User Fees and the FDA

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SUMMARY

• The Setting – 1980s
• The Breakthrough – ca. 1991
• The Effects
• The Growth
• What Next
• Is the attention to fees a diversion from the real problem?
Current FDA Picture

• FDA’s Total Budget - $3.4B
  - Appropriations - $2.4B
  - User Fees - $1B

• Staffing – 12,381 FTEs
  - From appropriations – 9,368
  - From user fees – 3,013
DRUG REVIEW - BACKGROUND

• U.S. pharmaceutical industry grew up with an FDA
• Limited pharmaceutical presence 1\textsuperscript{st} 3\textsuperscript{rd} of 20\textsuperscript{th} century
• FDA drug review begun in 1938
• Efficacy requirement in 1962
• Drug “lag” with Europe by 1972
Climate by Late 1980s

• FDA a “Black Hole”
• R&D moving to Europe
• Reviewers arrogant laggards (and not very bright either)
• Sponsors cynical
• “Box up the data, ship it to FDA, and wait three years”
Early 1990s

- Increasing demand for “reforms”
- Fast Tracking
- Lower efficacy standard
- “Deemed approved” after set time

- Success with cancer & AIDS
  - High reviewer ratio = <year
- FDA Proposal to industry
  - Support from VCs
The Fix

PDUFA

- Congressional imprimatur that speed matters
- Review timeframes in return for sufficient reviewers
- Run it like a business
- Project management, deadlines, much increased collaboration
- Move from Black Hole to Certainty
The Result

• 90% of truly new drugs – 6 months
• 90% of standard applications – 10 months

• Over 1500 new drugs/biologics approved
• Average time to approval dropped 60%
• Average development time dropped 10%
• First-cycle approval rates - 46% to 63%
The Result

PDUFA Fees Enabled Increased Staffing and Improved Systems for Drug Review

History of PDUFA Total Process and User Fee Funded FTEs

FTE = Full Time Equivalent staffing
FDA Staffing Declines

Food and Drug Administration
Full Time Permanent (FTP) Positions / Full Time Equivalents (FTEs)

* Prior to 1980, FDA counted each federal employee as a Full Time Permanent (FTP) position.
** Listed are program level FTPs or FTEs only. User Fees, Revolving Fund for Certification and Other Services, Advances & Reimbursable, and Parklawn Computer Center FTPs or FTEs are NOT included in the FDA S&E column.
*** Source: DHHS/FDA Justification of Estimates for Appropriations Committees
**** Source: FDA’s data submission to Bio and PhRMA PDUFA IV information request; Source: MDUFMA Industry Chart; Source: ADUFA Industry Chart
THE RESULT

- **Clinical Phase**
- **Approval Phase**

Years:
- 1984-86
- 1987-89
- 1990-92
- 1993-95
- 1996-98
- 1999-01
- 2002-04
- 2005-07

PDUFA Enacted
The Result

- Inflation and workload adjustments
- Good review practices
- More collaboration, increase in app quality
- Guidance on innovative trial design
- Better AER reporting/analysis
- Risk management tools
- Review deadlines
- Better predictability & certainty
FDA Approves Drugs Faster than EMA

23 new cancer drugs were approved by both FDA & EMA

- Of 23 new cancer drugs approved by both FDA and EMA, FDA approved 21 first
- All 23 came to the U.S. market before they reached the European market
FDA vs. EMA Review Times

Median Number of Days to Approve New Oncology Drugs

- **FDA**: 261 days
- **EMA**: 373 days
57 New Drugs Approved by FDA & EMA (2006-2010)

2 out of 3 new applications were approved by FDA first
Fee payments / fee funding have increased significantly

(Fee funding in thousands)
Has PDUFA Affected Safety?

Withdrawal Rates

• 1970s – 1980s (Pre-PDUFA) - 3%

• 1990s – Present (Post-PDUFA) - 3%
Medical Devices

- Next user fee program
- Analogous goals - e.g., 90% of 510(k)s in 90 days
- Lower fee structure than PDUFA
- More complicated results
- Thus, less buy-in by industry
MDUFA II 510(k) Tier 1 Performance

*SE and NSE decisions only

**Cohorts still open as of Sept. 30, 2010, FY 2009 data may change
CDRH Average Time to Decision

*SE and NSE decisions only; times may not add to total due to rounding
Generic Drug Fees

- Enacting legislation highly possible
- Highly cooperative negotiation process
- Facility & application fees ($<PDUFA$)
  - $299M/yr $1.5B/5 years
- 10 mo. Application review/reduced cycling
- Eliminate application backlog over 5 yrs
- Parity in foreign/domestic inspections
- Proposal to Congress in January
Other Enacted Fees

- Family Smoking Prevention and Tobacco Control Act ($477M in FY12, $712M in FY 19 and beyond)
- Animal Drugs - $17M (FY 11)
- Animal Generic Drugs - $5M (FY11)
- Mammography - $19M (FY11)
- Color Certification - $8M (FY11)
- Biosimilars – FDA directed to create
Enacted Fees, continued

- Foods (newly authorized)
  - Food Reinspection ($15M)
  - Export Certification ($1.3M)
  - Voluntary Qualified Importer Program ($71M)
  - Recall ($12M)
New Fees?

• Foods
• To implement FSMA
• Substantial need - $400-500M
• New standards, preventive controls, inspections, import surveillance, science capacity, Federal-state integration, outbreak response
• Facility Registration
WHERE ARE WE IN 2011?

