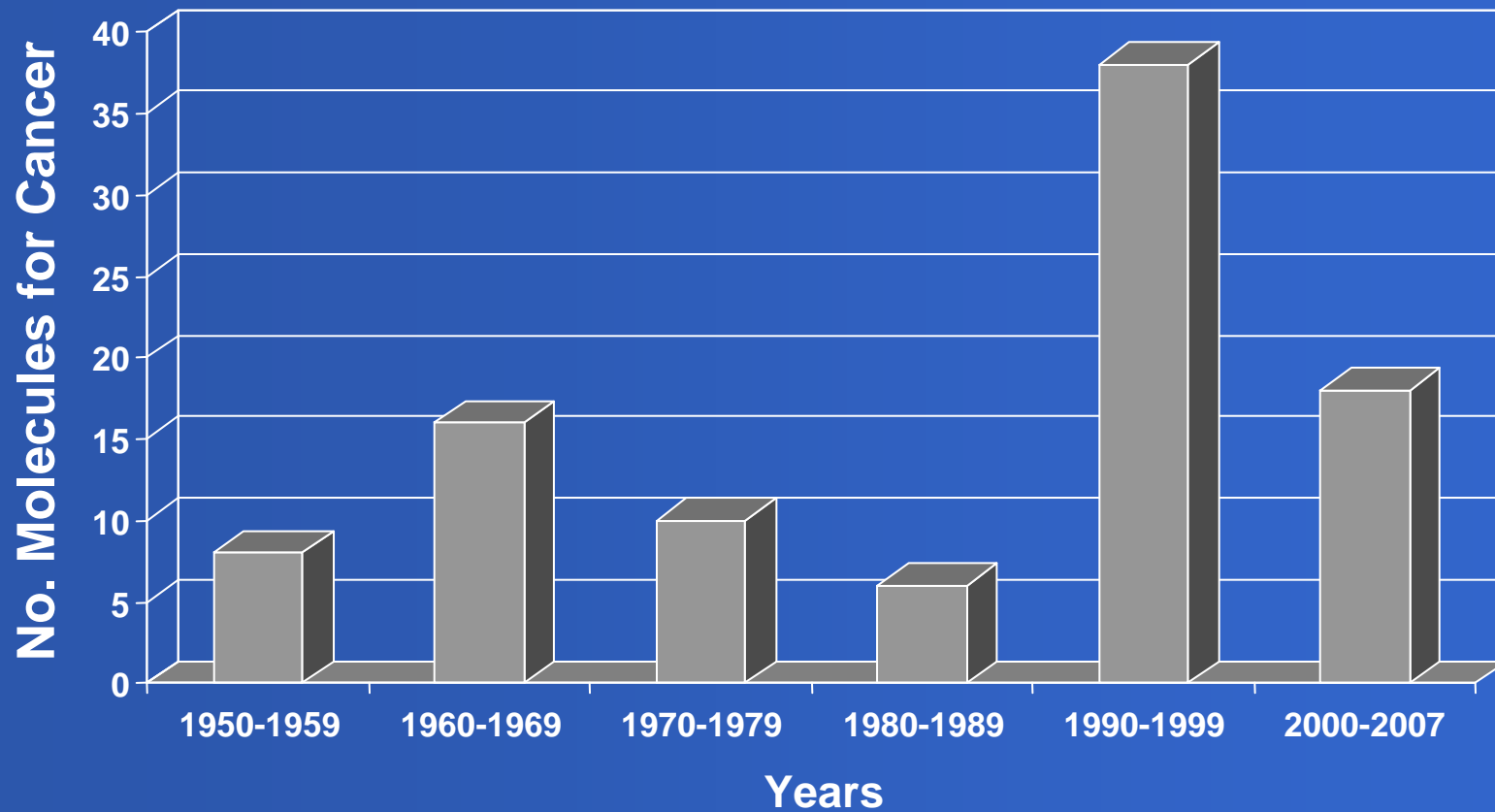
NIH funding in '94, '03 was \$13.4 and \$26.4 billion

New Cancer Therapeutics Entering Clinical Trials



Tufts CSDD, 9: Sept/Oct '07

Approved New Molecules for Cancer



Issues Facing Oncology Drug Development

- ▶ Oncology drugs are different
 - More often: priority/expedited, orphan
- ▶ Longer development time and expense
 - Median clinical trial time longer (7.8 yrs. vs. 6.3 yrs.)
 - Approval rate 8% vs. 20%
- ▶ Increased bureaucracy/regulation
 - Institutional Review Boards
 - Contracts office
 - FDA
- ▶ Offshoring due to slow accrual
 - 41% of FDA-regulated studies performed outside U.S.

