PDUFA V: What you need to know about the upcoming Prescription Drug User Fee Act

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Agenda

- Overview
- PDUFA I – IV Through the Years
- PDUFA V Possibilities
- PDUFA V Practical Expectations
- Discussion

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Prescription Drug User Fee Act (PDUFA)

Under a user fee program, industry agrees to pay fees to help fund a portion of the FDA's drug review activities while the FDA agrees to overall performance goals such as reviewing a certain percentage of applications within a particular time frame.

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Parallel Legislation to PDUFA

Biologics Price Competition and Innovation Act (BPCIA)

Generic Drug User Fee Act (GDUFA)

Medical Device User Fee Act (MDUFA)

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PDUFA (Major) Stakeholders

American Public	Patient Advocate Organizations	Consumer Organizations	**Congress**
FDA	**Pharmaceutical Industry**	Medical Device Industry	Health Care Industry
	Academia	Other Government Agencies (NIH, DOD)	

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Pharmaceutical Industry Stakeholders

- Pharma Companies
- Biotech Companies
- Generic Companies
- Industry Trade Organizations
- CROs

Poll: What element of the pharmaceutical industry do you represent?

- Pharma
- Biotechnology
- Regulatory Authority
- Government or Academic Institution
- CRO
- Other

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PDUFA Through the Years

- 1993 - 1997
- 1998 – 2002
- 2003 – 2007
- 2008 –2012

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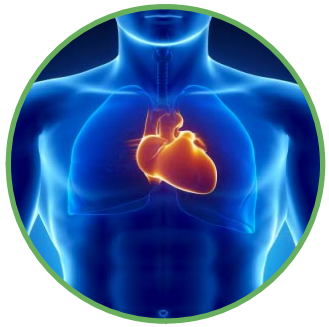
Historical Events Influencing PDUFA Legislation

Human Immunodeficiency Virus Pandemic (1980s)

Death of a Clinical Trial Subject in a Gene Transfer Study (1999)



Post Marketing Cardiovascular Effects "Discovered" in Merck's Vioxx (2004)

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PDUFA IV Performance

Meeting targets	• Mandate of Review of 90% of Marketing Applications within Designated Timeframes
Meeting targets	• Mandate of 90% of Development Meeting Conduct within Designated Timeframes
Improving	• Proprietary Name Review
Checkered performance	• Issuing of Guidances

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PDUFA V Possibilities Considered

* Source of possibilities
  - Technical Letter Negotiated by the FDA, Industry Representatives, and Patient Groups in 2011

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PDUFA V Possibilities Considered

- Improve Review Performance Goals Overall
- Improve New Molecular Entity NDA and Original BLA Performance Goals
- Improve First Cycle Review Performance
- Improve Review of Proprietary Names to Reduce Medication Errors
- Expedite Major Dispute Resolution
- Facilitate and Expedite Resolution of Clinical Holds

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PDUFA V Possibilities Considered

- Expedite Special Protocol Assessment and Agreement
- Improve Meeting Management Goals
- Enhance Regulatory Science and Expedite Drug Development
- Enhance Benefit-Risk Assessment in Regulatory Decision Making
- Enhance and Modernize the FDA Drug Safety System

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PDUFA V Possibilities Considered

- Improve the Efficiency of Human Drug Review
  - Required Electronic Submissions
  - Standardization of Electronic Drug Application Data
- Improve Progress Reporting for PDUFA V and Continuing PDUFA IV Initiatives
- Emphasize Information Technology Goals
- Improve FDA Performance Management

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PDUFA V Stretch Possibilities

- Contribute Funding for Comparative Effectiveness Research
- Combine CDER and CBER
- Combine 21CFR Part 314 and Part 601

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FDA Recommendations for PDUFA V

Continued Timely Review of Critical Prescription Drugs

Advance the Development of Drugs for Rare Diseases

Enhanced Communication with Emerging Companies

Improve the Use of Standardized Electronic Data

Use of New Clinical Endpoints that Improve Timelines to Help Address Unmet Medical Needs

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Biotechnology Industry Organization (BIO) Proposed Big Ideas

1. Progressive Drug Approval
2. Approval based on weight of evidence
3. Include Innovation in FDA's Mission Statement
4. Independent FDA
5. Six-year Term for FDA Commissioner
6. Enhanced Access to External Scientific Experience
7. Funding for Reagan/Udall Foundation
8. Disclose Reasons for Non-approval
9. Experimental Space for Regulatory Science
10. External Management Review Board
11. Improve Clinical Research with Electronic Health Records

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Poll: What is your highest priority desired consequence of PDUFA V implementation?

