Innovation or Stagnation: Challenges for Clinical Development (The Critical Path Initiative)

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Tomorrow's Medical Breakthroughs

- **Many serious diseases afflict our populations and are waiting for quicker/more accurate diagnoses and better treatments:**
  - **autism, addictive disorders, Alzheimer's disease, HIV/AIDS, bipolar disorders, cancer, cystic fibrosis, heart diseases, diabetes, morbid obesity, multiple sclerosis, muscular dystrophy, rheumatoid arthritis, osteoarthritis, systemic lupus, schizophrenia, stroke, and many more**

Advances in Basic Sciences: Best yet to come?

- Genomics / Proteomics
- Nanotechnology
- Biomedical Info Technology

- More effective, more targeted, individualized medical therapy
  - Able to treat disease at a genetic level and able to treat patients at an individual level such that products need only be given to patients who have the highest probability to benefit and who will have the least probability of an adverse reaction

Figure 1: 10-Year Trends in Biomedical Research Spending

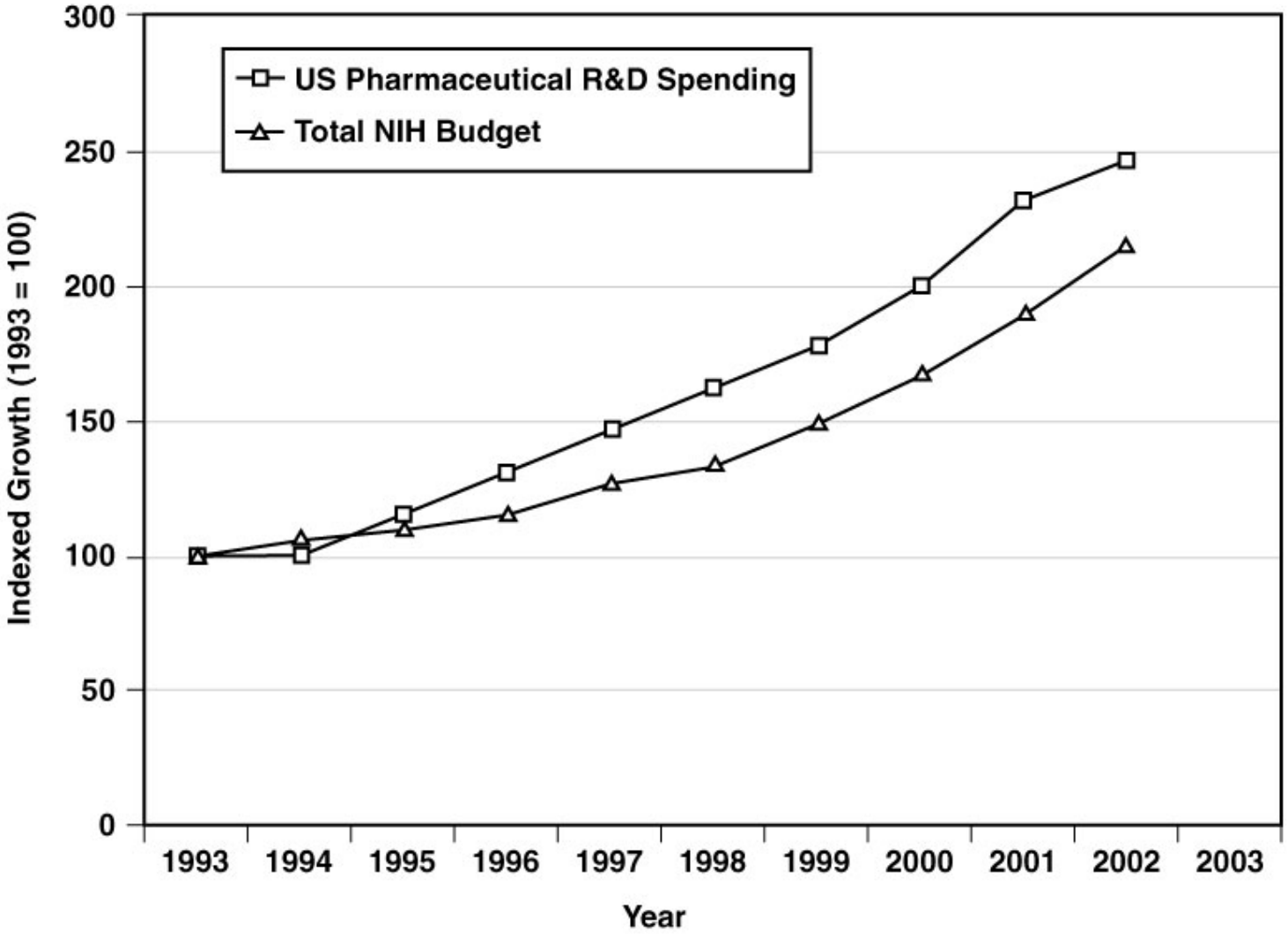
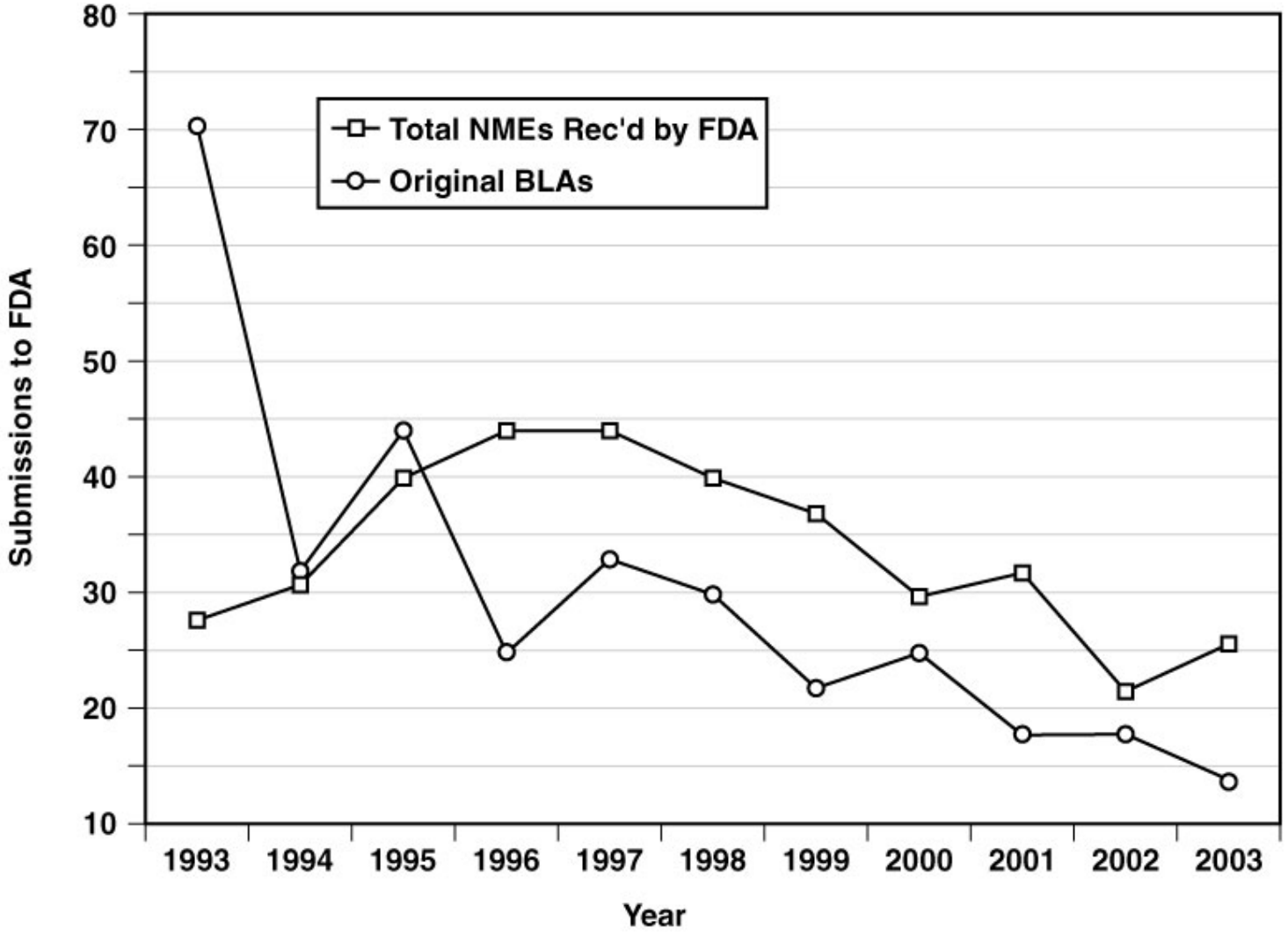
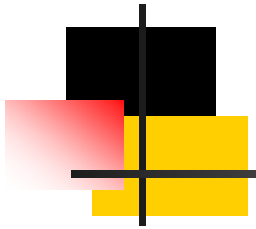


Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA





Begs the Question

- **Is the "innovator" industry really innovative any more?**

"Innovation" In the Eyes of the Stakeholder

- **Patient**
  - **If it cures ME, it's *innovative.***
- **Physician**
  - **If it offers ME a better or easier way to treat my patient, it's *innovative.***
- **Health Payer**
  - **If it offers ME a cheaper alternative, it's *innovative.***
- **Pharmaceutical Company**
  - **If it let's ME pay my shareholders a bigger return, it's *innovative.***

"Innovation" In the Eyes of a Critic

- **"The [pharmaceutical] industry's best-kept secret is that it's not very innovative at all. In 2002, the Food and Drug Administration approved 78 new drugs, of which only 7 were truly innovative – defined as containing new active ingredients and likely to be better than drugs already on the market to treat the same condition."**

