A Tale of Three UFAs

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Congress is Evaluating three Drug User Fee Proposals

- PDUFA V
- Generic Drug User Fee
- Biosimilars User Fee

Benefits of Multiple Fee Programs

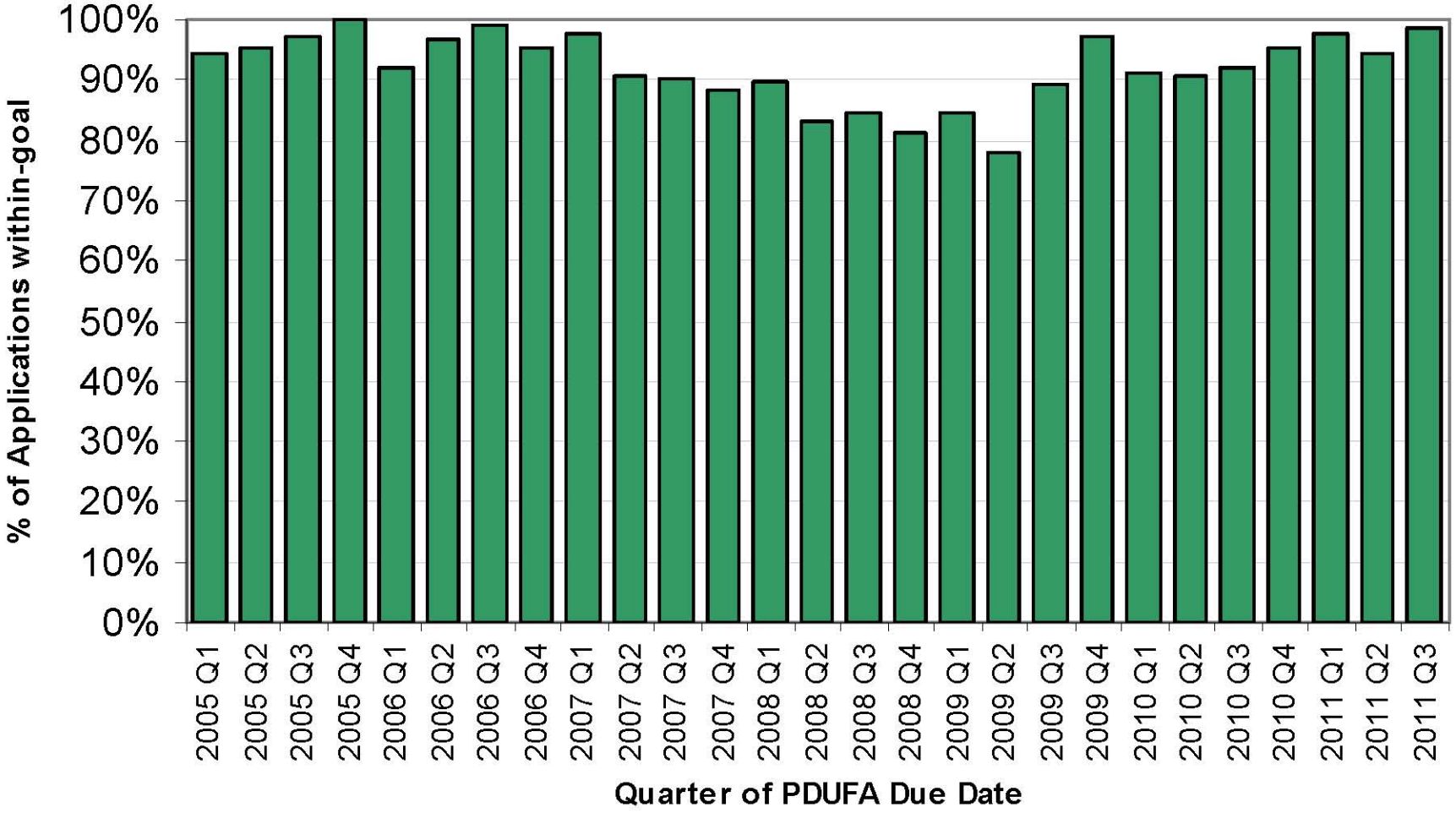
- Since 1992, parts of CDER have had a “poor stepchild” attitude, since not covered by PDUFA and thus relatively more poorly resourced
- Improved in late 90’s with broadening of PDUFA to include postmarket safety in PDUFA 3
- Currently proposed programs will include most Center activities

Ability to Modernize Cross-cutting Programs

- Drug registration and listing
- Postmarket safety surveillance (often includes generics)
- Build a single consistent program for regulating pharmaceutical quality across ORA and CDER (as well as CBER and CVM)
- Ordering, conducting and assessing a facility inspection