Cost for New Drug Development

EXHIBIT 5
Probability Of Market Entry, Durations, And Costs For New Drugs, By Disorder And Primary Indication

Disorder	N	Entry probability (%)			Duration (months)			Cost (\$)
		Phase II	Phase III	Approval	Phase I	Phase II	Phase III	
Blood	163	60	57	25	18	32	33	906
Cardiovascular	280	69	42	22	14	35	30	887
Dermatological	122	84	44	29	13	29	24	677
Genitourinary	120	92	58	37	21	28	25	635
HIV/AIDS	108	75	50	36	19	23	19	540
Cancer	681	78	46	20	21	30	29	1,042
Musculoskeletal	134	73	41	22	19	39	30	946
Neurological	192	73	47	22	20	39	32	1,016
Antiparasitic	20	100	67	53	18	33	13	454
Respiratory	165	68	31	16	18	30	36	1,134
Sensory	53	88	60	40	11	44	30	648
Primary indication								
Alzheimer's disease	46	65	46	25	17	37	18	903
Rheumatoid arthritis	51	91	33	23	18	36	39	936
Asthma	74	81	36	26	18	33	31	740
Breast cancer	54	96	58	44	17	37	37	610
HIV/AIDS	89	83	56	44	22	22	19	479

SOURCE: Authors' calculations.

NOTES: Phases are for human clinical trials. New drug application (NDA) durations are as for the average drug. Cost is the total expected capitalized cost per new drug (in millions of 2000 dollars).

Adams et al. Health Aff 2006; 25:420

Institutional Review Boards

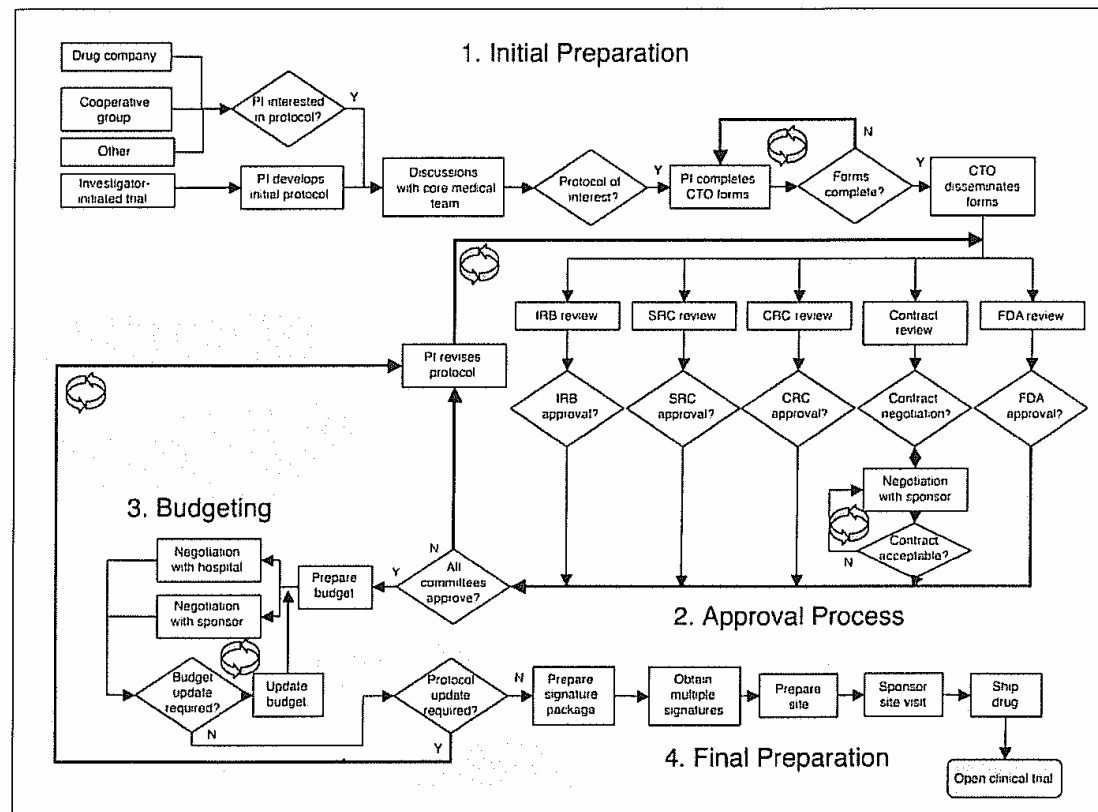


Fig 1. Level 0 process flow map for opening an oncology clinical trial. (As a result of printing restrictions, Figure 1 is a highly aggregated view of the process flow of opening a clinical trial. For a more comprehensive view, go to <http://www.cmrhc.org/ClinicalTrialsProcess/ProcessMap.pdf>.) PI, principal investigator; CTO, clinical trials office; IRB, institutional review board; SRC, scientific review committee; CRC, clinical research center; FDA, Food and Drug Administration; Y, yes; N, no.

