Prescription Drug User Fee Act (PDUFA IV)

Department of Health and Human Services
Food and Drug Administration

February 16, 2007

PDUFA Background

PDUFA History

- PDUFA I: FY93-FY97
  - Primary focus – decreased review times
- PDUFA II: FY98-FY02
  - Re-authorized in 1997 as part of FDAMA
  - Primary focus - decreased review times and shortened development times
- PDUFA III: FY03-FY07
  - Re-authorized in June 2002 as part of Bioterrorism Preparedness and Response Act
  - Focus: Expanded interaction and communication during 1st cycle review and support for post-market risk management for first 2-3 yrs post-approval

PDUFA Success

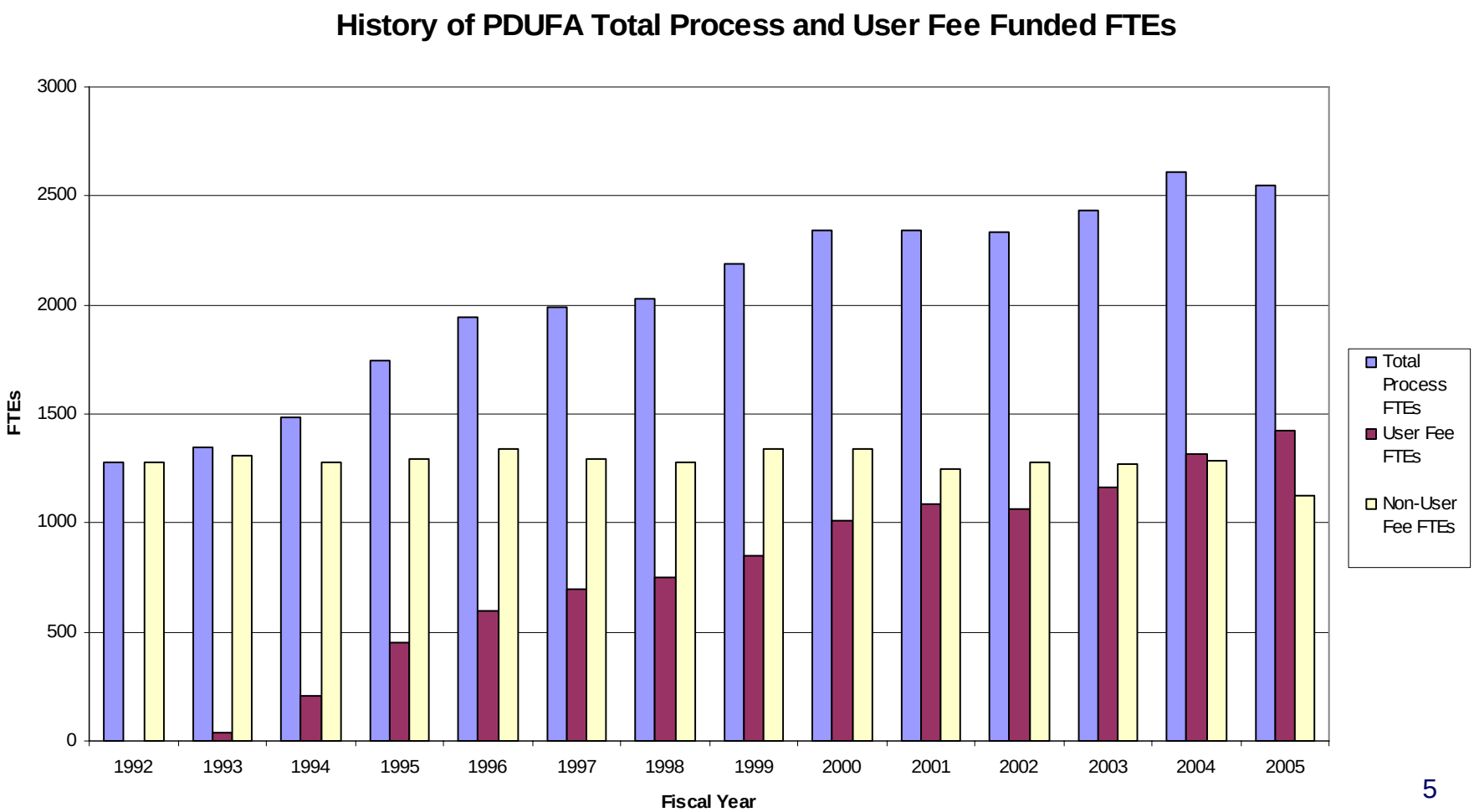
- User fees added resources for more review staff to improve review timeliness and make drug development more efficient through meetings with industry
- FDA agreed to meet specific performance goals

Result

"Revolution in regulation of pharmaceutical products"