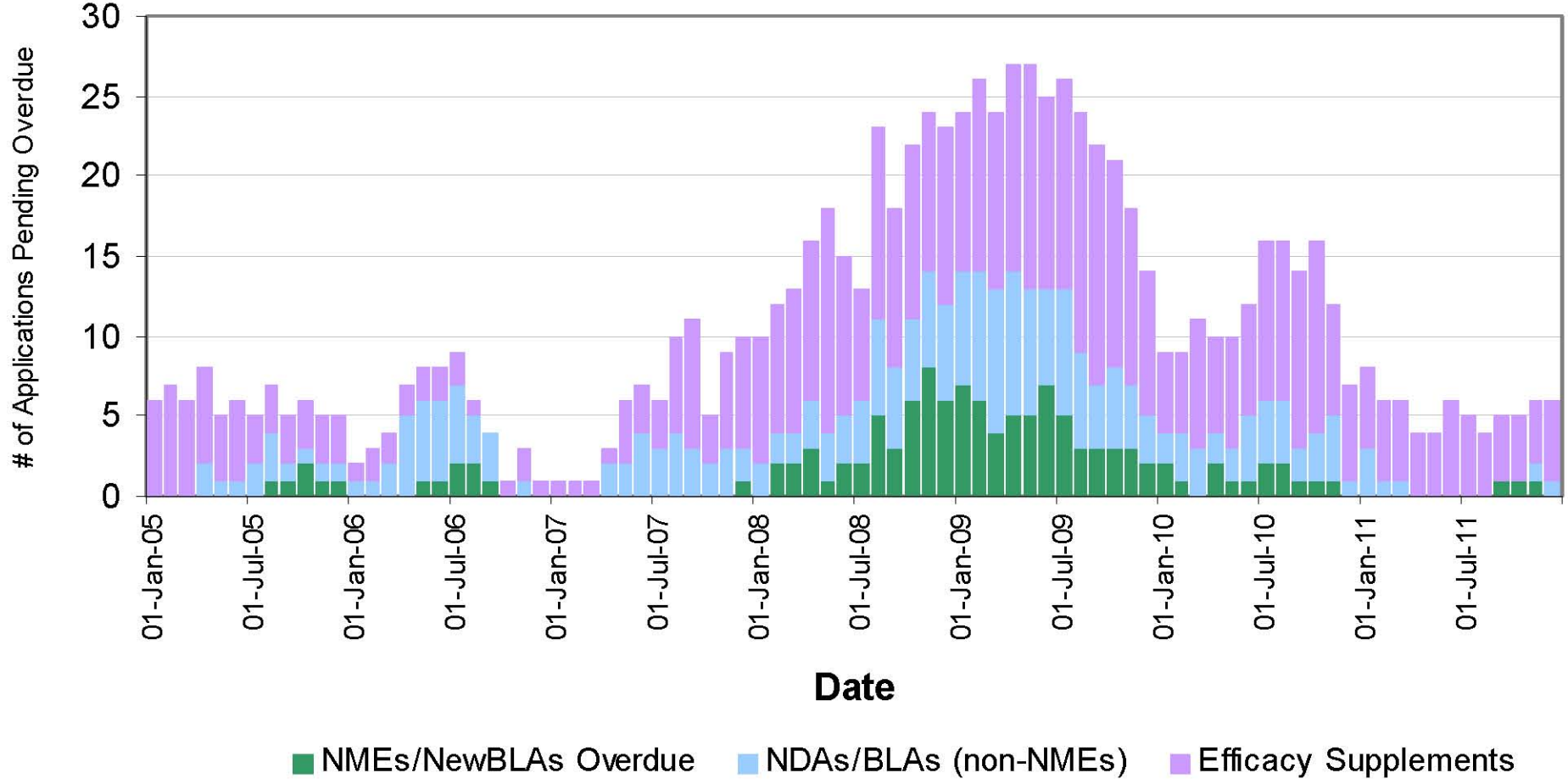
PDUFA

CDER PDUFA Application Review Performance (NDAs, BLAs, Efficacy Supplements) 2005 - 2011



CDER data as of 11/30/2011. Figures reflect aggregate performance for all NDAs, BLAs, and Efficacy Supplements based on the month of the PDUFA review goal.

CDER Pending Applications with Overdue PDUFA Goals

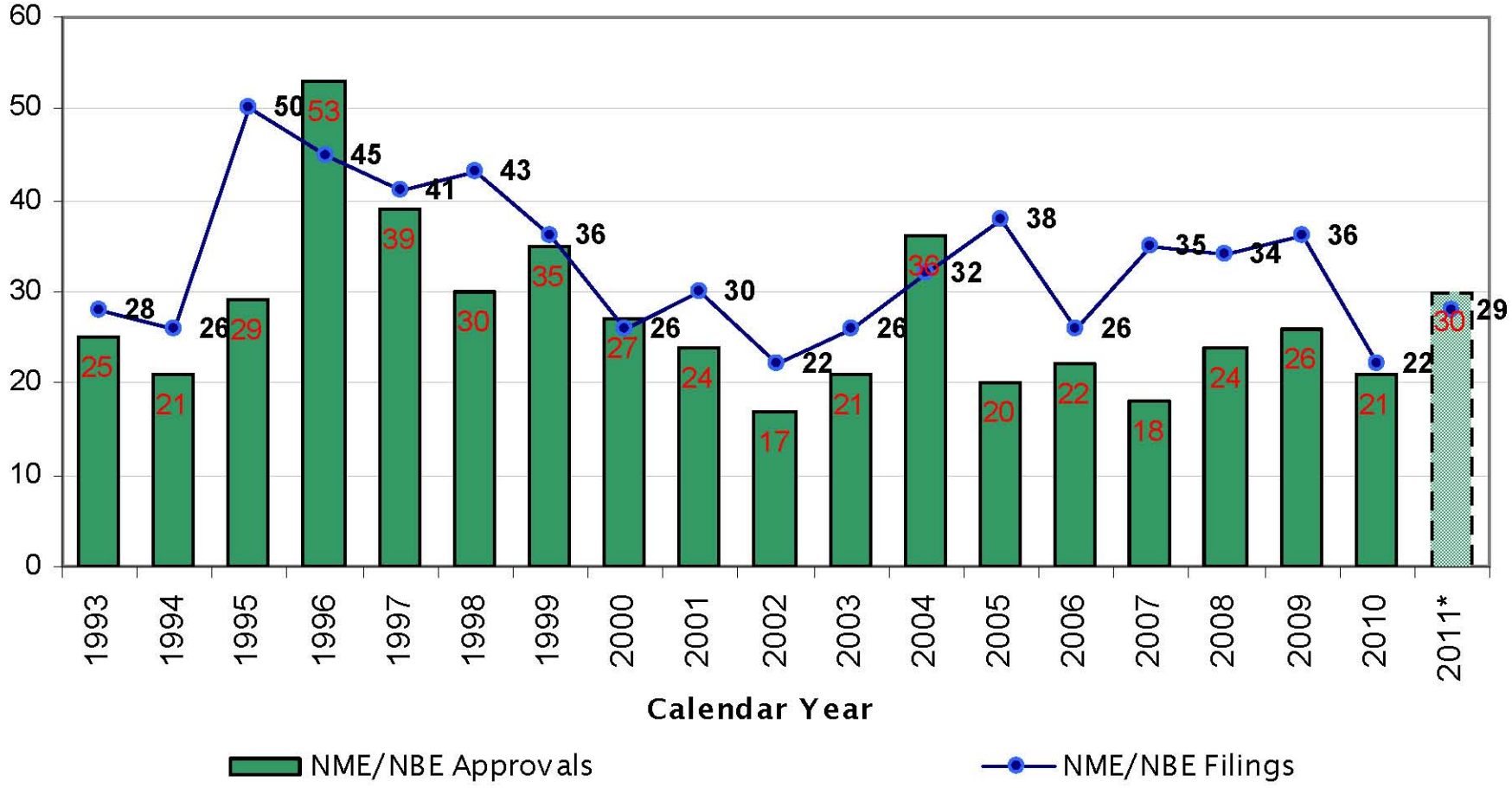


CDER data as of 11/30/2011. Figures reflect the number of NDAs, BLAs and efficacy supplements pending and overdue on their PDUFA goal date, evaluated on the first day of each month.

What about new drug approvals?