- Decreased marketing application review time
- Facilitation of more frequent meetings with FDA during development stages
- Expedite Special Protocol Assessment and Agreement
- Standardization of electronic product application data

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Legislative Deadlines

Unofficial Deadline for Renewal

Expiration of PDUFA IV

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House Energy and Commerce Health Subcommittee

1 February 2012 – PDUFA Reauthorization	9 February 2012 – Generic and Biosimilar User Fees	15 February 2012 – Medical Device User Fee Reauthorization
• Margaret Hamburg, FDA Commissioner	• Janet Woodcock, Director CDER	

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Senate Committee Hearings

Senate Committee on Health Education, Labor, and Pensions (HELP)

Hearing on PDUFA

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Senate HELP Hearing on PDUFA

- Emphasis on timely passage of PDUFA
  - Ensure new products delivered to patients without interruption
  - Avoid 2,000 FDA layoffs
  - Maintain America's leadership in biomedical innovation
  - Minimize legislative additions by Congress
    - Avoid legislation that would add "cost, complexity, and controversy"

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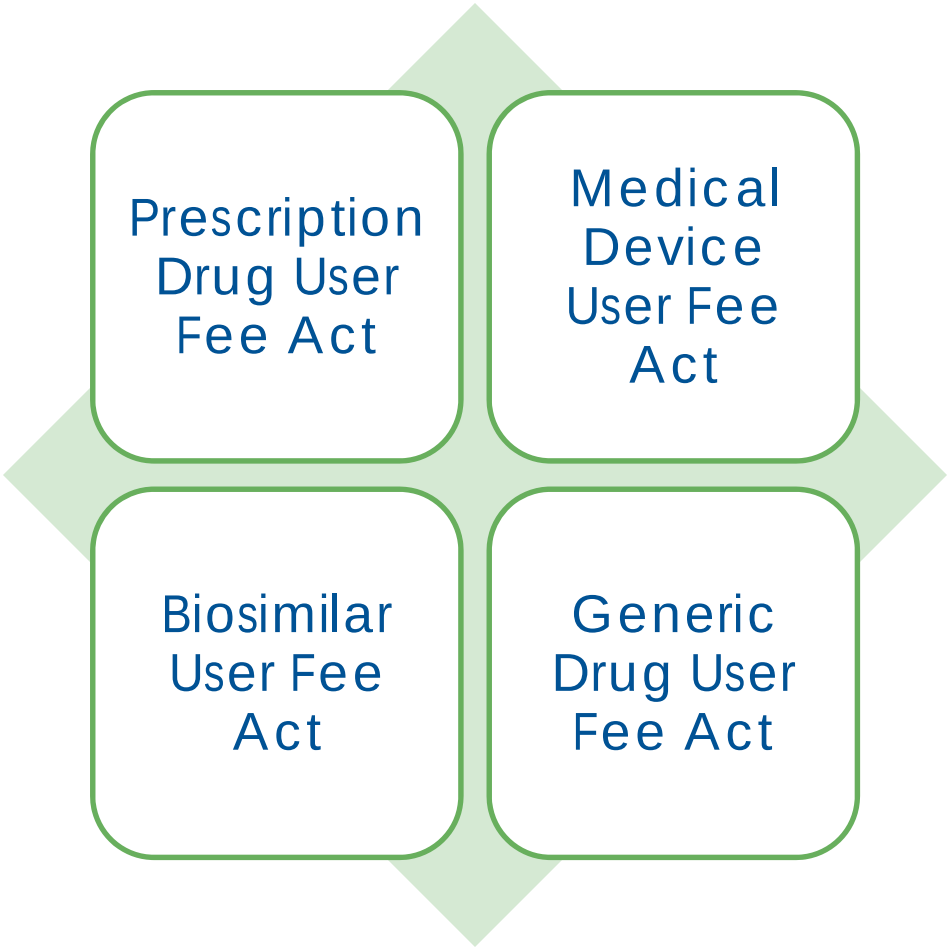
Omnibus Bill Anticipated



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What are the Possibilities?

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Improve Review Performance Goals

