FDA Regulation and Cutting Edge Technology – What Pharmaceutical and Medical Device Companies Should Know

18th Annual Pharmaceutical and Medical Device Compliance Congress

Ginny Beakes-Read
Executive Director/Special Counsel
Regulatory Strategy and Law
Eisai Inc.

hhc
human health care

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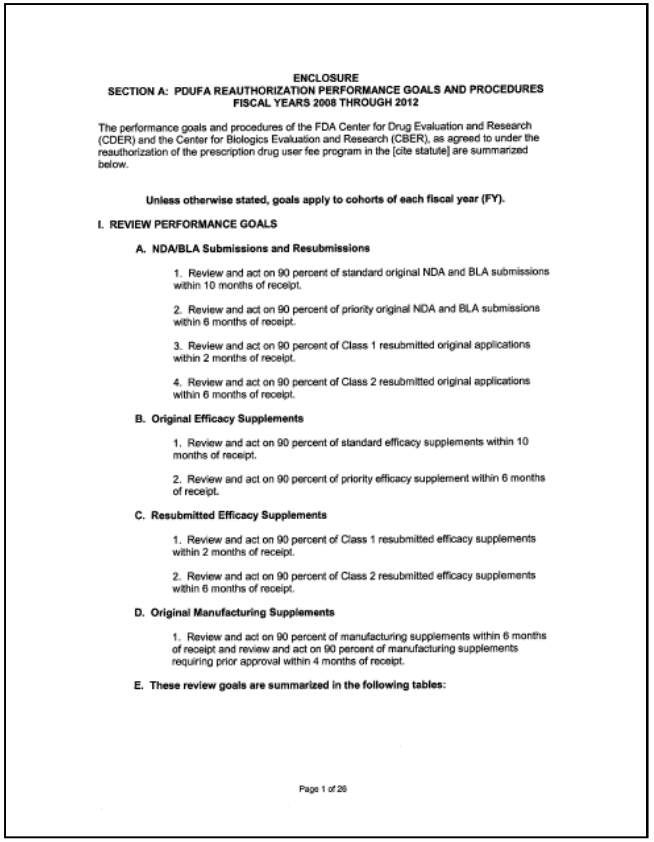
Agenda

- **Prescription Drug User Fee Act**
  - Overview of the Program
  - Relationship to FDA "reform" legislation
- **Recent FDA-Related Legislation**
  - Food and Drug Administration Reauthorization Act
  - 21st Century Cures
- **Select Initiatives and Topics of Interest**

PDUFA Structure

Two documents outlining the PDUFA agreement:

1. PDUFA Goals Letter



ENCLOSURE
SECTION A: PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES
FISCAL YEARS 2008 THROUGH 2012

The performance goals and procedures of the FDA Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the reauthorization of the prescription drug user fee program in the [cite statute] are summarized below.

Unless otherwise stated, goals apply to cohorts of each fiscal year (FY).

I. REVIEW PERFORMANCE GOALS

A. NDA/BLA Submissions and Resubmissions

1. Review and act on 90 percent of standard original NDA and BLA submissions within 10 months of receipt.

2. Review and act on 90 percent of priority original NDA and BLA submissions within 6 months of receipt.

3. Review and act on 90 percent of Class 1 resubmitted original applications within 2 months of receipt.

4. Review and act on 90 percent of Class 2 resubmitted original applications within 6 months of receipt.

B. Original Efficacy Supplements

1. Review and act on 90 percent of standard efficacy supplements within 10 months of receipt.

2. Review and act on 90 percent of priority efficacy supplement within 6 months of receipt.

C. Resubmitted Efficacy Supplements

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements within 2 months of receipt.