- IN CY2011 FDA approved 31 NME applications, the highest number since 2004
- NME approvals in 2011 include a number of "breakthrough" drugs that provide much needed new treatment options for patients
- Nearly a third of CY2011 NME approvals
  - Are for rare diseases
  - Were submitted by "emerging" sponsors
- Average first cycle approval rates for NME applications in PDUFA IV are at the highest levels for both priority and standard review since the start of PDUFA

CDER New Molecular Entity and New Biologic Entity Filings and Approvals

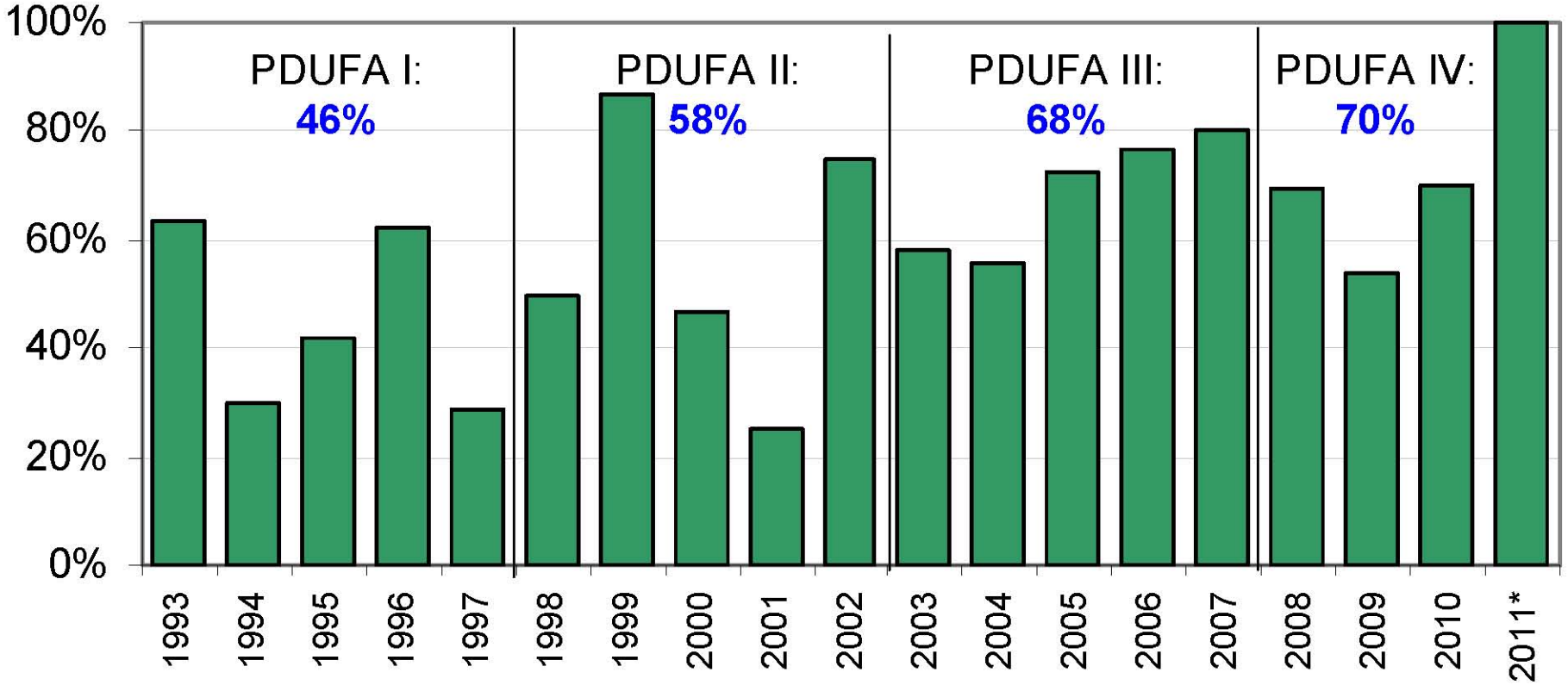


*CDER data as of 11/30/2011. New Biologic Entities are included in CDER figures beginning in 2004, when review authority for therapeutic biologic products was transferred from CBER to CDER.

Looking beyond NME *quantity*

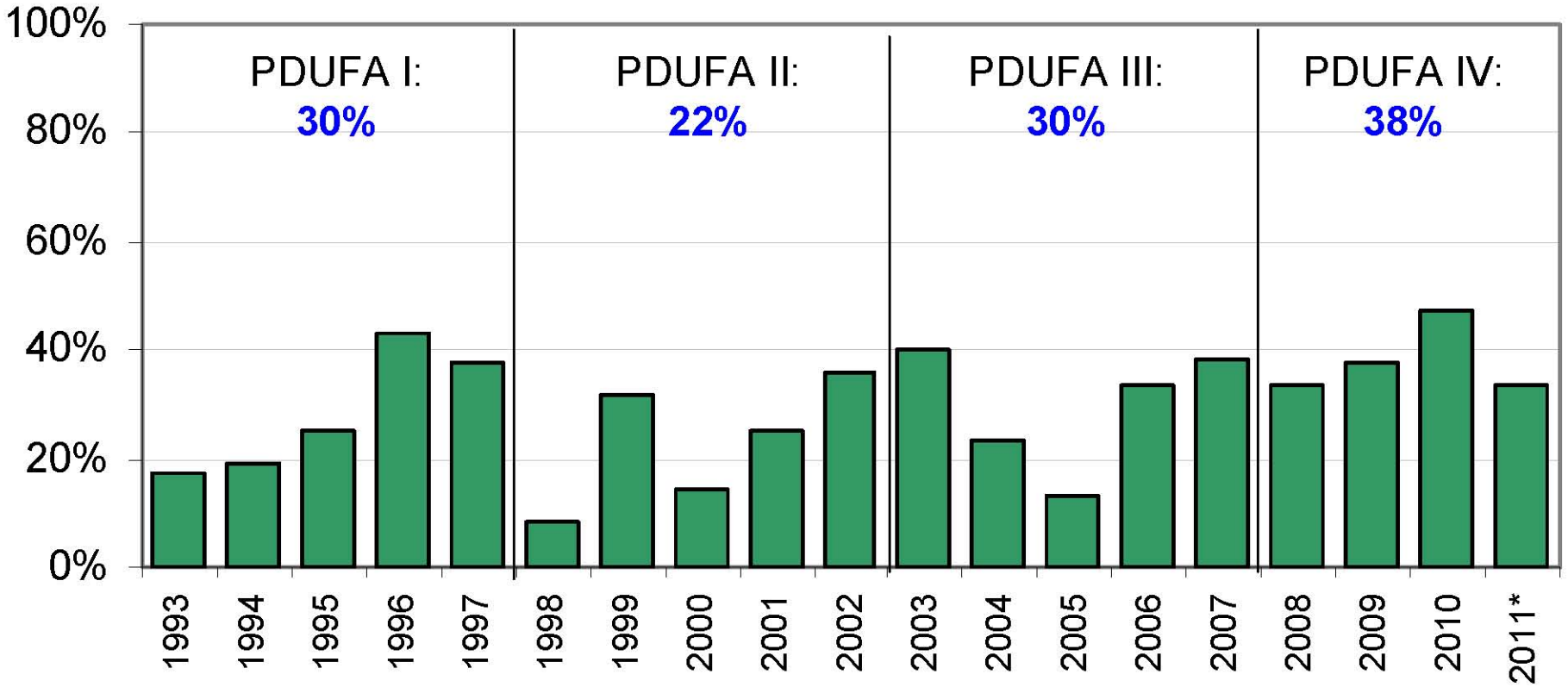
- Many of the NMEs approved in CY2011 were "breakthrough" therapies for patients and represent a significant advance for patients and public health
- 12 of the 30 NMEs were the first drugs approved in their therapeutic class
- Two are novel targeted cancer drugs based on predictive biomarkers with concurrently approved companion diagnostic tests
- Half of the NMEs approved in CY2011 received priority review, which is based on demonstrating a significant benefit over available therapy
- 14 of the CY2011 approved NMEs had "Fast Track" designation, the highest number ever for that program
- 11 of the CY2011 approved NMEs were for rare diseases

CDER First Action Approval Rates for Priority NMEs/NBEs



*CDER NME and new BLA actions as of 11/30/2011. Ten FY 2011 priority NMEs/NBEs have reached a regulatory action to date, with four currently pending first-cycle review.

