PDUFA V: Long-term Perspectives

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. Prevision Policy LLC
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. National Health Policy Forum
Agenda

- **The Process**
  - Five-year maintenance schedule
  - Aligned project management

- **The Impact**
  - Lasting initiatives from previous PDUFAs
  - The pre-PDUFA bump
  - Post-PDUFA depression

- **Predictions**
  - Patient group involvement in Benefit-Risk equation
  - Less public NME decision process
  - Better generic quality; higher generic prices
Scheduled Maintenance

“Desperation” funding mechanism from 1992 develops into a fixed schedule for FDA tune-ups.

Sequential mechanics:
major constituencies get a chance to look under the hood, make suggestions and then work with FDA to turn over suggestions for improvements to Congress.

Improves FDA internal management process and political awareness.

Five-Year Tune-up Cycle

Dependable, Durable Chevy Pickup
Two Types of Overhauls

**Safety Features**

Better brakes = market withdrawal

Better sensors = Sentinel surveillance

**High Performance**

Super sparks = tight review deadlines

Racing wheels = special protocols
Collaborative Mechanics

For PDUFA V, FDA held:

• **11** general stakeholder meetings between July 1, 2010 - May 20, 2011
  • One per month
  • Another scheduled for October 24
• **38** meetings with regulated industry
  • One every 8.5 days

Practical Outcomes

• Shadow images of project management
  • FDA keeps up with best practices in private sector
  • Sponsors can devise internal processes to meet FDA goals – no excuse for not knowing the key points of the process

• Aligned policy objectives for PDUFA on Capitol Hill
  • Has played key role in past – ameliorating the legacy of crisis legislation
  • Clean Bill
## Beyond Funding from Previous PDUFAs

<table>
<thead>
<tr>
<th>Lasting Initiatives</th>
<th>Unfulfilled Ideas</th>
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<tbody>
<tr>
<td><strong>PDUFA 1</strong></td>
<td>Actionable deadlines, broader delegation of approval authority within FDA</td>
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<td><strong>FDAMA Modernization</strong></td>
<td>Meeting schedules, special protocol assessments; fast-track, rolling NDA submissions</td>
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<td><strong>PDUFA 3</strong></td>
<td>Good review practices; Pediatric drug testing</td>
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<td><strong>FDAAA Drug Safety</strong></td>
<td>REMS, Phase IV mandatory studies, NIH clinical trial registry, active post-market surveillance (Sentinel)</td>
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Post-PDUFA Slowdown


- Drug review process slowed down after each bill
  - Pronounced drop (30% drop) in number of approvals: 1998 vs. 1997
  - FDA permitted drug review teams to extend deadlines in 2008 to adjust to new FDAAA mandates – but NME approval numbers actually increased
- A complicated PDUFA can be counterproductive
- Well-recognized side-effect on Capitol Hill
- Fast implementation of 2012 program built into FDA proposal

“The Democrats’ last PDUFA reauthorization slowed you down. Let’s hope that this reauthorization doesn’t perform similarly.”

Michael Burgess (R-TX)
July 7, 2011
A Patient Solution to Benefit/Risk

Quantified Benefit-Risk Approval Criteria

- Long-term objective of industry, drug sponsors
- European drug approval body is working on benefit-risk project
- FDA began preparing two years ago for benefit/risk as a key component of PDUFA V
  - FDA’s new twist – tie benefit-risk to more input by patient groups into early assessment of key outcomes from drug treatment
  - New FDA rhetoric: Traditionally, FDA has asked what the doctor thinks about a treatment; but who cares what the doctor thinks? It is the patient who counts.
  - FDA is already getting underway to convene some patient groups to define outcome measures – obesity could be first project.

Will reaffirm pharma ties to patient groups: money that was going to educational/promotion spending on medical professionals will shift to patient groups.
What Patient Focus Will Look Like

Exhibit 1

Patient Perspective on Xarelto: A Look at Future of Benefit/Risk

J&J included two slides on what patients and doctors want from new anticoagulants during the September 8 FDA Cardio-Renal Advisory Committee review of rivaroxaban. The slide below shows how the key safety and efficacy effects of the drug array when compared to patient rating of objectives from anticoagulant therapy. This attempt to create a patient-oriented forest plot addresses FDA’s growing interest in looking at benefit/risk from a patient perspective.

ROCKET AF: Risk Differences by Clinical Severity/Impact*  
All Patients  
SafetyOn-Treatment

<table>
<thead>
<tr>
<th>Endpoint</th>
<th># of Events (10,000 patient-years)</th>
<th>Risk difference (10,000 patients-yrs (95%CI))</th>
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<tbody>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Warfarin</td>
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<tr>
<td>Atrial fibrillation</td>
<td>188</td>
<td>222</td>
</tr>
<tr>
<td>Disabling Stroke</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>Non-CNS systemic embolism</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Non-disabling stroke</td>
<td>79</td>
<td>77</td>
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<tr>
<td>Myocardial infarction</td>
<td>91</td>
<td>112</td>
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<tr>
<td>Major bleeding</td>
<td>360</td>
<td>345</td>
</tr>
<tr>
<td>Non-major clinically-relevant bleeding</td>
<td>1190</td>
<td>1137</td>
</tr>
</tbody>
</table>

*Endpoints in order of health state utility, a value that reflects preference for health states relative to perfect health and death from Tute’s ECA registry.

Source: J&J Pharmaceutical Research & Development
Drug Review in 2013: Closed & Efficient

“The Program”

• Based on more, formal, scheduled meetings on NMEs
  • Key meeting is “late-cycle” meeting that is scheduled to occur about two weeks before open advisory committee – a last chance to work out differences between agency and sponsor before having to air them in public
  • The new system is a bit at odds to FDAAA mandate for all NMEs to have open committees unless FDA could explain why they weren’t necessary
    • Led to logistical burden for agency
    • Some FDA review areas have learned to work around – Oncology

Fewer advisory committees on new product review: more on post-market problems, and earlier, more general premarket approval issues. A significant change for FDA and sponsors.
Clean Bill Objective

Other UFAs: GDUFA; BsUFA

Other Likely Drug Stuff

1. **The Drug Safety Enhancement Act** – authority for FDA to control global drug production process
2. **Preserving Access to Life-Saving Medications** – to prevent drug shortages
3. **Generating Antibiotic Incentives Now**
4. **Conflict of Interest** rules for FDA advisory committee members
5. **Incentives for drug-diagnostic companion development**
Most Lasting Impact?

**Drug Safety Enhancement**

It quacks like a trade protection bill and should be recognized as such.

Combined with GDUFA, DSE will add to the manufacturer/marketer cost of producing and assuring quality active pharmaceutical ingredients.

That should halt the race to the bottom in generic prices – and could having salubrious effects on safety, traceability, shortages and domestic control over drug ingredients.

It could have slight negative effect (increase) on generic drug prices.

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**QEHC Act ???**

Quality, Employment, Higher Cost generic drug reform
Questions?

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