- More predictable, streamlined process
- Reduced review and approval times

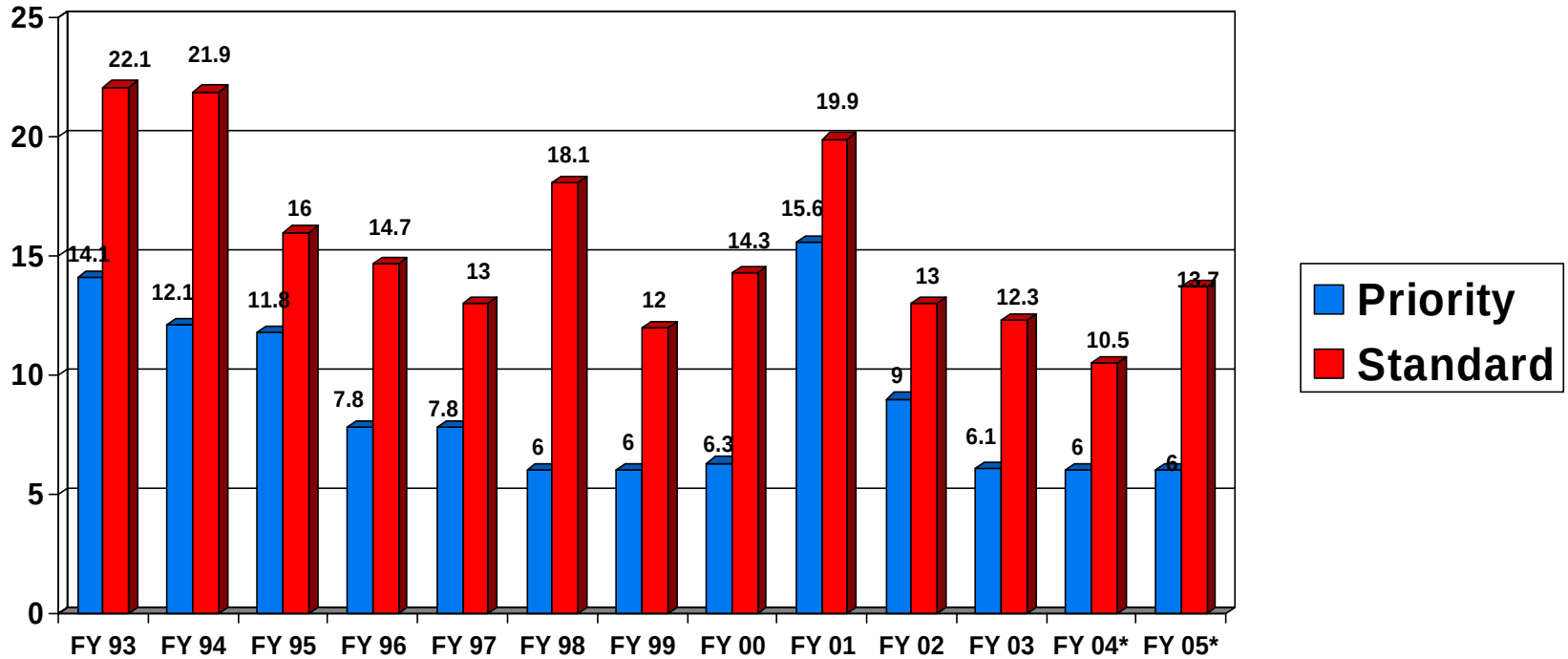
PDUFA Fees Enabled Increased Staffing and Improved Systems for Drug Review



FTE = Full Time Equivalent staffing

With More Staff and Better Managed Process FDA Reduced Overall Time to Marketing Approval

Median Approval Time for NDAs and BLAs by Year of Receipt (months)



NDA= New Drug Application; BLA=Biologic Licensing Application. *Estimates

"Priority" applications represent drugs offering significant advances over existing treatments. Applications for drugs similar to those already marketed are designated "Standard".

PDUFA Has Resulted in Significant Increase in Patient Access to New Drugs and Biologics

- From FY1993 through October 31, 2006, FDA has approved 1,103 NDAs and 117 BLAs, including:
  - 76 new cancer drugs
  - 111 drugs for metabolic & endocrine disorders
  - 178 anti-infective drugs (including 56 for treatment of HIV or hepatitis)
  - 115 drugs for neurologic & psychiatric disorders
  - 80 drugs for cardiovascular & renal disease

FDA Concerns Emerging During PDUFA III

- Pre-market review losing funding stability
  - Actual cost of inflation greater than adjustment for fees
  - Workload adjuster does not adequately account for actual increases in review work
- Post-market safety system demands are growing
  - Significant growth in reports of serious and unexpected adverse events
  - Post-market surveillance and analysis is understaffed; needs better tools and methods

Stakeholder Perspectives on Reauthorization

- Patient Advocacy Groups
  - Support PDUFA as vehicle for speeding access to new drugs
  - Suggest fees increase to fund post-market safety activities and add performance goals
- Consumer Advocacy Groups
  - Some prefer full funding with appropriated funds
  - Increase funding for post-market safety
  - Increase funding for DTC ad review; some suggested establishing a separate fee

Stakeholder Perspectives on Reauthorization (cont.)