2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

D. Original Manufacturing Supplements

1. Review and act on 90 percent of manufacturing supplements within 6 months of receipt and review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

E. These review goals are summarized in the following tables:

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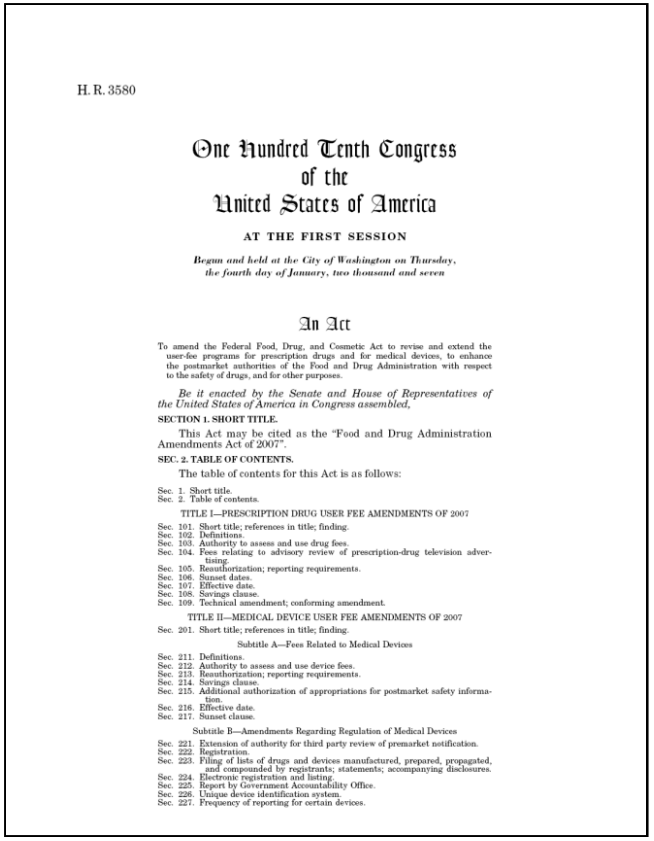
2. User Fee Authorizing Legislation



H. R. 3580

One Hundred Tenth Congress
of the
United States of America

AT THE FIRST SESSION

Begun and held at the City of Washington on Thursday, the fourth day of January, two thousand and seven

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Amendments Act of 2007".

SEC. 2. TABLE OF CONTENTS.

The table of contents for this Act is as follows:

PDUFA VI Goals Letter and FDA Reauthorization Act (FDARA)

PDUFA VI

- **Expanded Review Program**
- **Enhanced Communication**
- **Structured Benefit/Risk**
- **Patient Focused Drug Development**
- **Regulatory Science** (Biomarkers, PROs, Rare Diseases)
- **Drug Safety** (REMS & Sentinel Network)

FDARA

- **New User Fee Structure**
- **Orphan Drug (Clinical Superiority)**
- **Pediatrics Oncology**
- **Expanded Access**
- **Competitive Generic Designation and Exclusivity**
- **Generic Drug Priority Review**

PDUFA V - Expanded Scope of Negotiated Programs

- Introduced **Regulatory Science provisions**
- Agreement to pay for FTEs for specific programs
- Very specific deliverables for regulatory science programs, including patient focused drug development public meetings

IX. ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT

A. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

B. Advancing the Science of Meta-Analysis Methodologies

C. Advancing the Use of Biomarkers and Pharmacogenomics

D. Advancing Development of Patient-Reported Outcomes (PROs) and Other Endpoint Assessment Tools

E. Advancing Development of Drugs for Rare Diseases

X. ENHANCING BENEFIT-RISK ASSESSMENT IN REGULATORY DECISION-MAKING

XI. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

A. Measure the Effectiveness of REMS and Standardize and Better Integrate REMS into the Healthcare System

B. Sentinel as a Tool for Evaluating Drug Safety Issues That May Require Regulatory Action

C. Conduct and Support Activities Designed to Modernize the Process of Pharmacovigilance

PDUFA VI - Continued Expansion of Negotiations

- **Industry fees high (2016):**
  - **Application: $2,038,100**
  - **Product: $97,750**
  - **Establishment: $512,200**
- **Expectation that fees will result in significantly improved drug development process**
- **Regulatory science provisions expand (20 pp of goals letter)**
- **Manage hiring and use of FTEs**