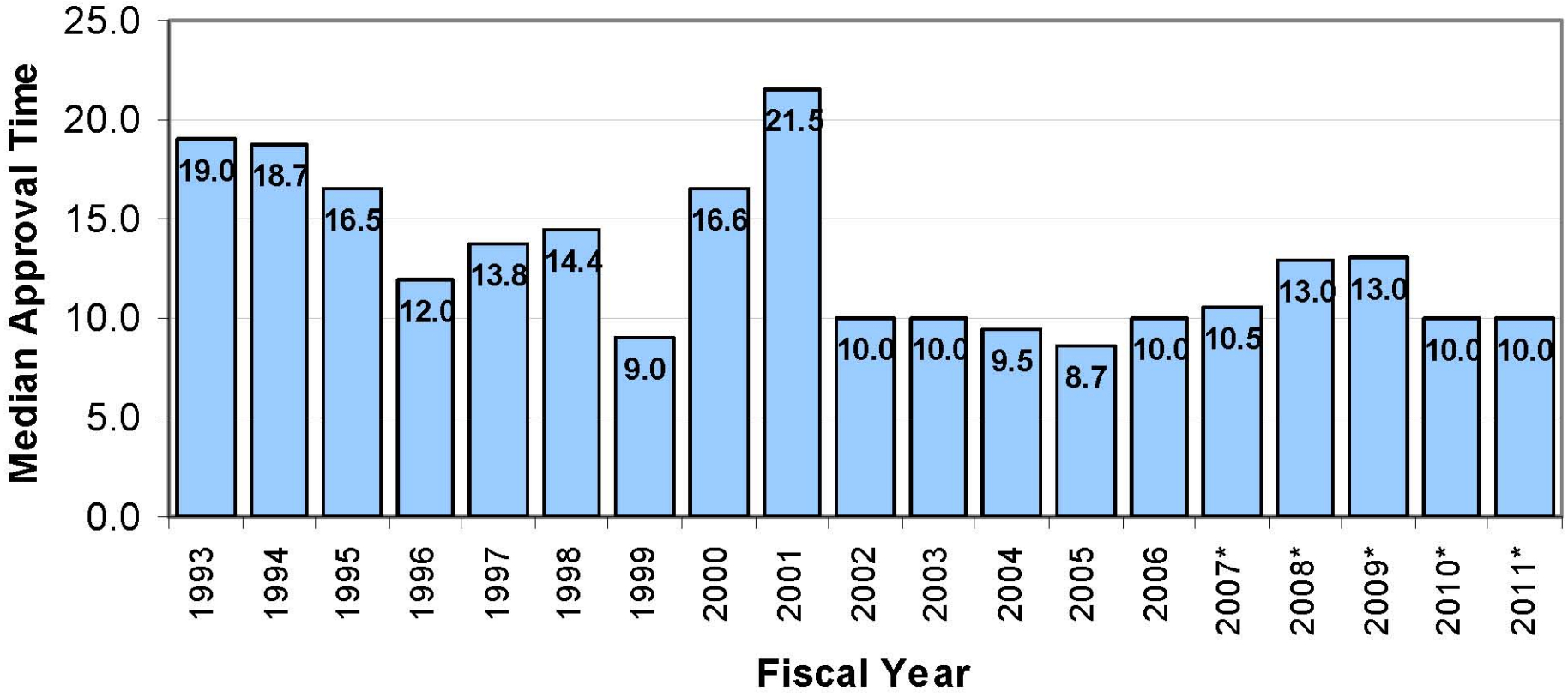
CDER First Action Approval Rates for Standard NMEs/NBEs



*CDER NME and new BLA actions as of 11/30/2011. Only three FY 2011 standard NMEs/NBEs have reached a regulatory action, with 14 currently pending first-cycle review.

CDER NME/NBE Median Approval Times

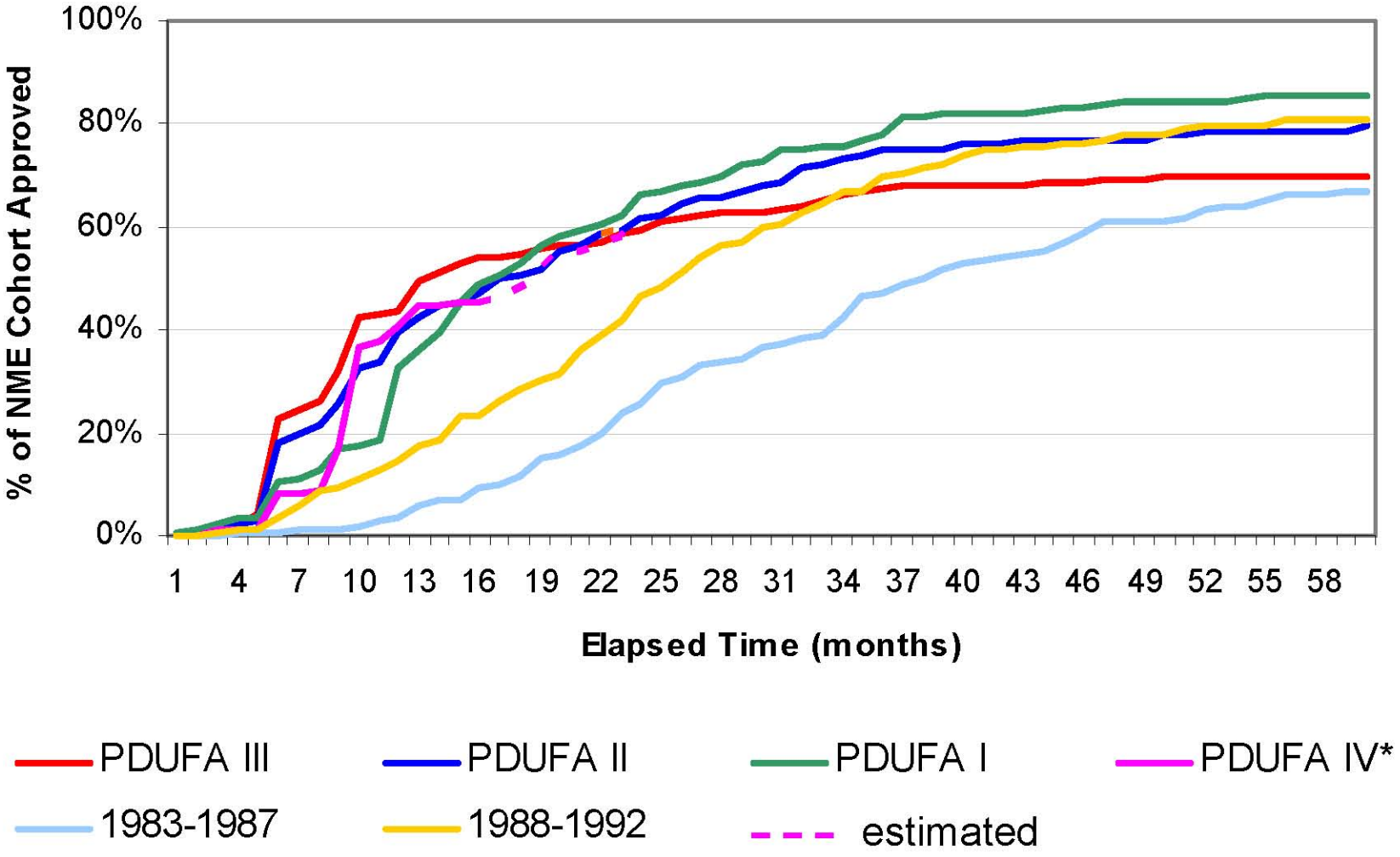
(by fiscal year of receipt)