Clinical Testing Ex-U.S.

Number of Investigators Completing 1572s to Participate in FDA-Regulated Clinical Studies in 2006: Top 13 Countries

(clinical investigators completing Form 1572s in 2006)

	Number of Investigators	% of Total
United States	13,629	59%
Canada	893	3.9%
France	600	2.6%
Germany	583	2.5%
Spain	576	2.5%
United Kingdom	462	2.0%
Russia	443	1.9%
Italy	389	1.7%
Argentina	358	1.6%
India	306	1.3%
Australia	287	1.2%
Poland	276	1.2%
South Africa	232	1.0%

*PAREXEL's Bio/Pharmaceutical R&D
Statistical Sourcebook 2007/2008; BMIS*

Regulatory System Hampering Oncology Drug Development and Stifling Innovation

- ▶ One size fits all
- ▶ Use of outdated endpoints and statistical methods
- ▶ Erosion of Accelerated Approval

One Size Fits All

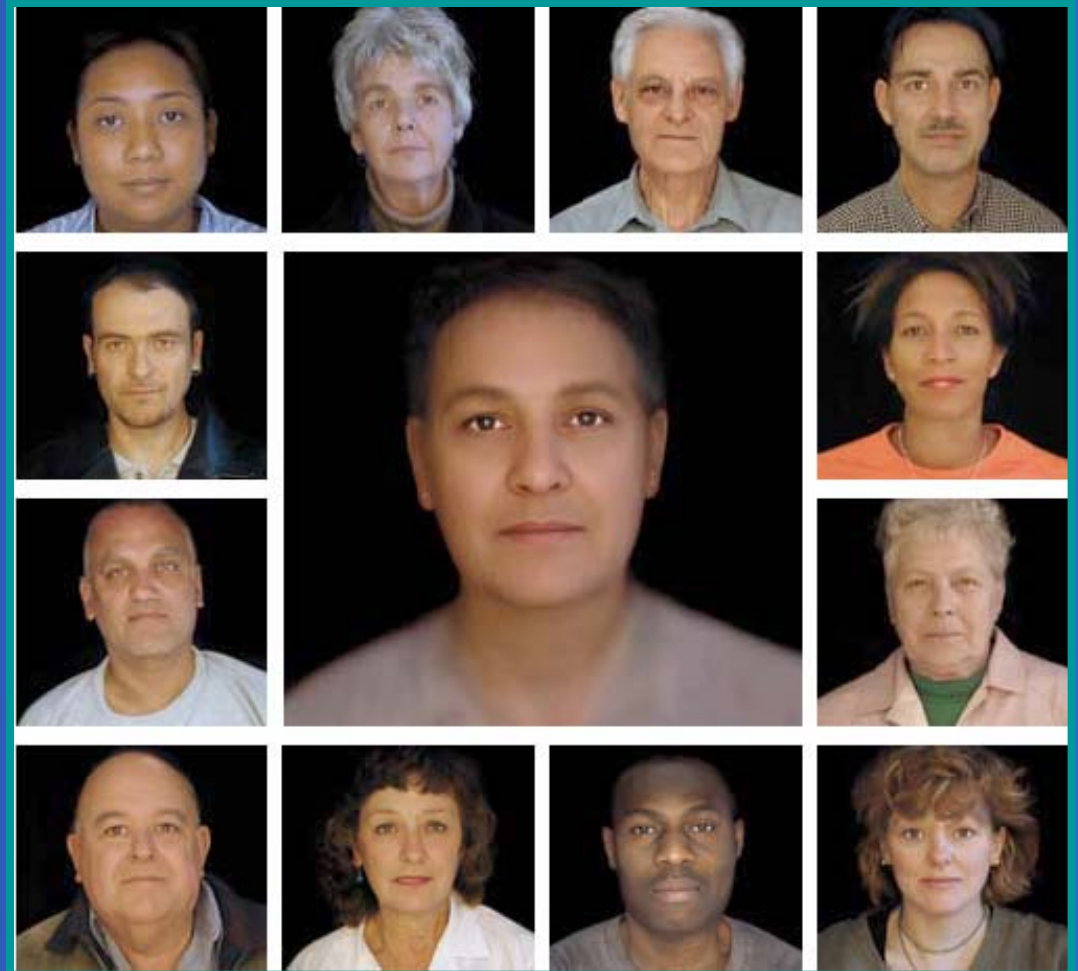
- ▶ Recent safety problems have made agency more risk-averse
- ▶ Demand more testing
 - Drug interactions
 - Effects on liver metabolism
 - Cardiac risk
 - More lengthy clinical trials
- ▶ Negative consequences
 - Stifle innovation in favor of “me-too” drugs
 - Abandon potentially useful drugs