I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM

- A. Review Performance Goals
- B. Program For Enhanced Review Transparency And Communication For NME NDAs And Original BLAs
- C. First Cycle Review Management
- D. Review Of Proprietary Names To Reduce Medication Errors
- E. Major Dispute Resolution
- F. Clinical Holds
- G. Special Protocol Question Assessment And Agreement
- H. Meeting Management Goals
- I. Enhancing Regulatory Science And Expediting Drug Development
- J. Enhancing Regulatory Decision Tools To Support Drug Development And Review
- K. Enhancement And Modernization Of The FDA Drug Safety System

II. ENHANCING MANAGEMENT OF USER FEE RESOURCES

- A. Resource Capacity Planning And Modernized Time Reporting
- B. Financial Transparency And Efficiency

III. IMPROVING FDA HIRING AND RETENTION OF REVIEW STAFF

- A. Completion Of Modernization Of The Hiring System Infrastructure And Augmentation Of System Capacity
- B. Augmentation Of Hiring Staff Capacity And Capability
- C. Complete Establishment Of A Dedicated Function To Ensure Needed Scientific Staffing For Medical Product Review
- D. Set Clear Goals For Drug Review Program Hiring
- E. Comprehensive And Continuous Assessment Of Hiring And Retention

Recent FDA-Related Legislation

FDA Reauthorization Act (FDARA)

- Signed August 18, 2017
- Reauthorized PDUFA VI, BSUFA II, GDUFA II, and MDUFA IV
  - Included structural changes to PDUFA VI
- Additional Provisions include:
  - Pediatrics
  - Expanded Access
  - Orphan Drugs
  - Improving Generic Drug Access

PDUFA VI Goals Letter and FDA Reauthorization Act (FDARA)

PDUFA VI

- **Expanded Review Program**
- **Enhanced Communication**
- **Structured Benefit/Risk**
- **Patient Focused Drug Development**
- **Regulatory Science** (Biomarkers, PROs, Rare Diseases)
- **Drug Safety** (REMS & Sentinel Network)

FDARA

- **New User Fee Structure**
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- **Pediatrics Oncology**
- **Expanded Access**
- **Competitive Generic Designation and Exclusivity**
- **Generic Drug Priority Review**

21st Century Cures

- Became law on December 13, 2016
  - 2-year bipartisan effort to overhaul and update drug development, including FDA review and approval process; focuses on spectrum from discovery, development, to delivery
  - Goals were to:
    - Help modernize and personalize health care
    - Encourage greater innovation
    - Support research
    - Streamline the system
- Approved funding for major health initiatives
  - National Institutes of Health (NIH)
    - $4.8 billion over 10 years for initiatives (Precision Medicine, Cancer Moonshot)
  - Food & Drug Administration (FDA)
    - $500 million over 10 years to implement provisions of Cures
  - U.S. States
    - $1 billion over 2 years for opioid abuse prevention and treatment activities

Cures, PDUFA VI, and FDARA
Related provisions and approach

- Several program areas addressed in multiple vehicles
- Cures was developed during time PDUFA VI was negotiated
  - Uncertainty about whether problem areas would be successfully addressed in Cures or through PDUFA VI (including implementing legislation – FDARA)
  - Preference for different vehicles
    - Statutory provisions are requirements
    - Goals Letter is an agreement with defined deliverables and reports
- FDARA enacted after Cures, expanding on some provisions, and adding others

FDA Funding and Hiring

Cures Sec. 3072	PDUFA VI	FDARA Sec. 102
• Increased flexibility for hiring, allows FDA to determine pay rate (not to exceed President's salary) • FDA must submit a report w/in 18 months covering the need for FTEs, plan to address issue, along with recommendations on how to recruit and retain staff • GAO study on FDA's hiring/training staff due by 2022	• Independent contractor to implement FTE-based management system • Hiring goal for 2018-2022 – 231 FTEs • Publish modernized time-reporting plan • Independent contractor to assess resource needs • 3rd party evaluation of PDUFA resource management during FY 18, 5-yr financial plan, annual meeting to review progress with above requirements	• Established new fee structure; 20% from application fees, 80% from product fees, no establishment fees • Products with multiple presentations pay no more than 5 product fees • Current exemptions remain • Replaced workload adjustment with capacity planner adjuster to better reflect workload and staff capacity • Base fee amount increased to $878 M from $718 M

