Introduction:

The Food and Drug Administration (FDA), specifically, the Center for Drug Evaluation and Research (CDER), is responsible for the review of prescription drugs before marketing. In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA) to provide resources for the FDA to review drugs in a timely manner. Since PDUFA I, there have been three reauthorizations of the act. PDUFA IV is set to expire September 30th, 2012, thus the FDA, stakeholders and the pharmaceutical industry are currently discussing new proposals and guidelines for PDUFA V.

History of PDUFA

PDUFA I: Fiscal Year 1993-1997
First enacted in 1992, PDUFA I granted the FDA permission to collect user fees from pharmaceutical manufacturers for use in the review of drugs. Before PDUFA I, the FDA’s sole source of funds were from direct appropriations, which were insufficient and lead to a backlog of drug applications. The main goal of PDUFA I was to eliminate the backlog. Application review fees, establishment fees and product fees each made up one-third of the total fees collected.

PDUFA II: Fiscal Year 1998-2002
The first reauthorization of PDUFA imposed stricter performance goals and expanded the FDA’s involvement in the drug review process to include the clinical investigational phase of drug development. It also required the Department of Health and Human Services to submit two annual reports to Congress.

PDUFA III: Fiscal Year 2003-2007
In reauthorizing PDUFA III, Congress allowed the FDA to adjust annual revenue targets based on workload changes. This version of PDUFA also permitted the FDA to use user fees for postmarket surveillance of products for up to three years after approval.

PDUFA IV: Fiscal Year 2008-2012
The main change in PDFUA IV was the expansion of postmarket surveillance of drugs the entire market life. New fees were also on manufacturers that want to advertise to consumers directly on television.

Key Takeaways

Increased review times for the most significant advances in drug development
- Priority drug review times have increased due to the increased number of requirements that the FDA is imposing on drug manufacturers leading to fewer approvals of the drugs that show the most significant therapeutic improvements.
- The percentage of priority drugs that are approved on the first cycle has decreased drastically since 2007.

Drug development is a long and complex process
- A new drug is only approved after a 10 to 15 year development process a costly 3-phase clinical trial period.

Risk-benefit analysis required
- Do a drug’s benefits outweigh its potential risks and side-effects?
- The next version of PDUFA will include risk-benefit analysis for drug review.
The Drug Development Process (Figure 1)

The development of a drug is a long and costly process that begins with thousands of molecules in the early stages and ends with a single approved drug or biologic\(^1\).

**Pre-discovery:** The goal in this phase is to understand the disease or condition. A key molecule, such as a protein or a DNA sequence, is usually determined and will serve as the target for the drug.

**Drug discovery:** In this phase, scientists search for a molecule that will act as the “lead compound,” which will hopefully become a medicine. Such molecules could be found in nature, created with the aid of advanced computer modeling or through biotechnology and the use of genetic engineering to produce a biological molecule. Lead compounds are subject to early safety tests and optimization.

**Preclinical:** Optimized compounds are tested for safety and both *in vitro* and in bacterial and animal models. Means to upscale the manufacturing process for clinical trials must also be worked out in this phase.

**Clinical trials:** Three phases of human trials that begin with dozens of volunteers and gradually increase to thousands of volunteers. Before a clinical trial can start, an Investigational New Drug Application (IND) must be submitted and approved by the FDA. Clinical trials are the most costly and time-consuming step in drug development. Once the appropriate data demonstrating drug efficacy and safety is gathered, a New Drug Application (NDA) or Biological License Application (BLA) must be submitted to the FDA for review.

Figure 1: The Drug Development Process\(^1\)

---

\(^1\) A biologic product is produced with the aid of a living organism and includes vaccines, blood and blood components, gene therapy and tissues.
**FDA decision:** The FDA has two routes through which it reviews a new drug: priority and standard. Priority status is designated to a drug that treats a serious disease or shows significant improvement over treatments currently on the market. A drug that offers only a minor improvement on market treatments is given standard status.

**Scale-up to manufacturing:** Pharmaceutical companies need to upgrade or build new facilities to produce sufficient quantities of a drug. Each facility must comply with the FDA’s guidelines for Good Manufacturing Practices (GMP).

**Postmarket surveillance:** Drug manufacturers are required to inform the FDA if they receive an adverse event report. These reports are stored in the Adverse Event Reporting System (AERS). Clinical reviewers evaluate the reports to see if further investigation is necessary. The FDA posts AERS data files and information regarding drug recalls on its website.

**Prescription Drug Approval Times**

The FDA’s goal is to complete priority reviews within 6 months and standard reviews within 10 months. Although the FDA meets these goals on over 90% of submissions, drugs rarely receive approval on the first review cycle (Figure 2). The FDA frequently requires additional information from the drug manufacturer, dragging out the overall approval process to over a year, even for drugs that represent significant therapeutic gains over current drugs (Figure 3). This risk-averse attitude of the FDA keeps the most effective treatment options from patients and impedes innovation by occupying the resources of drug manufacturers that could be utilized for the development or improvement of other drugs. Evidence of the negative impact on drug manufacturers can be seen in the number of priority approvals in 2010, which decreased by 36.5% below the previous 5-year average (Table 1). Drug safety is without question the top priority for the FDA, but restricting access to potentially groundbreaking drugs is harmful to both patients and industry.

![Figure 2: Percent of Filed NDAs and BLAs Approved on First Review Cycle](image)

**Table 1: Priority and Standard Drug Approvals by Fiscal Year**

<table>
<thead>
<tr>
<th>Approval Process</th>
<th>Fiscal Year</th>
<th>2005-2009 Average</th>
<th>2010 versus 5-year average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority Approvals</td>
<td>30 29 25 18 24 16</td>
<td>25.2</td>
<td>↓ 36.5 %</td>
</tr>
<tr>
<td>Standard Approvals</td>
<td>87 67 70 62 82 79</td>
<td>73.6</td>
<td>↑ 7.3 %</td>
</tr>
</tbody>
</table>

The Future of PDUFA

The FDA and industry are holding meetings to discuss provisions and modifications for the reauthorization of PDUFA V. Both parties agree that transparency and communication during drug development and review needs to improve so that drug manufacturers can receive more timely guidance and feedback from the FDA. An initiative to bring about the enhancement of the drug review process through electronic submissions and the standardization of application data has been tentatively agreed upon. The FDA also agreed to enhance risk-benefit assessment into regulatory decision-making. A draft for all new proposals for PDUFA V must be submitted to Congress by January 2012.
The American Action Forum is a forward-looking policy institute. The Forum produces real-time, fact-based, innovative policy analysis and solutions for policy makers and the public alike. Our mission is to promote common-sense, innovative and solutions-based policies that will reform government, challenge outdated assumptions, and create a smaller, smarter government.

Operation Healthcare Choice is the Forum’s public policy center focused on promoting high-value healthcare and higher quality health insurance that expands consumer choice. Operation Healthcare Choice experts conduct research, offer commentary, and develop policies aimed at eliminating healthcare’s burden on the economy.

References

3 Food and Drug Administration. FY 2010 Performance Report to the President and Congress for the Prescription Drug User Fee Act.
4 Author’s calculations based on data found in PDUFA performance reports found at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm.
6 Food and Drug Administration. FY 2010 Performance Report to the President and Congress for the Prescription Drug User Fee Act.