Outdated Clinical Endpoints and Statistics

- ▶ Survival is often problematic
 - Cross-over
 - End-stage patients
 - Example: Avastin in breast cancer
- ▶ Many new drugs have unique mechanisms
 - Sorafenib (Nexavar)
 - Bevacizumab (Avastin)

Current Statistical Approaches Assess Average Effects

- ▶ Ignores baseline variables
- ▶ Misses subsets that benefit or are harmed



Kent et al. Amer Sci 2007; 95:60

Regression of Accelerated Approval

- ▶ 26 drugs for 30 indications approved between 1995-2005
- ▶ Only 2 drugs received AA in 3 years '05-'07
- ▶ Avastin for breast cancer 2008
- ▶ Now require confirmatory trial be completed

FDA Critical Path Initiative

- ▶ Slowdown in innovative medical products reaching patients
- ▶ Current development path is inefficient and costly
- ▶ Recent breakthroughs have not improved ability to identify successful drug candidates
- ▶ New “tool kit” required to increase efficiency
 - Assays, standards, computer modeling
 - Biomarkers
 - Clinical trial endpoints

Challenge and Opportunity on the Critical Path to New Medical Products. FDA Report March 2004

Subcommittee on Science and Technology Report

FDA's Science Infrastructure Failing

Bridget M. Kuehn

TWO DECADES OF INADEQUATE funding have rendered the Food and Drug Administration's (FDA's) scientific capacity insufficient to meet the growing demands of ensuring the public's health and safety, according to a report issued in December by an advisory group to the agency.

Advances in science, greater complexity in the products it regulates, and globalization of FDA-regulated industries are among the trends placing unprecedented demands on the FDA, yet resources for the agency's science infrastructure and staff have been stagnant, according to the 300-page report (http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf).

The report was published by a subcommittee of the FDA Science Board, which advises FDA Commissioner Andrew C. von Eschenbach, MD, and convened the subcommittee at his request. The report, which took 1 year to complete and drew on the expertise of 3 board members and 30 outside experts, was presented to and endorsed by the Science Board on December 3.

During the period between 1988 and 2007, the US Congress enacted more than 125 statutes related to the FDA's regulatory responsibilities. But due to inflation, the purchasing power of the agency's appropriations decreased by \$300 million during the same period and the agency's staff increased by only 9% (646 new staff positions), according to the report.

The subcommittee identified 3 key weaknesses in the FDA that have emerged as a result of such gross underinvestment: a weak scientific organizational structure, an insufficient science workforce, and outdated information technology systems. These vulnerabilities have left the agency unable to fulfill its duties, placing the public at risk from unsafe foods or medical products, according to the report. Examples of problems interfering with the agency conducting its duties include failure of the FDA's e-mail system during an investigation of an *Escherichia coli* outbreak and difficulties accessing valuable clinical trial data warehoused as paper copies.

"The world looks to the FDA as a leader—to integrate emerging understandings of biology with medicine, technology, and computational math-

ematics in ways that will lead to successful disease therapies," according to the report. "Today, not only can the Agency not lead, it cannot even keep up with the advances in science."

Correcting these deficiencies will require substantial new investment in the agency. The subcommittee estimates that each US individual currently pays about a penny and half each day for the FDA and at least double that would be reasonable, considering the importance of the services that the agency offers. Although the committee did not offer a total figure, this would amount to an annual appropriation of approximately \$3.2 billion per year based on the \$1.6 billion appropriated for the agency in 2007.

At a December 4 press conference sponsored by the Coalition for a Stronger FDA and FDA Alliance, 2 nonprofit organizations that lobby for greater funding for the agency, subcommittee members referred to these organizations for more specific FDA funding proposals. The Coalition for a Stronger FDA has advocated an annual increase of 15%, or \$225 million, in the agency's budget over several years, an amount the subcommittee concluded in its report would be insufficient. The FDA Alliance has proposed a \$2 billion annual budget

Conclusions

- ▶ Rational and flexible regulatory policy
 - Diseases are different
- ▶ New clinical trial methods
- ▶ Accelerated approval
- ▶ Concerted efforts from government, academia and industry
- ▶ Oncology an area to test new methods
- ▶ Provide incentives to innovate

Collaboration