Drug Surveillance Requirements

Cures Sec. 3075	PDUFA VI	FDARA Sec. 606
• FDA to post best practices for use of FAERS and posting adverse events • Removes FAERS requirements for FDA to conduct bi-weekly screenings, and to post summary analyses following approval of a new drug • Amends REMS ETASU provision to include activities by DSARM Ad Comm, and changes annual evaluation of ETASU drug(s) requirement to periodic reevaluation	• Augment data available through Sentinel by expanding data sources, enhancing communication with sponsors, evaluation of how involve the public • Hold public meeting to facilitate development of Sentinel • Integrate Sentinel into review program, and analyze impact on regulatory programs • Develop MAPPs/SOPs to inform sponsors about use of Sentinel, and evaluate program	• Expands REMS communication plan elements to include disseminating info to HCPs about drug formulations or properties, including information about limitations or patient care implications, and how drug properties may relate to serious adverse events

Qualification of Drug Development Tools

Cures Sec. 3011	PDUFA VI
• FDA must establish a process for qualification of DDTs, including specific elements in statute • FDA must base acceptance of plan on scientific merit, may prioritize review, must conduct full review of qualification packages, and make decisions based on scientific merit • FDA may use outside experts to review packages • FDA must publish status of submissions, including several specifics identified in law • FDA must publish guidance within specific timeframes on qualification standards and processes; includes input from outside experts	• Pilot process to engage external experts; public workshop on taxonomy, standards, elements of biomarker (BM) qualification plan • Guidance on taxonomy, context of use, evidentiary standards • Publish list of BM qualification and submissions • Early consultation on use of BMs as new surrogate endpoints • New Type C meeting to address novel surrogates as primary endpoint

Expanded Access to Investigational Drugs

Cures Sec. 3032	FDARA Sec. 610
• Sponsors must make publicly available their policy on evaluating and responding to expanded access requests • Policy must include company contact info, criteria for evaluating requests, time for company to acknowledge request, link to trial record on ct.gov with information about expanded access • No guarantee to access	• FDA must work with NIH/others to hold a public meeting within 270 days to discuss clinical trial inclusion/exclusion criteria • FDA must publish a report on meeting within 90 days addressing specific criteria described in law • Comptroller General must report to HELP/E&C 1 year after FDA report, addressing specifics in law • FDA must issue guidance addressing eligibility for trials, and ways sponsors can develop appropriate criteria • FDA must issue guidance to streamline IRB approval • Expands Cures to require sponsors to post EA policies within 15 days of designation of Breakthrough, Fast Track, or Regenerative Advanced Therapy

Right to Try Bill - S. 204

- S. 204 passed by Senate on August 3, 2017; referred to House E&C Committee
  - House companion bills (H.R. 2368, H.R. 878, H.R. 1020); Health Subcommittee hearing on Oct. 3
- Allows eligible patients to receive an eligible investigational drug
  - Patients with life-threatening disease or condition
  - Investigational drug completed phase I, remains under investigation, is being actively developed or produced, and is not on clinical hold
- Sponsors that comply with Act would be exempt from certain FDCA and PHS Act provisions, specified regulations, and would have enhanced protection from liability
- FDA could not use clinical outcomes of RTT drug to delay or adversely affect review/approval, unless critical to consider, or requested by sponsor
- Sense of the Senate:
  - Law establishes national standards for access
  - Law does not establish a new entitlement

Other Highlights from Cures and FDARA

- Pediatrics (FDARA)
- Orphan Drug (FDARA)
- Health Care Economic Information (Cures)
- Summary Level Reviews (Cures)
- Human Subject Protection (Cures)
- Access to Generic Drugs (FDARA)