- Health Professional Groups
  - Support PDUFA to maintain efficient process and availability of new drugs
  - Increase fees for post-market safety; remove or revise time limit and include older drugs
  - Increase fees to support review of DTC ads
- Regulated Industry
  - Support stabilizing and strengthening base program
  - Support modernization of post-market safety system
  - Support separate fee for advisory review of DTC TV ads

PDUFA IV Proposed Recommendations

Proposed Recommendations: Ensure Strong Pre-Market Review and Transform Post-Market Safety System

- **Sound Financial Footing**
  - Ensure funding keeps pace with program costs
- **Enhance Pre-Market Review**
  - Communication of planned review timeline to sponsor
  - Initiatives to expedite drug development
- **Transform Post-Market Safety System**
  - Modernize pharmacovigilance and post-market safety system
  - Reduce medication errors by enhancing proprietary name review
  - Increase FDA capacity for review of DTC television ads

Sound Financial Footing: Flaws in PDUFA III Adjusters

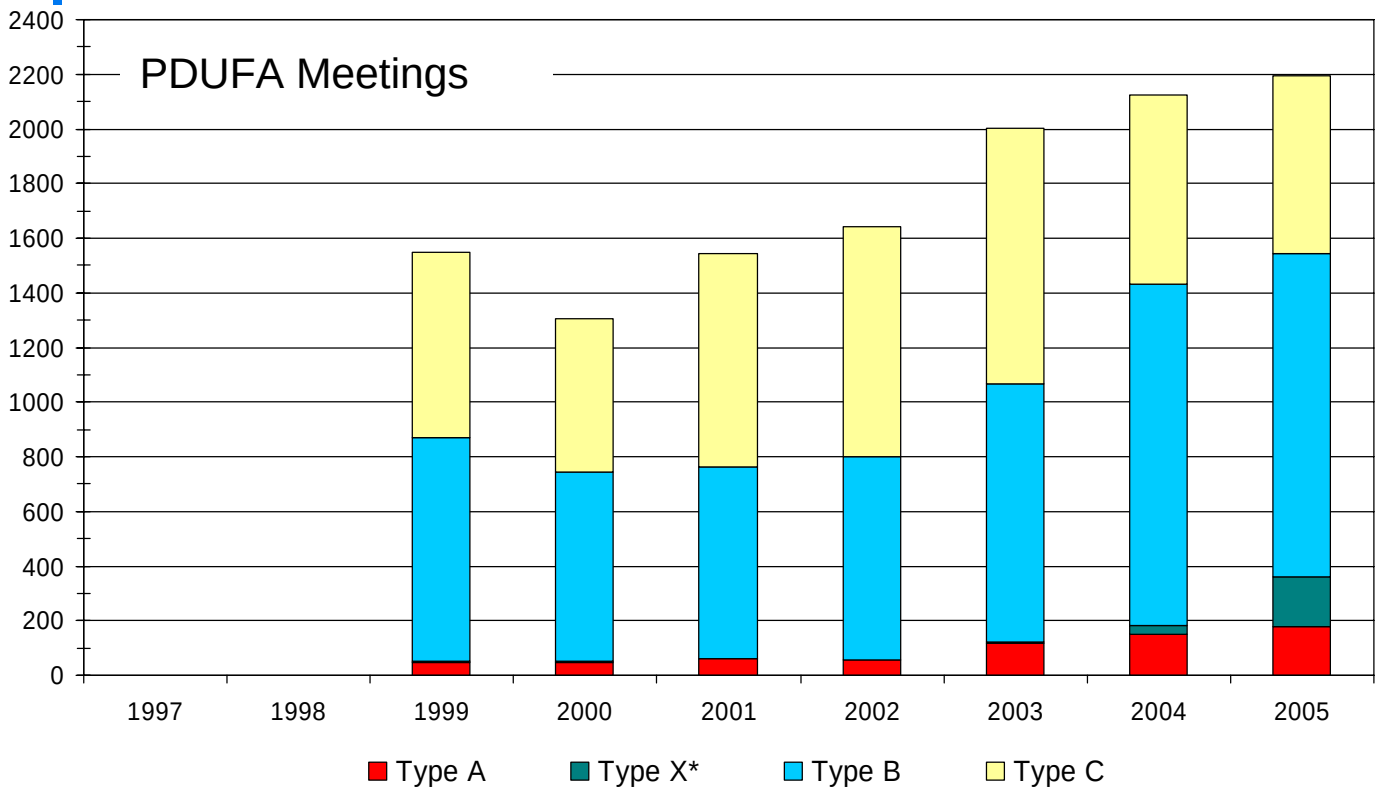
- Current law provides for fee adjustment to account for inflation and increased workload but…
  - Inflation adjuster in statute includes cost of federal salary but *omits* other increases in payroll costs (e.g., federal health benefits, retirement)
  - Workload adjuster in statute includes growth in number of applications (e.g., NDAs, BLAs, Commercial INDs) but *omits* growth in sponsor-requested meetings, special protocol assessments and other major increase areas
  - RESULT: Under-adjustment of PDUFA III fees in the face of major growth in workload