CDER data as of 11/30/2011

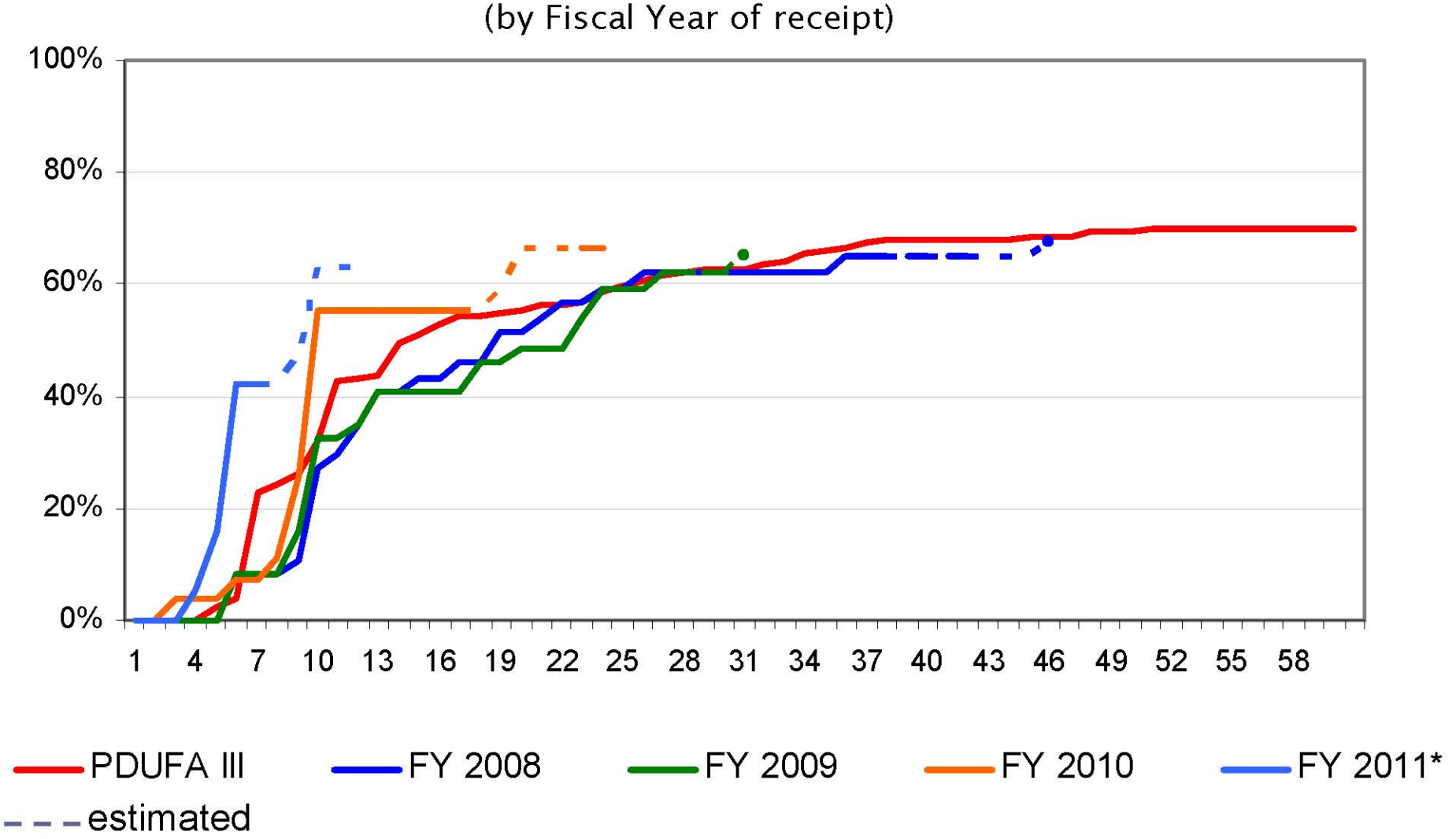
* Estimated median approval time. These figures are based on NME approvals to date, elapsed time of NMEs in process, and the historic approval rate of 75-80% of NMEs filed in a given year eventually gain FDA approval.