Proposed Increase in the Application Review Time

Mid-cycle Communication

Discipline Review Letters

Late-cycle Meeting

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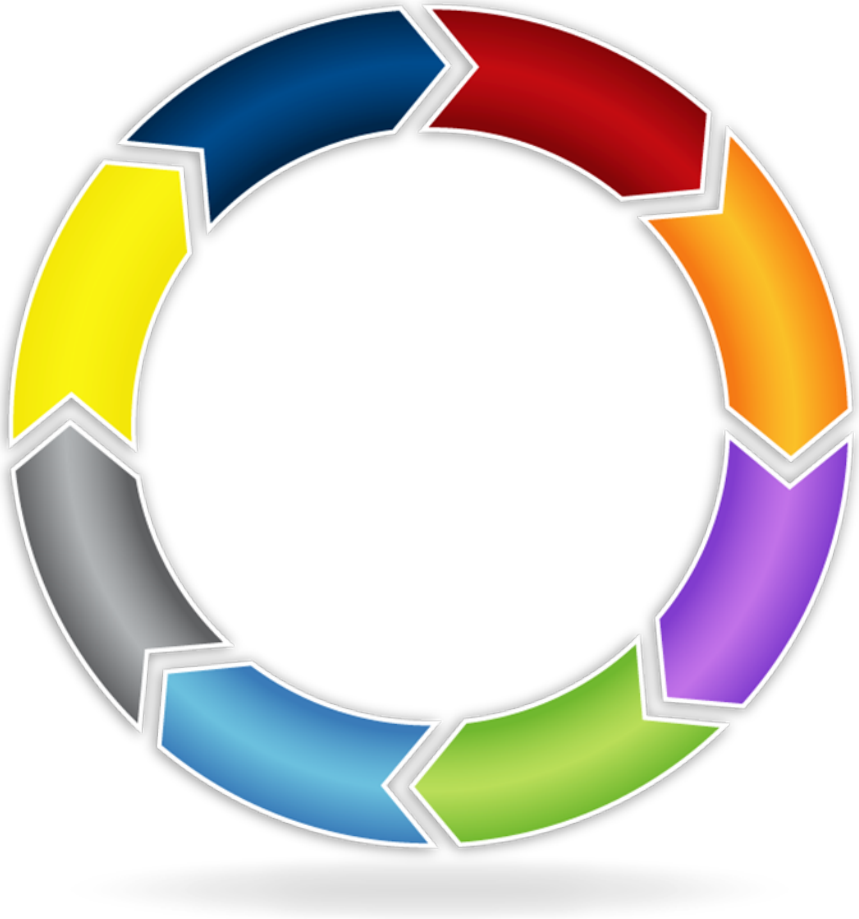
Improve First Cycle Review Performance?



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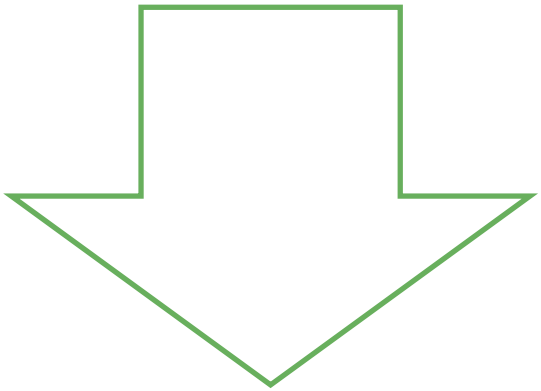
FDA Mission Statement Modification?

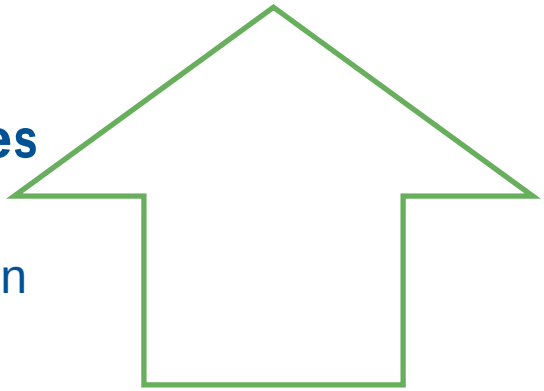


Bills Pending in Congress Propose Including Job Creation and Economic Growth

- FDA forcing jobs and innovation offshore by requiring too much data

Commissioner Hamburg Opposes This Idea

- Advocates science-based decision making



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FDA Mission Statement - 2003

The FDA is Responsible for Advancing the Public Health by Helping to Speed Innovations that Make Medicines and Foods More Effective, Safer, and More Affordable

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FDA Mission Statement – Pink Sheet 2012

Promoting Public Health by Promptly and Efficiently Reviewing Research and Acting on the Marketing of Regulated Products in a Timely Manner, in part by Assuring Human Drugs are Safe and Effective, According to the FD&C Act

Also:

Work with Other Governments to Reduce the Burden of Regulation

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FDA Mission Statement – Margaret Hamburg (2010)

Promote and Protect the Health of the Public

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Desired Result

FDA Consensus Mission Statement

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Poll: What do you think will be the greatest challenge to implementation of a productive PDUFA V legislation?