PDUFA III Inflation: Fee Increases Not Keeping Pace with Actual Growth in Pay, Benefits, and Other Costs

Average Personnel Compensation & Benefit Cost (PC&B) per FTE provided by FDA OFM						
Fiscal Year	**CDER Average PC&B**	**Percent Change**	**CBER Average PC&B**	**Percent Change**	**FDA Average**	**Percent Change**
2000	$92,200	--	$87,100	--	$81,700	--
2001	$97,700	6.0%	$91,900	5.5%	$85,600	4.8%
2002	$105,100	7.6%	$98,400	7.1%	$90,400	5.6%
2003	$111,600	6.2%	$102,900	4.6%	$94,400	4.4%
2004	$119,700	7.3%	$108,000	5.0%	$102,400	8.5%
2005	$125,800	5.1%	$117,200	8.5%	$108,200	5.7%
5-year avg.		**6.4%**		**6.1%**		**5.8%**

- Federal pay raise: 5-year average of 4.2% versus 5-year average increase of 5.8% in FDA Personnel Compensation & Benefit cost
- FY2001-2005: Rent costs have gone up over 21% per FTE and the rate of increase is accelerating as more of White Oak comes on line
- FY2001-2005: FDA contract services costs per FTE have increased 58%

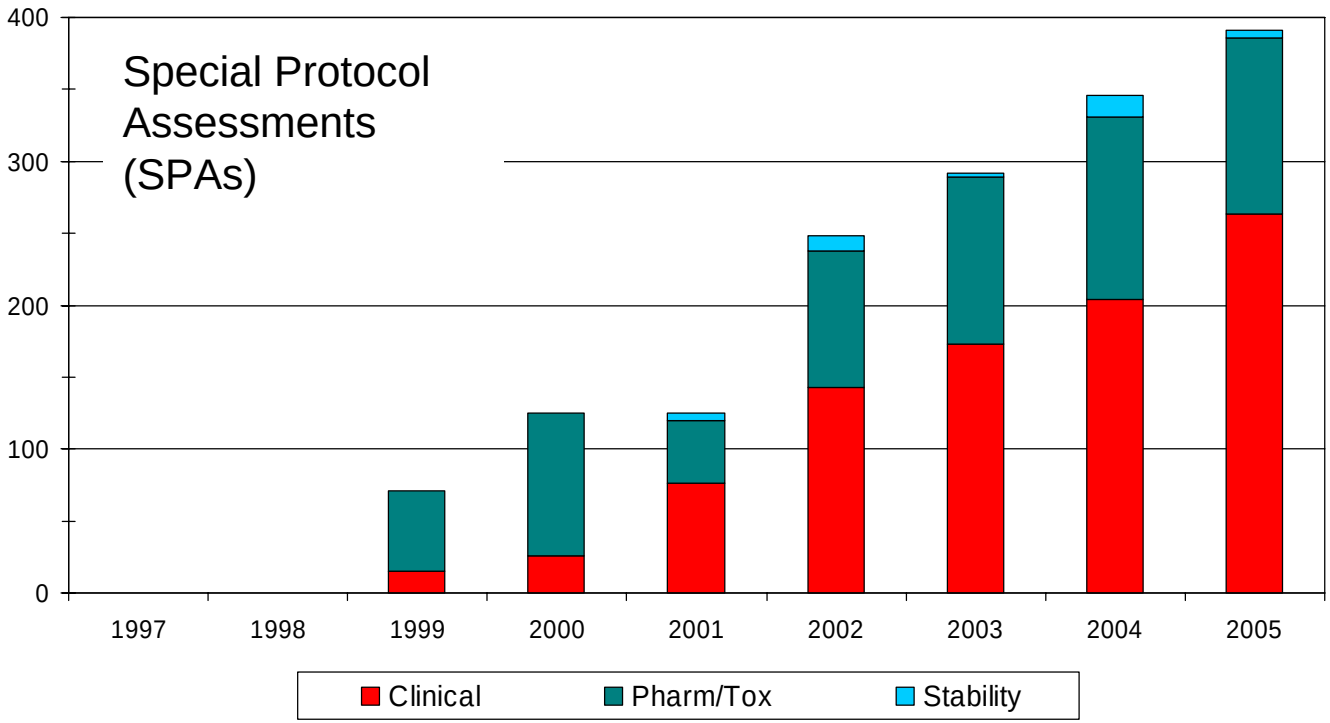
PDUFA III Workload: Significant Increase in Industry Sponsor Requests for IND-Phase Meetings



Type A Meetings requested/ scheduled grew more than 200% in past 3 yrs.

