FDA’s Critical Path Initiative: Why, What, and Future Directions

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WHY
This is a “Golden Age” for Biomedical Discovery

- Sequencing of human genome reveals new candidate targets
- Combinatorial chemistry, high throughput screening, biosynthesis provide thousands of candidate drugs
- Electronics innovations, nanotechnology, materials science drive device innovation
- Transgenic animals, new technologies (e.g., RNAi) for evaluating activity
Ten Year Investment in U.S. Biomedical Research

- Increased from $37B in 1994 to $94B in 2003 (doubling when inflation-adjusted)
- 57% of funding from industrial sector
- 33% of funding from government (28% NIH)
- 10% private sources
Matching Acceleration of Product Development Has Been Expected
10-Year Trends in Major Drug and Biological Product Submissions to FDA

- Total NMEs Rec'd by FDA
- Original BLAs
Ten Year Trends Worldwide

- 2004 marked a 20-year low in introduction of new medical therapies into worldwide markets

- DiMasi, et al. (2003) estimated that the capitalized cost for self-originated NMEs developed by multinational pharma & approved in 2001 would be about $1.1 B per NME.

- Disincentive for investment in less common diseases or risky, innovative approaches
Problem: Biomedical Discoveries are Not Effectively Translated

- Huge Investment in U.S. Biomedical Research
- Lack of corresponding new products available to patients
- Major increases in medical product development costs
- Major rise in healthcare costs
Predictability Problem

Product development success rate has declined:

• New compounds entering Phase I development today have 8% chance of reaching market, vs. 14% chance 15 years ago.

• Phase III failure rate now reported to be 50%, vs. 20% in Phase III, 10 years ago.
WHAT
What’s the Diagnosis?

- Investment and progress in basic biomedical science has far surpassed investment and progress in the medical product development process.

- The *development process* – the critical path to patients – becoming a serious bottleneck to delivery of new products.

- We are using the evaluation tools and infrastructure of the last century to develop this century’s advances.
What is the “Critical Path”? 

- There is a “critical path” stretching from candidate identification to commercial product 
- Involves serial evaluation of product performance through preclinical testing and clinical evaluation 
- The Critical Path Initiative focuses on the science used for these evaluations
The Critical Path for Medical Product Development Is Now the Bottleneck
"Critical Path”
Dimensions

Evaluative science to address 3 key product performance dimensions:

- Assessment of Safety – how to predict and assess the risks of a potential product?
- Proof of Efficacy -- how to predict and demonstrate that a potential product will have medical benefit?
- Industrialization – how to manufacture a product at commercial scale with consistently high quality?
We Now have the Tools to Bolster these Scientific Disciplines

- Utilize new scientific knowledge to improve the medical product development process
- Develop robust applied research program into critical path scientific areas, to lead to generalized knowledge
- Strengthen academic bases for critical path disciplines
- Intensify FDA involvement in critical path research and standards development
The Critical Path Initiative

A serious attempt to bring attention and focus to the need for targeted scientific efforts to modernize the processes and methods used to evaluate the safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture.
Guiding Principles of the Initiative

- Collaborative efforts among government, academia, industry and patient groups
- Infrastructure and “toolkit” development, not product development
- Build support for academic science bases in relevant disciplines
- Build opportunities to share existing knowledge & database
- Develop enabling standards
Steps to Date

- Published Initial Report 5/04
- Opened Docket for public comment
- Discussed with FDA Science Board and other Advisory Committees
- Initiating multiple public-private partnership consortia with non-profit conveners
- Publication of “Critical Path Opportunities Report and List” in March 06: projects report soon
Major Opportunities for Modernization

- Biomarker Qualification
  - In-vitro diagnostics
  - Imaging
  - Preclinical toxicogenomics

- Clinical Trial Modernization
- Bioinformatics
- Modernizing Manufacturing
- Pediatric Treatments
- Public Health Emergencies
Biomarker Qualification

- “Biomarkers” are quantitative measures of physiology or pathophysiology or pharmacological/physical etc. effect
- Examples: liver function tests, ECGs, radiographs, psychological tests
- Biomarker discovery is fast, but understanding of clinical meaning develops very slowly
Biomarker Qualification

- “Qualification” of a biomarker means developing the correlative information that lets us understand its clinical meaning in a given situation.
Biomarker Consortia

- C-Path Institute (Tucson)
  - Predictive safety consortium (animal toxicology molecular diagnostics)
- FNIH Biomarker Consortium
  (FDA/NIH/PhRMA/Bio)
- Genetic basis of adverse events
- OBQI (FDA/NCI/CMS)
Why Public-Private Biomarker Consortia?

- Successful biomarker qualification is quite uncommon
- New biomarkers are critical to clinical medicine and efficient product development
- No single entity charged with accomplishing qualification
- All parties (government, industry, insurers, academia, patients) have a big stake however
FUTURE DIRECTIONS
Modernizing Clinical Trials: Opportunities

- Move to automated environment
- Develop new methodological approaches to evaluation
- Move towards greater mechanistic understanding, incorporating biomarkers
Modernizing Clinical Trials: Automation

- E-clinical trials initiative: trial conduct and regulatory submission
  - Clinical trial networks (Ca-BIG)
  - FDA e-submission standards (ICH)

- Continue development of standards
  - CDISC—trial standards organization
  - Case Report Form standards

- BiMo Initiative (FDA project)
  - Modernize FDA oversight of clinical trials and IRBs
Modernizing Clinical Trials: Move Away from Trial and Error Evaluation

- Employ rigorous, informative assessments in preclinical and early clinical studies; build generalized knowledge from results

- Will require new processes and pathways

- Will require development and regulatory acceptance of new evaluative tools; extensive utilization of diagnostic biomarkers

- Final trials would be confirmatory—however, confirmatory trial process also needs to be redesigned
Current Development Process: Impact On FDA Regulation

- High level of residual uncertainty about product performance leads to need for additional data/or taking a risk
- Lack of biomarkers in early development leads to imprecision in dose finding and estimation of treatment effect
Current Development: Impact On FDA Regulation

- Absence of predictive safety biomarkers leads to difficult benefit risk assessments and inability to proactively manage safety concerns
Critical Path Payoff for Development Process

- More predictable process; higher success rate, lower development costs
- More information about product safety and effectiveness
- Continuous improvement of development science and processes
Critical Path: Payoff for Patients

- Larger treatment effects via more targeted therapy
- Avoidance of side effects and injury through prevention
- Better/earlier product availability
- Higher quality healthcare
Summary

● As part of the Critical Path Initiative, FDA is
  ● Developing new regulatory pathways for diagnostics linked to drug development
  ● Developing consortia to provide venues for the clinical evaluation of new diagnostics
  ● Working with NIH and the pharmaceutical industry to engage them in the qualification effort
  ● Working with CMS

● FDA is also engaged in ongoing policy development in the molecular diagnostic area