- Difficult to imagine FDA without fees
- Future appropriations uncertain
- Triggers may help protect against cuts
- Fees likely to be increasing % of agency
- Concerns about consequences, e.g., over-reliance on industry
- Does debate on user fees cloud more important issues?
10-Year Trends in Biomedical Research Spending

- ❄️ US Pharmaceutical R&D Spending
- ▲ Total NIH Budget

Indexed Growth (1993 = 100)

Year:
- 1993
- 1994
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
Recent declines in NME submissions and consequent NME approvals raise questions about the drug pipeline.
Ebb in Drug Pipeline Worldwide 
But US Share Has Increased

US Still Dominates As Region of Launch for NMEs 1st Marketed

CMR International /2007 Pharmaceutical R&D Factbook
Looking Forward: A Growing Number of Commercial Investigational New Drugs (INDs) Under Active Development

*CDER and CBER INDs
# The “Cliff” for Brand Name Drugs

## Current Spending for Top-Selling Drugs with Anticipated Patent Expirations

### Retail Sales of Selected Drugs with Expected Patent Expiry in 2007 - 2011

<table>
<thead>
<tr>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Norvasc $2.1B</strong></td>
<td><strong>Advair Diskus $3.1B</strong></td>
<td><strong>Prevacid $3.3B</strong></td>
<td><strong>Effexor XR $2.2B</strong></td>
<td><strong>Lipitor $6.6B</strong></td>
</tr>
<tr>
<td><strong>Ambien $1.9B</strong></td>
<td><strong>Risperdal $1.7B</strong></td>
<td><strong>Topamax $1.8B</strong></td>
<td><strong>Atorvastatin $800M</strong></td>
<td><strong>Plavix $2.2B</strong></td>
</tr>
<tr>
<td><strong>Toprol-XL $1.5B</strong></td>
<td><strong>Lamictal $1.3B</strong></td>
<td><strong>Valtrex $1.2B</strong></td>
<td><strong>Fosamax $1.6B</strong></td>
<td><strong>Seroquel $2.1B</strong></td>
</tr>
<tr>
<td><strong>Zyrtec $1.1B</strong></td>
<td><strong>Olanzapine $1.0B</strong></td>
<td><strong>Imitrex $0.65B</strong></td>
<td><strong>Zyprexa $1.1B</strong></td>
<td><strong>Protonix $1.0B</strong></td>
</tr>
<tr>
<td><strong>Lotrel $1.3B</strong></td>
<td><strong>Carisoprod $0.25B</strong></td>
<td><strong>Celebrex $0.95B</strong></td>
<td><strong>Actos $1.9B</strong></td>
<td><strong>Levaquin $1.4B</strong></td>
</tr>
<tr>
<td><strong>Coreg $1.2B</strong></td>
<td><strong>Diltiazem $0.40B</strong></td>
<td><strong>Fibric Acid $0.28B</strong></td>
<td><strong>Fosinopril $0.35B</strong></td>
<td><strong>Enalapril $0.50B</strong></td>
</tr>
<tr>
<td><strong>Lamisil Tablets $1.13M</strong></td>
<td><strong>Amiodarone $0.20M</strong></td>
<td><strong>Metformin $0.20M</strong></td>
<td><strong>Quinapril $0.20M</strong></td>
<td><strong>Lisinopril $0.20M</strong></td>
</tr>
</tbody>
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*Retail Sales Data - “Top 200 Brand-Name Drugs by Retail Dollars in 2009”, DrugTopics*
FDA Review is a Small Part of Drug Development

The Drug Development Process

- **Basic Research**
- **Discovery**
  - 3.2 years**
- **Preclinical**
  - 6.6 years**
- **Clinical Development**
  - Phase 1 (safety)
  - Phase 2 (efficacy)
  - Phase 3 (side effects)
  - 1.4 years**
- **NDA filing/ FDA review**
- **Post-Market**
  - Phase 4 Studies
  - Safety Surveillance
  - Patent Expiry *
  - Generic competition

**Average Total Time: 11.2 years**

**Average total cost-per-success in bringing new chemical entity to market: $930 M ($2006)**

* The full patent term is 20 years from the date a patent is filed.
** Average total elapsed time. Source: Tufts Center for the Study of Drug Development; (includes the cost of failures)
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
BUT

• Current methods of testing safety and efficacy are decades old and have poor predictiveness
• Leading to costly late-phase failures
• Phase III failure rate now 50%, vs. 20% 10 years ago
• New compounds entering Phase I have 8% chance of reaching market, vs. 15% 15 years ago
SO

- FDA has halved review times since Pre-PDUFA days
  - 6 and 10 months may be essentially the limit for review times
  - Recent NDA contains 10 gigabytes
SO

• If FDA has halved review times since Pre-PDUFA days
  - 6 and 10 months may be essentially the limit for review times
• And R&D funding is providing the basic research, then,
What’s Missing?
Biomedical Discoveries Not Effectively Translated

• Investment in biomedical science far surpasses investment in medical product development process

• The development process is becoming a bottleneck to delivery of new products

• We are using evaluation tools and infrastructure of the last century to develop this century’s advances
Opportunities for Modernization

- Biomarkers/surrogate endpoints
- Genetic markers to predict adverse reactions
- Computer modeling
- Clinical trial modernization
- Bioinformatics
- Pediatrics
The Opportunity for Industry

- FDA willing to step beyond its traditional drug “review” role and promote drug development and innovation
- Enormous potential payoff
  - More predictable process
  - Increased % of compounds entering Phase I reaching market
  - Reduced Phase III failure rate
  - Lower drug development costs
And for Patients?

- Larger treatment effects via more targeted therapy
- Avoidance of side effects and injury
- Better/earlier drug availability
- Higher quality health care
- Lower health care costs