Type B Meetings requested/ scheduled grew more than 60% in past 3 yrs.

PDUFA III Workload: Surge in Sponsor Demand for Special Protocol Assessments by FDA



Pharm/Tox protocol assessments increased more than 50% in past 3 yrs.

Clinical protocol assessments increased more than 160% in past 3 yrs.

PDUFA IV: Recommend New Inflation & Workload Adjuster

- **Recommended revision to Adjuster for Inflation**
  - Change statutory provision for calculation of inflation adjustment to include actual FDA rate of increase in costs of pay and benefits per FTE over the most recent 5-year period
- **Recommended revision of Review Workload Adjuster**
  - Change the surrogate for IND workload in the statute from the numbers of new commercial INDs received each year to the total number of active commercial INDs each year.
  - Proportionately adjust numbers of Active INDs and NDA/BLAs to account for impact on workload of
    - Increased meetings and special protocol adjustments for INDs
    - Increased meetings, labeling supplements and annual reports for NDAs and BLAs.

PDUFA IV: Financial Baseline and Enhancements (FY 2008)

Financial Baseline	Dollars	FTE
FY 2007 Baseline -- Adjusted for Inflation	$ 305,455,400	1539
Inflation Adjustment for FY 2008	17,716,600	
Adjustment for Increased Rent and Rent-Related Costs	11,721,000	
Adjustment for Increased Work per IND & NDA PDUFA III	20,000,000	87
PDUFA IV Baseline Before Enhancements	**$ 354,893,000**	**1626**
Enhancements		
Premarket –Expediting Drug Development	$ 4,600,000	20
Premarket – Improving IT Infrastructure for Drug Review	4,000,000	
Postmarket –Modernizing and Transforming Safety System	$ 29,290,000	82
PDUFA IV Total[1] for FY 2008	**$ 392,783,000**	**1728**

[1]Further workload adjustment, to account for work levels in FY07, is expected to add about $45,000,000 and 195 FTEs for a final total of about $438,000,000 and 1925 FTE for FY 2008.

PDUFA IV: Enhancing Pre-Market Review

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- Focus on achieving the goals stated in the Good Review Management Principles/Practices Guidance
  - With current workload and staffing levels, reviewers struggle to complete application reviews by the PDUFA goal date
  - Completion of primary reviews late in review cycle limits time for important end-of-review activities including:
    - Supervisory review and decision making
    - Labeling discussions with sponsor
    - Agreement on any postmarketing study commitments
    - Review and agreement on any necessary risk management plans

PDUFA IV: Enhancing Pre-Market Review

- With new resources and staffing proposed under PDUFA IV, FDA can commit to:
  - Maintain current review goals for applications
  - Develop a review plan for each application that includes target dates for completion of various review activities
    - Review plan to be based on application as submitted
  - Communicate the planned review timeline to the sponsor in the “74-day letter” to increase transparency of review
    - Include targets dates for labeling and PMC discussions
    - Review plan may be modified by submission of major new data or analyses that FDA agrees to review

PDUFA IV: Expediting Drug Development

- Publish for comment new draft guidances to clarify current FDA thinking on certain critical trial design issues
  - Clinical Hepatotoxicity - FY2008
  - Non-inferiority Trials – FY2008
  - Adaptive Trial Designs – FY2008
  - End of Phase 2(a) Meetings – FY2008
  - Multiple Endpoints in Clinical Trials – FY2009
  - Enriched Trial Designs – draft by end of FY 2010
  - Imaging Standards as End Point in Clinical Trials - FY2011
- Work to clarify regulatory pathways in 3 important areas
  - Predictive toxicology
  - Biomarker qualification
  - Missing clinical trial data

PDUFA IV: Other Pre-Market Review Changes

- Pilot programs for Continuous Marketing Applications will not continue in PDUFA IV
  - Booz-Allen Hamilton study found that the overall benefits of the pilots programs did not outweigh the added costs to sponsors and FDA
- Program that allowed sponsors to request that FDA engage an independent consultant to assist in the review of certain biotechnology development programs will not be continued
  - FDA has received no requests under the program during PDUFA III
  - FDA has existing mechanisms to allow for consultation with outside experts as needed to inform our review and decision-making on biotechnology products

PDUFA IV: Improving Information Technology Infrastructure

Goal: Speed Progress Toward Fully Automated Human Drug Review

- Build on Information Technology (IT) accomplishments of PDUFA III
  - Electronic Common Technical Document (eCTD) standard for submitting NDAs and BLAs electronically
  - FDA Electronic Gateway – single portal for electronic submissions to FDA via the Internet
  - Progress toward consolidated IT infrastructure
  - Improved communications and technical interactions
- Build toward FDA's vision for operations in the 21st Century