- Inability to pass a bill unencumbered with congressional self interests
- Ambiguity of FDA Laws and Regulations
- Lack of knowledge/understanding of existing regulations and FDA practices
- Hyperfocus of legislators on life threatening and orphan diseases

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Ambiguity of FDA Laws and Regulations

Knowledge of Existing Regulations and FDA Practices

Example: FDA's Current Programs for Expedited Development and Approval

- Fast Track Designation
- Accelerated Approval
- Priority Review

"Progressive" Approval vs. Expansion of Accelerated Approval

- Unlocking Lifesaving Treatments for Rare Diseases Act (ULTRA)
- Transforming the Regulatory Environment to Accelerate Access to Treatment (TREAT) Act

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ULTRA

Rare Disease Approvals Based on Surrogate Endpoints

"Shall not require clinical treatment data or other historical clinical data"

Sponsors-

- Rep Cliff Stearns, R-Fla
- Rep Edolphus Towns, D-NY

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TREAT Act

Goal

- To greater utilize Accelerated Approval pathway to bring more products to market faster

Basis for Approval

- An effect on a surrogate endpoint that is reasonably likely to predict clinical benefit
- An effect on a clinical endpoint that is reasonably likely to predict an effect on mortality or other clinical benefit

Additional Considerations for Approval

- Disease rarity
- Severity
- Availability of alternative treatments

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Issues with Accelerating the Development and Approval Process

Lack of scientific understanding of the disease

Lack of scientific understanding of the product's mechanism of action

Inability to define an appropriate surrogate endpoint

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Attempts to Define More Surrogate Endpoints

Harmonize the Patient Population	• Pharmacogenomics • Personalized medicine
Understand the Science of the Disease and Mechanism of Action	• Takes time and money
Is This Where the PDUFA V Funds Should Be Focused?	• Pharmacogenomics • Biomarkers

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Some Surrogate Endpoint Successes (Oncology)

Approvals Granted in <6months

Xalcori (crizotinib)	Zelboraf (vemurafenib)	Avastin (bevacizumab)
• approved for ALK(+) patients with non-small cell lung cancer (NSCLC)	• approved for BRAF(+) patients with late stage melanoma	• withdrawn for HER(-) patients with metastatic breast cancer

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Some Surrogate Endpoint Failures

- Reduction in Ventricular Ectopic Contractions/Decreased Cardiovascular-related Mortality
- Increase in Exercise Tolerance/Decreased Cardiovascular-related Mortality
- Prostate-specific Antigen/Mortality from Prostate Cancer
- Complete Response Plus Partial Response/Mortality from Colorectal Cancer

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Product Developers Beware

A Correlate Does Not a Surrogate Make, Rather the Intervention's Effect on the Surrogate Endpoint Must Predict the Effect on the Clinical Outcome

Consequently FDA is Constantly Requesting "Clinical Benefit" as the Basis For Risk/Benefit Evaluation

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Pharmacogenomic Success Story

Vertex's Kalydeco for Cystic Fibrosis Patients

- Stephen Spielberg, Deputy Commissioner FDA hails Kalydeco development as a paradigm
- Touts alliances with Patient Advocacy Groups
- Treats 4% (338 total patients) of the people with Cystic Fibrosis

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene Discovered Over 20 Years Ago

- Extremely active area of physiological research
- Functional activity of CFTR protein well-understood
- Genetic mutations well-understood

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Personalized Medicine

Don't Throw the
Baby Out with the
Bathwater

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Personalized Medicine

Don't Let the **Tail**
Wag the **Dog**

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Loosening of Conflict of Interest Rules for Advisory Committees?

Complaints of Lack of Sufficient Expertise on Advisory Committees

- FDA Restrictions Too Severe?
- National Organization for Rare Disorders

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Drug Shortage Prevention Strategies

No Formal Bills Introduced Addressing Economic Issue	• 340B Drug Discount Program • Expected to be a part of PDUFA V
Bills Currently Circulating	• Requiring manufacturers to notify FDA of production interruption • Early warning system requiring creation of an critical drug shortage list

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Harmonization of Data, Terminology, Tools, and Process Standards

FDA's Study Data Standards Resources Web Page

Good Terminology Practices

Design Process for Adequate and Well-controlled Studies

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Biosimilar User Fee Act

$20M in Revenue Projected by FDA for 2013

Assume Comparable $1.8M User Fee

Would Require 11 Applications in 2013, or

Development Fees for Biosimilars

- Similar to EMA Scientific Advice Meeting Fees

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Generic Drug User Fee Act (GDUFA)

Generic Drug Marketing Applications are on the Rise

- 800 to 900 annually

$299M in Revenue Projected by FDA for 2013

GDUFA Fee of ~ $350K

- Method of fee calculation based initially on backlog
- Drug Master File Fee

Emphasis on Increasing Inspections of Foreign Manufacturing Facilities

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PDUFA V Practical Expectations

Marketing Application Review Process	Overall Development Process	Conflict of Interest for Advisory Committee Members
Biosimilar User Fees	Generic User Fees	Prescription Drug and Medical Device User Fees

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There Will be a Disconnect Similar to the PDUFA IV Risk Evaluation and Mitigation Strategy (REMS)Confusion

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Poll: What global region do you represent?

- Americas
- EU
- Asia Pacific
- Africa and Middle East

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Q & A

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