PDUFA NME Approval Rates



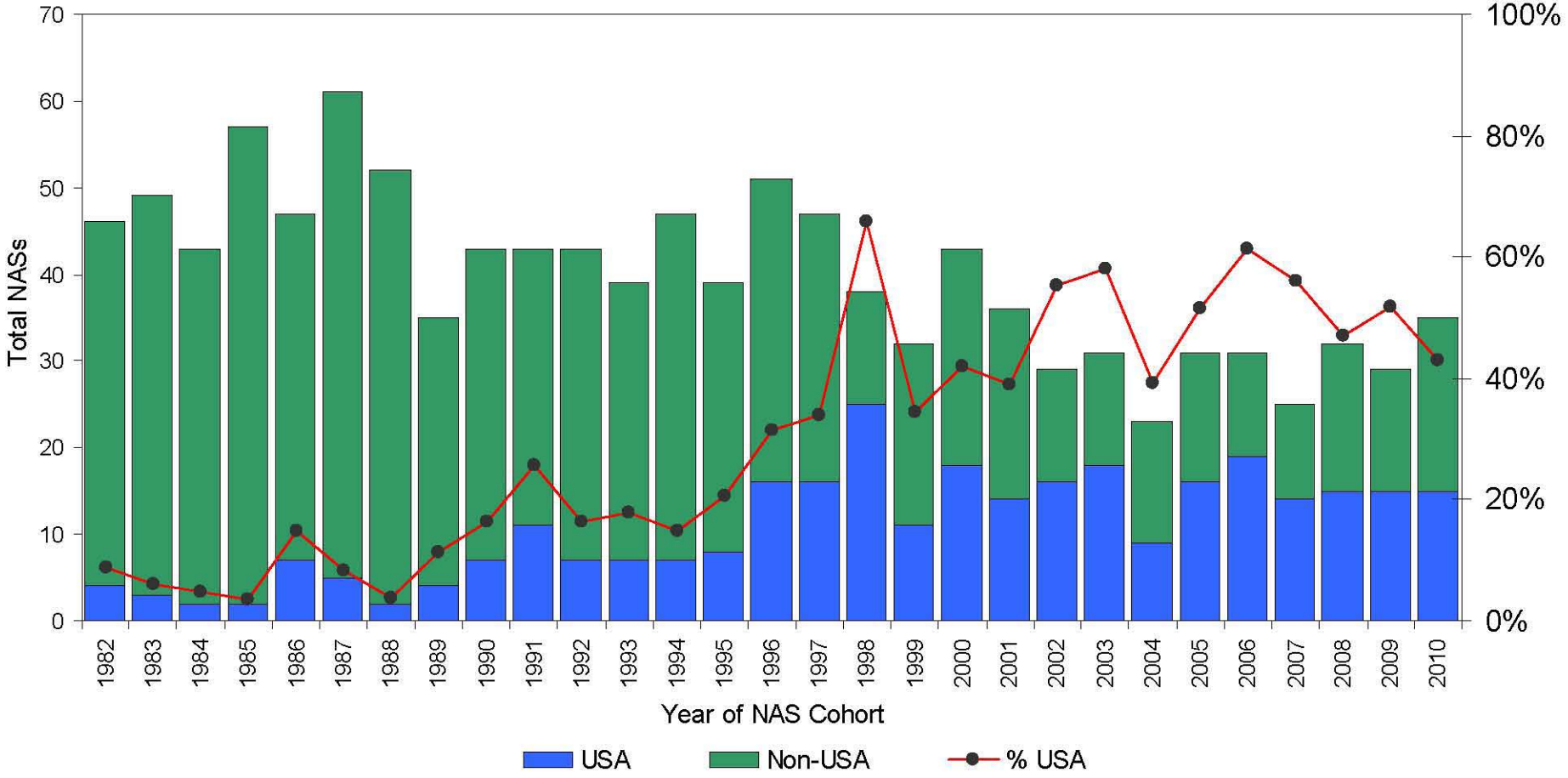
*CDER data as of 11/30/2011 and includes NMEs and NBEs filed by CDER. PDUFA IV (in progress) includes NMEs filed in FY 2008 – 2010. Estimates are based on approvals to date, elapsed time of pending applications, and historic approval rates for NMEs

PDUFA IV NME Approval Rates for Individual Years



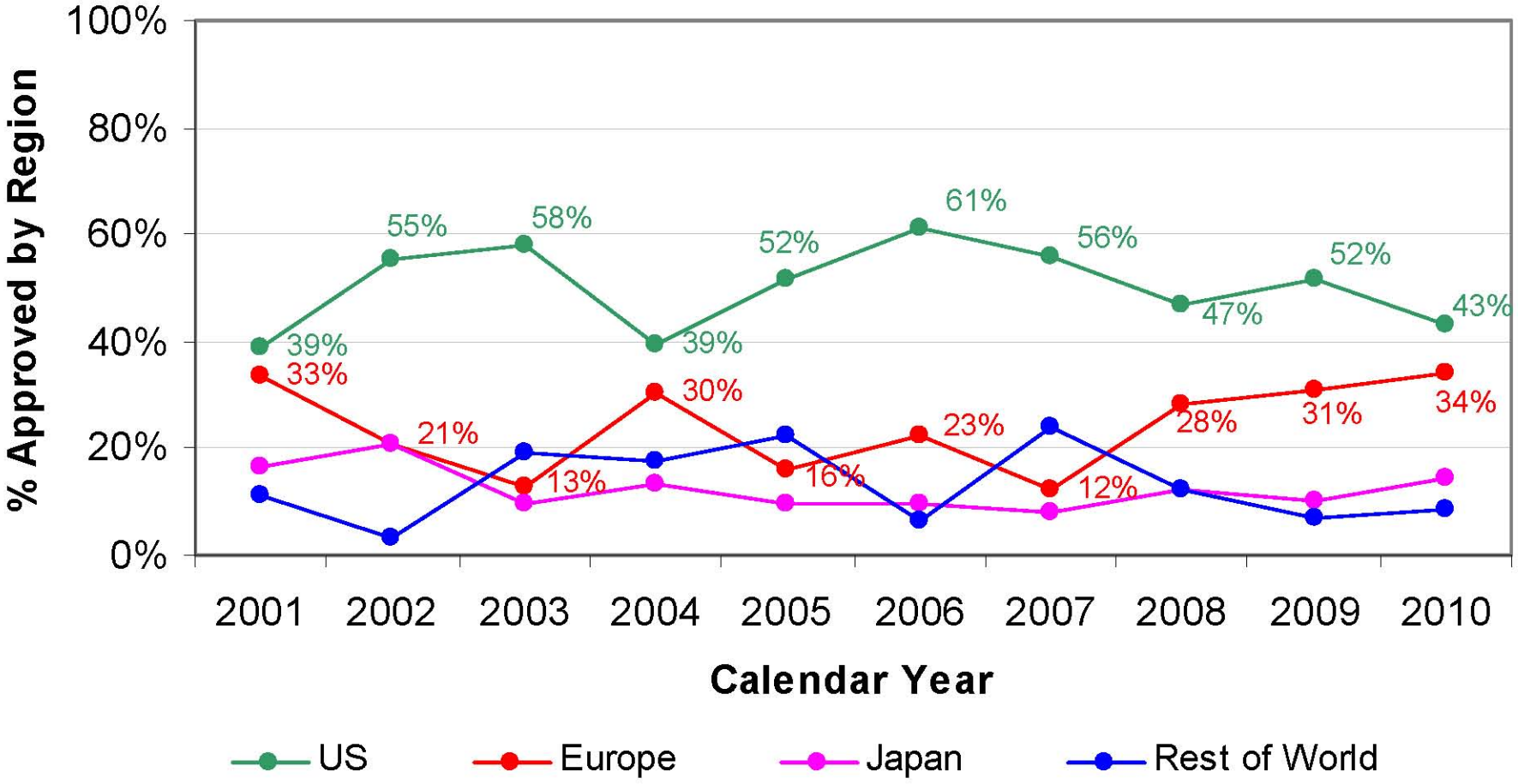
*CDER data as of 11/30/2011 and includes NMEs and NBEs filed by CDER. PDUFA IV (in progress) includes NMEs filed in FY 2008 – June 30, 2011. Estimates are based on approvals to date, elapsed time of pending applications, and historic approval rates for NMEs

USA Share of NASs First Launched on World Market



Source: Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 -2005),
PharmaProjects/Citeline R&D Annual Review (2006-2010)