PDUFA IV IT Proposal: Outcomes

- By the end of PDUFA IV:
  - Industry will be able to send in their electronic applications with automated cross-links to previously submitted data and information, so that they only have to submit things once
  - FDA reviewers will be able to retrieve all relevant submissions and related data electronically from their work station, and have efficient tools for searching and analyzing data to support their review
  - FDA will be able to manage drug labeling submittals and labeling discussions with sponsors in a modular manner using Structured Product Labeling electronic format, assuring integrity and configuration of the product labeling information
  - FDA will have capability to handle two-way regulatory correspondence with industry, accelerating movement toward all-electronic submission and review environment, and reducing paper submission management systems

PDUFA IV IT Proposal: Process and Measures

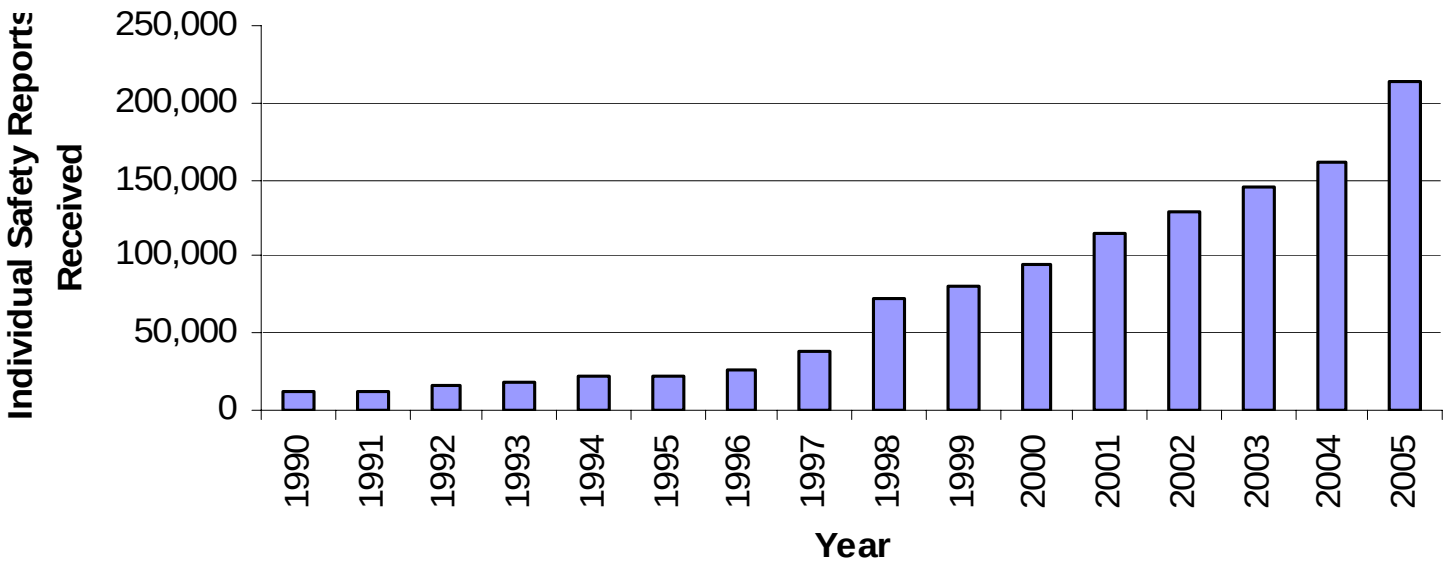
- Rolling 5-year IT Plan for technical approach to a more integrated, standards-based automated regulatory electronic submission and review environment
  - Draft IT Plan will be published for public comment
  - IT Plan will be reviewed and approved through appropriate FDA governance process
  - Annual assessment of progress
- Quarterly meetings with industry to discuss implementation of the IT Plan and potential impacts of current and future activities on stakeholders
- Measures of progress toward achievement of objectives
  - Metrics on how often industry is submitting material electronically and how well they are complying with electronic submission standards
  - Metrics on how well FDA is transitioning from legacy IT systems to new-generation common systems

Benefits to patients, industry, and FDA from IT investments

- Improved public health through better information and analysis
- Improved productivity and efficiency
- Greater consistency across FDA
- More predictable technology improvement path
- Improved harmonization with international standards