Pediatric Oncology Drug Development (Sec. 504 FDARA)

- "RACE Act"
- Expands PREA for original applications for a new active ingredient intended to treat an adult cancer and directed at a molecular target that is "substantially relevant" to a pediatric cancer
  - FDA may require "a" study
  - Study shall provide clinically meaningful data on dosing, safety and preliminary efficacy to inform potential pediatric labeling
  - Effective 3 years after enactment
  - Orphan drug waiver does not apply to these drugs
- Substantially relevant requirement:
  - Within 1 year, FDA must publish and maintain (1) a list of molecular targets substantially relevant to the growth and progression of a pediatric cancer, and (2) a list of molecular targets of new cancer drugs and biological products in development for which the requirement will be automatically waived
- FDA and NCI must hold a meeting of researchers, patients, and stakeholders to get input on development of these drugs

Orphan Drug Development (Sec. 607 FDARA)

- **Codified clinical superiority requirement in current FDA regulations**
  - **To obtain exclusivity for a drug that is otherwise the "same drug" as a previously approved product, sponsor must show the drug is clinically superior**
  - **Can show by establishing greater efficacy, greater safety, or by providing a major contribution to patient care**

Health Care Economic Information (Sec. 3037 Cures)

- Amends sec. 502(a) on manufacturer dissemination of HCEI to clarify and expand FDAMA Sec. 114
- Broadens audience eligible for communication
  - Includes "a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis"
- States that HCEI is not considered false or misleading if it "relates" (rather than "directly relates") to an approved indication for a drug or biological product.
  - If HCEI materially differs from the approved labeling, a "conspicuous and prominent statement" describing the differences must be included
- Broadens definition of HCEI to mean "any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcome, of the use of a drug."

Summary Level Reviews (Sec. 3031 Cures)

- **Amends sec. 505 of the FDCA and sec. 351 of the PHSA to allow FDA to rely upon "qualified data summaries" to support approval of a supplement for a "qualified indication" for an approved drug or biologic.**
  - **Qualified data summary: a summary of clinical data that demonstrates the safety and effectiveness of a drug with respect to a qualified indication.**
  - **Qualified indication: an indication that FDA determines to be appropriate for summary level review.**
- **A supplement is eligible for summary review if:**
  - **There are existing data available and acceptable to FDA demonstrating the drug's safety; and**
  - **All data used to develop the qualified data summary are submitted as part of the supplement.**

Human Subject Protection

- **Harmonization of Rules (sec. 3023 Cures)**
  - **Common Rule and FDA human subject protection regulations must be harmonized (by December 2020)**
  - **IRB process for trials at multiple sites streamlined**

- **Informed Consent (sec. 3034 Cures)**
  - **FDA may waive or alter informed consent for clinical trials with minimal risk, when they include appropriate safeguards to protect the rights, safety, and welfare of subjects/patients**

Access to Generic Drugs

- **Priority Review of Generic Drugs (sec. 801 FDARA)**
  - **FDA must prioritize review of generic drugs (or supplements) with no more than 3 competitors, or are on drug shortage list, and take action within 8 months**

- **Information about Drugs with Limited Competition (sec. 804 FDARA)**
  - **NDA and ANDA holders must notify FDA:**
    - **180 days before withdrawing a drug from sale, or asap but no later than date of withdrawal**
    - **Within 180 days of approval if the drug will not be available for sale within 180 days of approval**

Access to Generic Drugs

- **Competitive Generic Therapies (sec. 803 FDARA)**
  - **FDA may, upon request of sponsor of a designated competitive generic therapy (no more than 1 approved drug) that is a reference listed drug, expedite development and review of an ANDA**
  - **When FDA grants request, FDA must take actions to expedite review and approval including:**
    - **Meet with sponsor through development process**
    - **Provide timely advice**
    - **Involve appropriate senior staff for combination or complex products**
    - **Assign a cross-disciplinary project lead to facilitate review and be scientific liaison with sponsor**

Thank you!