FDA “Critical Path” Initiative: Closing Productivity Gap in Medical Product Development

October 4, 2004
What is the problem?

R&D Spending Has Accelerated Since 1990

And FDA Review Efficiency Has Increased...

But New Product Submissions Are Flat or Even Down
Problem: Productivity Gap in Development of New Medical Technologies

- Development Process Itself Now a Bottleneck
  - Many basic research breakthroughs BUT product development still uses decades-old tools/technology.

- Development is High Risk, High Cost
  - Only 22 percent of new compounds entering Phase I get market approval.
  - Patent life is limited, subsequent generic competition fierce (in the U.S.).
  - Not all approved drugs become blockbusters.
Problem: Productivity Gap in Development of New Medical Technologies

- 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.
  - Annual growth in capitalized costs was 7.4 % relative to earlier study, after inflation.
  - Real capitalized clinical costs grew at 11.8 %.
    - Growth in trial sizes was 7.5 %
    - Medical inflation beat general inflation by 3.7 %

*New Molecular Entity
That Has a Negative Impact on Public Health

- Companies focus on revenue 'blockbusters'
  - Clinically important therapies that don't promise largest revenues —not being developed
  - Examples: antibiotics, vaccines, medical countermeasures, blood products, products that target smaller populations (e.g., Parkinsons')

- We need more innovation where public health need is urgent

- More affordable medicine: Higher development cost limits innovation and price competition
Why is FDA Concerned?

FDA Statutory Mission -- Not only to protect but also to advance public health, by access and availability of safe and effective new medical products.
What is on "Critical Path" to Medical Product Development?

Applies basic science to address 3 key dimensions:

- 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?
Applied Science Needed to Better Evaluate and Predict on 3 Key Dimensions on 'Critical Path' of Development

FDA oversees this process and plays a unique role
What is at Stake?
What Patients are Telling Us

- “FasterCures is strongly supportive of and encouraged by the FDA’s new Critical Path Initiative. This effort has the potential to contribute to the goal of saving lives by saving time in making new therapies available for use sooner.” FasterCures

- “…We heartily endorse the FDA for its leadership in launching the Critical Pathway Initiative.” Prostate Cancer Foundation

- “We particularly welcome the Critical Path Initiative’s attention to improving models and technology for enhancing the clinical relevance and predictive value of preclinical assays, especially those related to pharmacology and toxicology.” -- AIDS Treatment Activist Coalition

- “We commend you for the serious effort you are making to resolve the dilemma we face, and offer you our support and help as we address these challenging questions.” -- National Osteoporosis Foundation

- “We wish to congratulate the Food and Drug Administration (FDA) for its excellent report…” – National Organization for Rare Disorders
Need Better Tools: 
Public Health Challenges

- Patients – Need new treatments for serious diseases
  - E.g., autism, addictive disorders, Alzheimer’s disease, bipolar disorders, cancer, cystic fibrosis, heart diseases, diabetes, morbid obesity, multiple sclerosis, muscular dystrophy, rheumatoid arthritis, osteoarthritis, systemic lupus, schizophrenia, stroke, …

- Physicians – Need tools to better diagnose disease,
  - Target therapies at the patients most likely to benefit
  - Measure individual patients’ responses [at molecular level]

- Payers -- Need tools to better identify and pay for most effective treatments; best buy for health-care buck
Examples: A Little FDA Science Could Go A Long Way

- Smaller, Smarter Clinical Trials
  - Research to validate cutting edge statistics and innovative trial designs.
  - Reduce paperwork burden -- consensus development to facilitate standard electronic submissions.

- Biomarker Validation
  - set scientific standards for validation, so industry can do the necessary validation work
What is Next Step on Critical Path?

Fall 2004: Announce **National Critical Path Challenges List** -- Identify and prioritize opportunities for build better tools to speed product development
Interactions Between Drug Development and Regulatory Procedures
FDA scientists are involved in review during product development -- they see the successes, failures, and missed opportunities.

FDA sets the standards that innovators must meet.
- New knowledge and applied science tools needed not only by innovators – *must also be incorporated into agency review.*

FDA guidance documents are known to foster innovation and improve chances of success.
FDA Has Frequent Interactions With Innovators During Product Development
Example: Drug and Biologics Development
Better Standards to Evaluate & Predict Safety & Effectiveness

- Would improve product quality and lower cost of development
- This would keep more promising therapies in the pipeline
  - E.g., If time in Phase III could be reduced by 50%, total capitalized costs would decline by $90 m per NME approved.

<table>
<thead>
<tr>
<th>Reduce Phase Length</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>1.0%</td>
<td>0.6%</td>
<td>1.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>20%</td>
<td>2.0%</td>
<td>1.1%</td>
<td>3.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>30%</td>
<td>2.9%</td>
<td>1.7%</td>
<td>4.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>40%</td>
<td>3.8%</td>
<td>2.2%</td>
<td>6.1%</td>
<td>9.0%</td>
</tr>
<tr>
<td>50%</td>
<td>4.7%</td>
<td>2.7%</td>
<td>7.5%</td>
<td>11.2%</td>
</tr>
</tbody>
</table>

Source: Tufts Center for Study of Drug Development.

* Based on Estimate of $802M on average to develop & get approval for NME in the US
Improving Predictability & Productivity of Development Process

Improving predictability of process reduces risk of developing new products—encourages continued development of more new innovative therapies

- Shifting 5% of clinical failures from Phase 3 to Phase 1 reduces out-of-pocket cost $15.5-20.0M and capitalized clinical cost by $23.8-29.4M
- Shifting 25% of failures from Phase 2 to Phase 1 reduces out-of-pocket cost $12.4-21.4M and capitalized cost by $21.9-37.8M

<table>
<thead>
<tr>
<th>% of Investigational drugs shifted to earlier failure: Phase II to Phase I</th>
<th>Reduction in Clinical Cost per approved NCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Out-of-Pocket Cost</td>
</tr>
<tr>
<td>5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>10%</td>
<td>3.0%</td>
</tr>
<tr>
<td>15%</td>
<td>4.6%</td>
</tr>
<tr>
<td>20%</td>
<td>6.1%</td>
</tr>
<tr>
<td>25%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

Source: Tufts Center for Study of Drug Development.

* Based on Estimate of $802M on average to develop & get approval for NME in the US
Increasing Share of New Drugs Get to US Patients First

- U.S. leads world with investments in pharmaceutical R&D -- US: $27.3B; Europe: $19.1B; Japan: $7.9B, NAS=new active substance.
What is on "Critical Path" to Product Development?

Applying basic science to address 3 key dimensions of product performance:

- 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?
International benefits

- Faster development of better drugs is global public good, can reduce disease burden everywhere.
- Objective science-based standards relating to approval will help harmonization of drug approval worldwide.
Comments on LDCs

- Chile and Mexico have as many manufacturers per product as Canada and France.
- Use of generics is higher in Chile than Canada (62 vs 26) and higher in Mexico than France (26 vs 14)
- Per capita consumption by age of drug
  - Chile is less than U.S. especially for new drugs.
  - Mexico is less than U.S. even more so for new drugs.

Comments on LDCs

- Prices in Chile and Mexico (relative to U.S. prices) are much higher than in Canada and France.
- Taking into account income differences, prices relative to the U.S. are much greater in Chile and Mexico than in Canada and France.