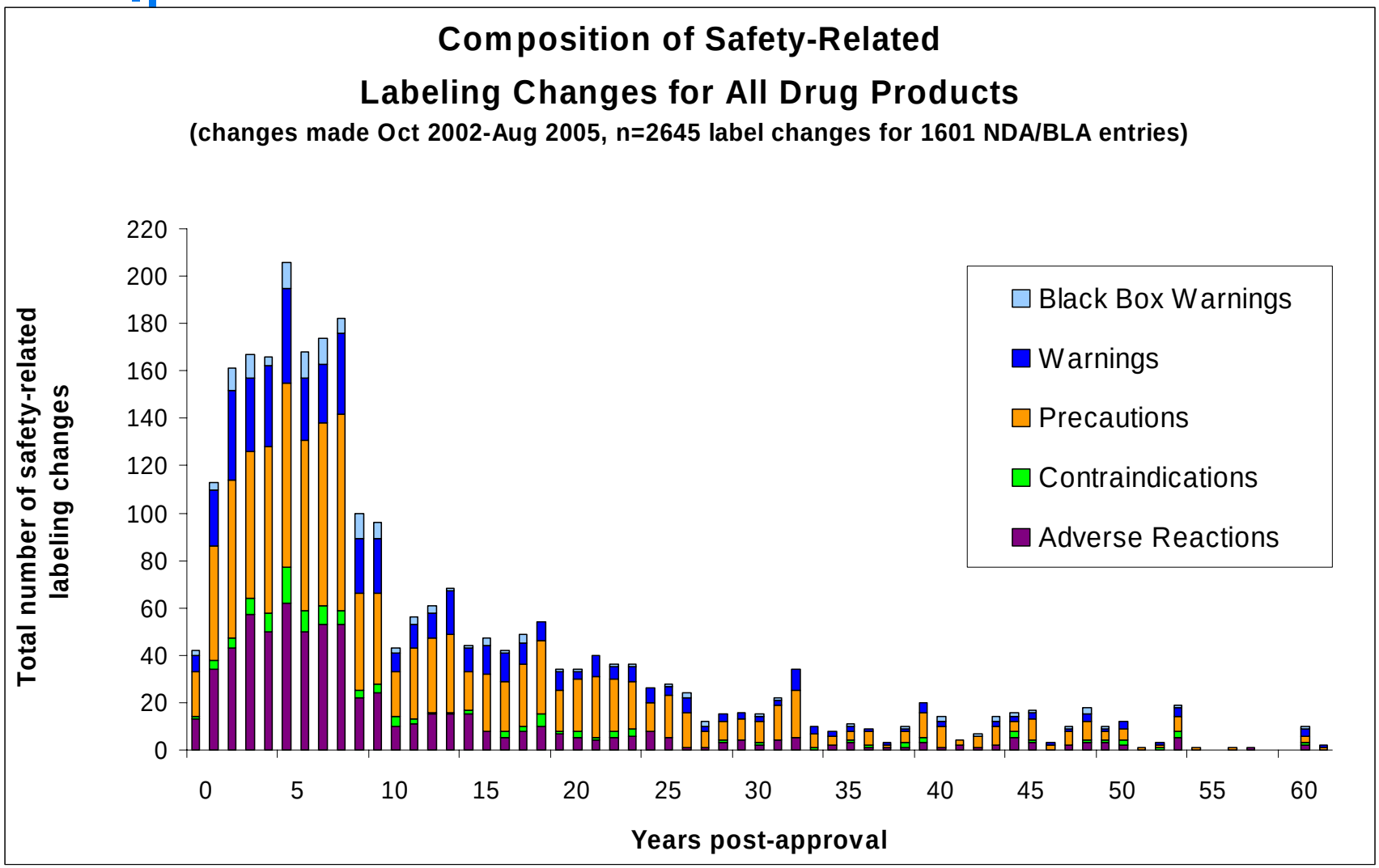
PDUFA IV: Modernizing and Transforming the Post-market Drug Safety System

Post-market Drug Safety Challenges: Growing Volume of Adverse Event Reports



Growth in reports of serious and unexpected Adverse Events (Manufacturer 15-day reports) demands more capacity for FDA surveillance and risk management

PDUFA III gave FDA new authority for Fee-funded Post-Approval for 3 Years' Risk Management-- But Safety-Related Changes Remain High for Much Longer Period



Post-market Drug Safety Challenges

- Inadequate resources to address:
  - Dramatic increase in the number of serious adverse event reports
  - Substantial portion of critical post-market risk management that occurs far beyond the current 3-year fee-funded window
- Inability to keep pace with rapidly evolving science of safety, technology and emerging linked databases
- Inadequate IT infrastructure, including AERS, linked data handling and tracking systems
- Need for more predictable, timely and scientific process for proprietary name review

Proposed PDUFA IV Solution

- Transformational strategy to enhance and modernize the drug safety program
- Adopt new scientific approaches and maximize the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events
- Produce guidance in critical areas
- Increase pre- and post-market staff interactions
- Enhance informatics infrastructure

PDUFA IV: Post-market Safety Program Elements

- Provide adequate resources to address increased workload throughout the product life cycle: Elimination of 3-year post-approval restriction on use of fees
- Activities designed to modernize the process of pharmacovigilance
  - Contract study
  - Epidemiology best practices
  - Expanding database resources
  - Development and validation of risk management/communications tool
- Enhance informatics infrastructure
- Improve communication and coordination
- Enhance and modernize proprietary name review

PDUFA IV: Post-Market Safety Modernizing Pharmacovigilance

- **Contract study: maximizing the public health benefit of adverse event collection throughout the product life cycle**
- **Identify epidemiology best practices and develop guidance document**
  - With input from academia, industry and the general public, achieve consensus regarding epidemiology methods and best practices to optimize use of observational studies

PDUFA IV: Post-Market Safety Modernizing Pharmacovigilance (cont.)