  Marcia Angell, former editor *NEJM*

"Innovation" Drug Regulatory Authorities

- **EMEA – Definition of a Product for a "Fast Track" Review of Marketing Authorisation Application**

  - **Major interest in the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure (150 days)**

    [New legislation: 20 November 2005]

  - **1996 criteria set out for accelerated review: life-threatening or heavily disabling diseases and for compelling public health reasons**

    [used for HIV and cancer drugs primarily]

"Innovation" Drug Regulatory Authorities

- **FDA – Definition of a Product for "Priority" Review of Marketing Authorization Application**
  - **The drug product, if authorized, would be a significant improvement compared to marketed products. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination of substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.**

"Innovation" Drug Regulatory Authorities

	1999	2000	2001	2002	2003
Total MAA Submitted to FDA	127	134	104	105	113
MAA Given Priority Review	31 (24%)	33 (25%)	13 (13%)	15 (14%)	24 (21%)

Task of Innovation Harder

- **Heavy investment**
  - **Increasingly lengthy and costly business**

- **Hallmark – unpredictability**
  - **Long and uncertain development process**
  - **Depends on often fickle capital market**
  - **Regulatory processes can seem impenetrable and unresponsive**
  - **Marketplace – payment is hard to predict**
  - **"Low hanging" fruit has been picked**
  - **Impact is a marked decrease in "innovation"**

What Is Wrong?

- 4 out of 5 (80%) potential products that start *clinical* development fail to make it to market

- 50% of drugs that undergo *Phase 3* trials turn out to be too unsafe or not effective enough for marketing: benefit/risk calculus fails

What is Wrong?

- **This is *failure of prediction* on a large, no longer sustainable or affordable scale**
  - **Safety problems—product is too toxic**
  - **Product is not an effective treatment**
  - **Product cannot be manufactured at commercial scale with consistently high quality**

What is Wrong?

- **High Product Failure Rate Fuels Escalating Development Costs**
- **Cost of bringing a successful novel drug to market estimated at US$800M – *including the amortized costs of all the product failures***
- **High costs drive focus on "blockbuster" drugs with widespread chronic use in economically developed economies – only way to recover overall development costs**

What is Wrong?

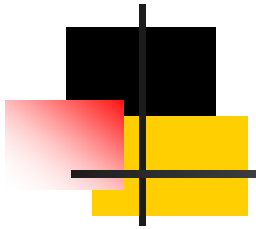
- **Decreased focus on curative or preventive interventions, on rare or less common diseases, on individualization of therapy, on diseases of developing economies**

- **Decreased focus on true innovation**

Bottom Line

- **Although rate of discovery rising, fueled by investment in biomedical science, there is a serious bottleneck between the laboratory and the bedside in product development**

What is Role of Regulators?



- So much hope and promise on one side
- So much risk and unpredictability and counter-intuitive economics on the other

- Regulators have a unique perspective on the problem because of their access to the data surrounding so many of the failures

"Critical Path" Research: Key to Improving Prediction

- **Coordinate and Engage in the science necessary to evaluate and predict safety and efficacy, and to enable consistent commercial manufacture**
  - **Different from the science that generates the new idea for a drug, biologic, or device.**
  - **Science of "development" / not "discovery"**
  - **Better choice of products to take into late development**

"Critical Path" Research: Key to Improving Prediction

- **CP research is complementary to basic and translational research, but results in the creation of new validated tools for more predictive new product development.**

- **New assays; new standards; relevant biomarkers; animal, *in vitro* and *in silico* models for safety & efficacy testing; 21st century manufacturing quality control and assurance systems**

Three Primary Questions of the Critical Path

- **Assessment of Safety – how do we more accurately and earlier in development predict if a potential product will be harmful?**
- **Proof of Efficacy -- how to more accurately and earlier in development predict if a potential product will have medical benefit?**
- **Commercialization – how do we more consistently and more cheaply manufacture a product at commercial scale with the necessary high quality?**

Critical Path Science Is Underdeveloped

- **Falls outside traditional areas of academic research and federal funding.**

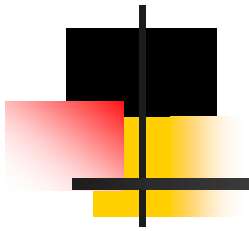
- **When innovators create critical path tools, typically applicable to their specific products and not shared with others in industry**

Initiative Goals

- **Develop new scientific toolkits that bring scientific advances into the product development process.**
- **Perform research on tools that remove specific identified obstacles in product development.**
- **Achieve robust product development pathways that are efficient and predictable**
- **Get more innovative products to patients.**

The Path Forward

- **Identify/prioritize the most severe development problems and areas that provide the greatest opportunity -- solicit input from wide variety of sources. Completed over summer and autumn 2004.**
- **Construct a national Critical Path Opportunities List and publicize it. Presently being finalized.**
- **Re-focus FDA and external research**
- **Requested Congressional funding of top priority research projects to develop and validate these new tools**



THANK YOU!