Global New Active Substance Launches by Region 2001 - 2010



Source: *Scrip Magazine* (2001 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2010)

Proposed Recommendations for PDUFA V (FY 2013-2017)

FDA Goals for PDUFA Reauthorization

- Ensure continued sound financial basis
- Stick to fundamental goals that drive public health outcomes
  - Improving the science of drug development
  - Improving the quality of evidence in submitted applications
  - More predictable and efficient process
  - Avoid proliferation of micro-process goals that distract from fundamentals
- Stakeholders feel that priority concerns are addressed
- Focus enhancements on:
  - Increasing quality and efficiency of current program
  - Maintaining public confidence
- Timely reauthorization

Reauthorization discussions yielded proposals:

- Review program for NME NDAs and Original BLAs
- Enhancing Regulatory Science and Expediting Drug Development
  - Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development
  - Methods for meta-analysis
  - Biomarkers and pharmacogenomics
  - Use of patient-reported outcomes (PROs)
  - Development of drugs for rare diseases
- Enhancing Benefit-Risk Assessment
- Enhancement and Modernization of the FDA Drug Safety System
  - Standardizing REMS
  - Using Sentinel to evaluate drug safety issues
- Required Electronic Submissions and Standardization of Electronic Application Data
- Modified Inflation Adjuster
- Additional Evaluations of Workload Adjuster

Review Program for NME NDAs and Original BLAs

Problem

- New requirements in drug review make current review goals – established in 1997 – challenging to meet, particularly for more complex applications like NME NDAs and original BLAs (e.g., REMS, increased use of AC meetings)
- Despite process improvements on the part of FDA, the first cycle approval rate for NMEs of approximately 50% still leads to delays and resubmissions
- Increased communication between FDA and sponsors during review has the potential to increase efficiency in the review process

Proposed Recommendations

- Increased communication with sponsors for NME NDAs and original BLAs: pre-submission meeting, mid-cycle communication, and late-cycle meeting
- Review clock begins after the 60-day filing period for both standard and priority applications for 12 and 8 month total review time, respectively
- Interim and final assessments of review program

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

- **Problem**
  - New drug innovators, including many small emerging companies, operate at the cutting edge of science but may have less experience with FDA regulatory procedures and requirements to ensure substantial evidence of safety and efficacy
  - Timely communication between FDA and sponsors during development, to ensure efficient and effective drug development, also helps achieve FDA's mission by making safe and effective new drugs available in timely manner
- **Proposed Recommendation**
  - FDA will develop a dedicated drug development communication and training staff in CDER and CBER, focused on enhancing communication between FDA and sponsors during development
  - The liaison staff will conduct a range of tasks including identification and dissemination of best practices for enhanced communication and development of training programs for review staff
  - FDA will publish a guidance describing its philosophy on timely interactive communications and the scope of appropriate interactions with sponsors during drug development

Development of Drugs for Rare Diseases

Problem

- Regulatory oversight of rare disease drug development is complex and resource intensive
- Recent trends in orphan designations may indicate an expected future increase in investigational activity and marketing applications for orphan products

Proposed Recommendations

- Develop guidance related to advancing and facilitating development of drugs for rare diseases
- Increase outreach to patient representatives and industry regarding development of these drugs
- Convene a public meeting to discuss complex issues in clinical trials for studying drugs for rare diseases
- Develop and implement training for all review staff on development and review of drugs for rare diseases as part of the core reviewer curriculum

Biomarkers and Pharmacogenomics

Problem

- Pharmacogenomics and the application of qualified biomarkers have the potential to decrease drug development time
- Qualified biomarkers can enrich clinical trials by demonstrating benefits, establishing unmet medical needs, and identifying patients with a predisposition to adverse events
- Regulatory submissions of this type have increased recently

Proposed Recommendations

- Increase clinical, clinical pharmacology, and statistical capacity to adequately address submissions that propose to utilize biomarkers or pharmacogenomic markers in development programs.
- Conduct a public meeting to discuss potential strategies to facilitate scientific exchanges in regulatory and non-regulatory contexts

Enhancing Benefit-Risk Assessment

Problem

- A framework that accurately and concisely describes benefit and risk considerations will help review staff apply a structured approach in regulatory decision-making
- An important consideration is the context of the decision – an understanding of the condition treated and the unmet medical need
- A more systematic and open discussion with informed patients could provide valuable insight on a given disease and the potential gaps or limitations in available therapies

Proposed Recommendations

- Develop and implement a plan to integrate a benefit-risk framework in the drug review process during PDUFA V, including two public workshops
- Conduct public meetings between review divisions and the relevant patient advocacy communities for reviewing the armamentarium for specific indications or disease states chosen through a public process

Use of Patient-Reported Outcomes (PROs)

Problem

- Study endpoint assessments are increasingly an important part of successful drug development, requiring rigorous evaluation and statistical design and analysis
- There is a high study-failure rate for PRO endpoints not qualified in advance of phase 3 trials. Early consultation could ensure that endpoints are well-defined and reliable.

Proposed Recommendations

- Enhance clinical and statistical capacity to address submissions involving PROS and other endpoint assessment tools, including providing IND consultation
- Convene a public meeting to discuss PRO qualification standards, new endpoint measurement theory, and implications for multi-national trials

Methods for Meta-Analysis

Problem

- Currently, there is no consensus on best practices in conducting a meta-analysis
- FDA is often forced to evaluate meta-analyses of published or unpublished clinical trials, usually addressing a high visibility safety problem for an approved product.
- Review and evaluation of a meta-analysis, sometimes conducting the agency's own meta-analysis, can exceed FDA's current scientific and computational capacity

Proposed Recommendations

- Develop a dedicated review team to evaluate scientific methods, limitations in the methods, and potential best practices for the conduct of meta-analyses
- Conduct public meeting on the current and emerging approaches to meta-analyses
- Develop guidance on FDA's intended approach to meta-analysis in the regulatory review process and in regulatory decision-making

Standardizing Risk Evaluation and Mitigation Strategies (REMS)

Problem

- Risk Evaluation and Mitigation Strategies (REMS) involve varying degrees of risk management – more serious risks require more restrictive distribution
- REMS can be challenging to implement and evaluate, involving cooperation of all segments of the healthcare system
- Multiple REMS developed from scratch create burdens on the healthcare system

Proposed Recommendations

- With public input, FDA will explore strategies and initiate projects to standardize REMS with the goal of reducing burden on practitioners, patients, and others in the healthcare setting
- FDA will conduct public workshops and develop guidance on methods for assessing the effectiveness of REMS and the impact on patient access and burden on the healthcare system

Using Sentinel to Evaluate Drug Safety Issues

Problem

- Post-market surveillance still relies on passive surveillance and lengthy sponsor-conducted studies to evaluate potential safety signals
- FDAAA requires FDA to:
  - Collaborate with external groups to develop and validate methods to actively gather safety information on marketed products
  - Evaluate safety signals using passive surveillance (AERS) and active surveillance (Sentinel) before requiring post-market studies from sponsors

Proposed Recommendations

- Initiate projects to establish the use of active surveillance in evaluating post-market safety signals in population-based databases
- This proposal will potentially reduce reliance on post-market study requirements by leveraging public and private health care data sources to quickly evaluate drug safety issues.