- **Expand databases for analyses of new drug safety data**
  - Support expanded access to important population databases for both additional epidemiologic research and targeted safety surveillance
- **Maximize risk management and risk communication tools and programs**
  - Conduct assessments of the effectiveness of identified Risk Minimization Action Plans and other risk management/risk communication tools
  - Hold public discussions and publish results of assessments

PDUFA IV: Post-Market Safety Program Elements

- **Enhance standards-based information systems to support post-market drug safety activities**
  - AE reporting systems and surveillance tools
  - IT infrastructure to support access and analyses of externally-linked databases
  - Workflow tracking systems
- **Improve communication and coordination between pre-market and post-market review components**
  - CDER's Office of Surveillance and Epidemiology and Office of New Drugs
  - CBER's Office of Biostatistics and Epidemiology and pre-market product review Offices

PDUFA IV: Post-Market Safety Program Elements (cont.)

- **Modernize the proprietary name review program**
  - Guidance development
    - Contents of a complete submission
    - Good naming, labeling and packaging practices
    - Good proprietary name evaluation practices
  - Complete review of proprietary name at end-of-Phase 2 with 180-day goal date
  - Supplemental/complete review of proprietary name at NDA/BLA submission with 90-day goal date
  - Pilot program using new review paradigm
  - Public process to explore proprietary name “reserve”
  - Public release of Phonetic and Orthographic Computer Analyses (POCA) tool

Separate User Fee Program for Review of DTC Television Ads

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- Stakeholders (consumers and Congress) have expressed concerns about DTC advertisements that overstate benefits and do not fairly convey risks
- Industry can **voluntarily** submit draft ads for FDA advisory review prior to first broadcast
- Timely FDA advisory review of draft DTC television advertisements, which reach the broadest audiences, will increase incentives for voluntary submissions resulting in better quality ads

Separate User Fee Program for Review of DTC Television Ads

- Why a separate user fee?
  - Fewer than 30 firms do DTC television ads
  - Only firms that submit DTC television ads for advisory review will pay fees
- How much are the fees?
  - **$6.25M** to be collected annually, adjusted for inflation and workload
  - Stable funding design: one-time participation fee in first year, and annual pre-payment for advisory reviews

Separate User Fee Program for Review of DTC Television Ads

- What will fees be used for?
  - Will fund 27 FTE for pre-market advisory review of TV advertisements
  - Metrics phased in: in year 5 of PDUFA IV, FDA will commit to review specified number of ads submitted for advisory reviews in 45 days, and specified number of resubmissions in 30 days

Separate User Fee Program for Review of DTC Television Ads

- Mechanism for collection – advisory review fees
  - 120 days before start of FY 08 (or start of program if statute delayed), FDA will issue FR notice asking persons to identify number of TV ads they intend to submit for advisory review during FY 08
  - Response will be a commitment to pay the advisory review fees for the identified submissions

Separate User Fee Program for Review of DTC Television Ads

- Mechanism of collection – advisory review fees
  - Based on the number of submissions identified, 60 days before start of FY 08 or program, FDA will issue another FR establishing the fees for FY 08.
  - Fees will be $6.25 million divided by the number of submissions identified; e.g., if 150 submissions are identified, fee will be $6.25 million ÷ 150 = $42,000.
  - Fee per submission may not exceed $83,000 in first year.

Separate User Fee Program for Review of DTC Television Ads

- Mechanism of collection – advisory review fees
  - FDA will invoice companies for fees.
  - Fees due and payable on or before October 1 of fiscal year.
  - Late fees: statute will provide for late fees for late payment of invoices and for advisory reviews not identified before start of fiscal year (50% late fees)
  - Works the same in later years

Separate User Fee Program for Review of DTC Television Ads

- Mechanism of collection – participation fee
  - One time only assessment, either before start of program in FY 08, or when company decides to seek advisory reviews
  - Designed to collect $6.25 million (one year of reserves)
  - FDA will assess each participating sponsor for an amount equal to that assessed for the annual advisory review fees in the first year of program
    - Payment is graduated based on number of advisory reviews

Separate User Fee Program for Review of DTC Television Ads

- Late participants: will be assessed at least as much as those who joined in FY 08
- Participation fee will capture all ads submitted for advisory review during first year of participation, even if identified late (and will be 50% more if late fees applied to advisory reviews)
- In FY 12, or if program ends early, any money remaining, less expenses needed to close down the program, will be returned to sponsors