Required Electronic Submissions and Standardization of Electronic Application Data

Problem

- The variability and unpredictability of submitted formats and data present a major obstacle to conducting a timely, efficient, and rigorous review within current PDUFA goal timeframes.

Proposed Recommendations

- Require standardized, fully-electronic submissions, to be phased-in through guidance according to an agreed timetable for all marketing and investigational applications
- Develop standardized clinical data terminology through open standards development organizations using a public process that allows opportunity for stakeholder input

GDUF Proposal

Proposal for Generic Drug User Fee Program

- Negotiated with the industry with public input
- Major objectives:
  - Create timely and predictable generic drug review process
  - Clear out backlog of pending generic drug applications
  - Create a “level playing field” of inspectional intensity between US and non-US manufacturing sites
  - Support regulatory science on determination of bioequivalence and related matters

Structure of Program

- $299M per annum; paid by fees from applications, marketed products and establishments including API manufacturers
- One-time “backlog” fee to sponsors with application in backlog—total of $50M
- Manufacturers will self identify into electronic system for fee collection
- Performance goals kick in after first few years, in general

Structure of Program

- 10 month goal for generic drug review
- Move to CR letter rather than fragmented by discipline
- Complex structure to deal with resubmissions intended to incentivize good quality applications
- Move to inspectional parity between US and ex-US sites by end of program

BSUF Proposal

Background

- The **Biologics Price Competition and Innovation Act (BPCI Act)** was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.

- BPCI Act creates an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with*** an FDA-licensed reference product.

What is an Abbreviated Licensure Pathway for Biological Products?

- A biological product that is demonstrated to be ***"highly similar"*** to an FDA-licensed biological product (the ***reference product***) may rely on certain existing scientific knowledge about the safety, purity, and potency of the reference product.

- This new licensure pathway permits a "biosimilar" biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

Definition: Biological Product

- BPCI Act revises the definition of **"biological product"** in the Public Health Service Act (PHS Act) to include "protein":

  . . . a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, ***protein (except any chemically synthesized polypeptide),*** *or analogous product … applicable to the prevention, treatment, or cure of a disease or condition of human beings …*

- Historically, some proteins have been approved as drugs under section 505 of the FD&C Act (e.g., human growth hormone), and other proteins have been licensed as biologics under section 351 of the PHS Act (e.g., blood factors, proteins involved in immune response).

- Under the BPCI Act, a protein, except any chemically synthesized polypeptide, will be regulated as a biological product.

Definition: Reference Product

Reference Product means:

the **single biological** product, **licensed under section 351(a),** against which a biological product is evaluated in an application submitted under section 351(k).

Definition: Biosimilarity

Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Definition: Interchangeability

Interchangeable or **Interchangeability** means:

- the biological product is **biosimilar** to the reference product;
- it can be expected to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product administered more than once, the **safety and reduced efficacy risks of alternating or switching** are not greater than with repeated use of the reference product without alternating or switching.

Note: The interchangeable product **may be substituted** for the reference product without the authorization of the health care provider.

General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product;
- Utilizes the **same mechanism(s) of action** for the proposed condition(s) of use -- only to the extent known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product;
- Has the **same route of administration**, **dosage form**, and **strength** as the reference product; and
- Is manufactured, processed, packed, or held in a facility that **meets standards** designed to assure that the biological product continues to be safe, pure, and potent.

General Requirements: 351(k) Application

The PHS Act requires that a 351(k) application include, among other things, **information demonstrating biosimilarity based upon data derived from**:

- **Analytical studies** demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed.

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.

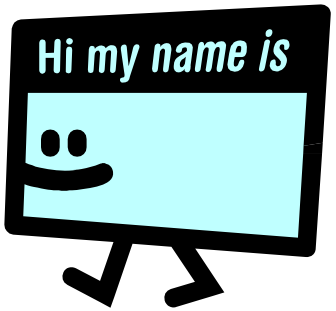
Standard for Licensure

- FDA shall license the biological product under section 351(k) if—
  - FDA determines that the **information submitted in the application (or supplement) is sufficient to show** that the biological product—
    - (i) is **biosimilar** to the reference product; or
    - (ii) meets the standards described in 351(k)(4), and therefore is **interchangeable** with the reference product; and
  - Applicant (or other appropriate person) consents to inspection of the facility, in accordance with section 351(c).

- Note: BPCI Act does not require that FDA promulgate guidance or regulation before reviewing or approving a 351(k) application.

Standards for Naming

- Establish policy related to naming of:
  - Biosimilar biological products
  - Interchangeable biological products
  - Related biological products not demonstrated to be biosimilar (i.e., 351(a) BLA)
- Naming objectives include:
  - Avoid confusion
  - Minimize medication error
  - Facilitate pharmacovigilance



Exclusivity: 1st Interchangeable Product

- The 1st biological product to be licensed as interchangeable is granted a period of exclusivity.
- During the exclusivity period, a subsequent biological product relying on the same reference product cannot be licensed as interchangeable.
- Exclusivity calculus is based on date of approval, date of first commercial marketing, and patent litigation milestones.

Pediatric Study Requirements

- Under the **Pediatric Research Equity Act** (PREA), all applications for **new active ingredients**, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable (see section 505B of FD&C Act).

- For purposes of PREA, a biological product determined to be:
  - **biosimilar is considered to have a "new active ingredient";**
  - **interchangeable is <u>not</u> considered to have a "new active ingredient."**

- FDA encourages applicants to submit plans for pediatric studies during the IND stage of product development.

Recently Released Guidances

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
- Q&A's Regarding Implementation of the BPCI Act of 2009
  - We will be able to add more Q&A's to this document
  - FDA will be having another public meeting on remaining questions

Scientific Considerations

- Take a stepwise approach with a foundation of analytical and functional comparisons
- Some animal studies may be helpful
- Human PK and if possible PD desired
- Human immunogenicity studies
- After the above: what are the remaining questions, what is needed to answer them?
- "Totality of evidence" approach

BSUF Proposal

- Modeled after PDUFA
- Problems: no existing industry (in US); no base appropriated program
- Anticipated that much early consultation will be needed
- Therefore: development meeting fee to be deducted from filing fee
- FDA agrees to supply $20M base if required

Other Proposals

- FDA Public Meeting March 22-23: "Conditions of Safe Use" to move drug products to nonprescription status
- Includes use of electronic media, or dispensing after pharmacist intervention
- Considers allowing Rx and nonprescription status simultaneously under certain circumstances
- May create controversy

Summary

- Multiple user fee programs before Congress
- Biosimilars and generics will support innovations in drug regulation
- Some proposed aspects of PDUFA also innovative (Benefit-risk; patient involvement)
- If passed, will keep CDER and the Food and Drug Bar busy over the next decade!