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CDER New Drug Review: 2011 Update

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Housekeeping

Data and analyses presented on the following slides are thought to be accurate, but have not undergone the same thorough quality control as is performed for official FDA reports

- Analyses of NME/original BLA filings and approvals will be abbreviated to "NME"
- Many staff in CDER provided data, analyses, and PowerPoint expertise for this talk
  - A special acknowledgement to Michael Lanthier and Nelson Cheung for their outstanding help in conceiving and conducting many of the analyses. Their behind the scenes work makes me look good.
  - Thanks to Theresa Mullin for the summary slides on PDUFA V, which I have modified slightly from her originals.

Topics to be covered

- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
- "Emerging" role of emerging sponsors
- Looking ahead to PDUFA V

What about PDUFA Goals?

- FDA continues to take PDUFA goals very seriously
  - These are commitments that we made to Congress and the American public for how we will do our work
- In November 2007 I granted permission for OND managers to exercise greater flexibility regarding PDUFA goals due to workload/resource constraints related to FDAAA
- In October 2009 I instructed OND managers to begin moving back to our prior posture of meeting PDUFA goals whenever possible
- Two years later we are meeting nearly all of our PDUFA goals for application review

CDER FY10 Application Review

(applications submitted in FY10, status as of September 30, 2011)

Submission Type	Number Filed*	2010 Performance Goal	Current Performance
NDAs/BLAs			
Standard	83	90% in 10 months	98%
Priority	18	90% in 6 months	100%
NMEs/New BLAs			
Standard	17	90% in 10 months	100%
Priority	10	90% in 6 months	100 %
NDA / BLA Resubmissions			
Class 1	12	90% in 2 months	100%
Class 2	39	90% in 6 months	95%
NDA / BLA Efficacy Supplements (ES)			
Standard	101	90% in 10 months	96%
Priority	19	90% in 6 months	95%
NDA / BLA ES Resubmissions			
Class 1	14	90% in 2 months	100%
Class 2	14	90% in 6 months	86%
NDA / BLA Manufacturing Supplements			
Requiring Prior Approval	721	90% in 4 months	87%
CBE	1079	90% in 6 months	94%

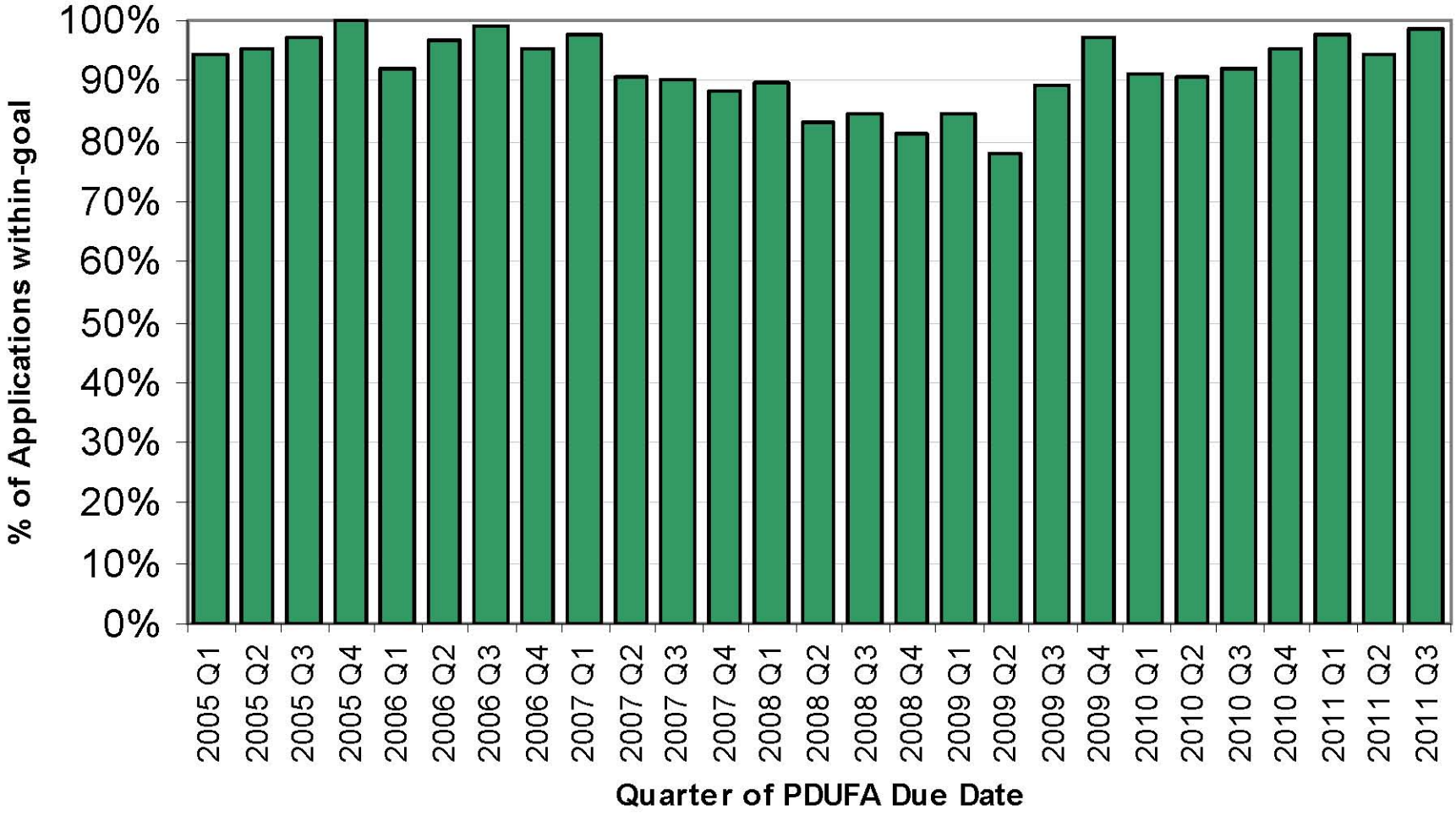
CDER FY11 Application Review

(applications submitted in FY11, status as of September 30, 2011)

Submission Type	Number Filed*	2010 Performance Goal	Potential Performance*
NDAs/BLAs			
Standard	77	90% in 10 months	100%
Priority	23	90% in 6 months	96%
NMEs/New BLAs			
Standard	16	90% in 10 months	100%
Priority	15	90% in 6 months	93 %
NDA / BLA Resubmissions			
Class 1	11	90% in 2 months	100%
Class 2	49	90% in 6 months	100%
NDA / BLA Efficacy Supplements (ES)			
Standard	89	90% in 10 months	100%
Priority	23	90% in 6 months	96%
NDA / BLA ES Resubmissions			
Class 1	14	90% in 2 months	71%
Class 2	17	90% in 6 months	94%
NDA / BLA Manufacturing Supplements			
Requiring Prior Approval	634	90% in 4 months	96%
CBE	1238	90% in 6 months	99%

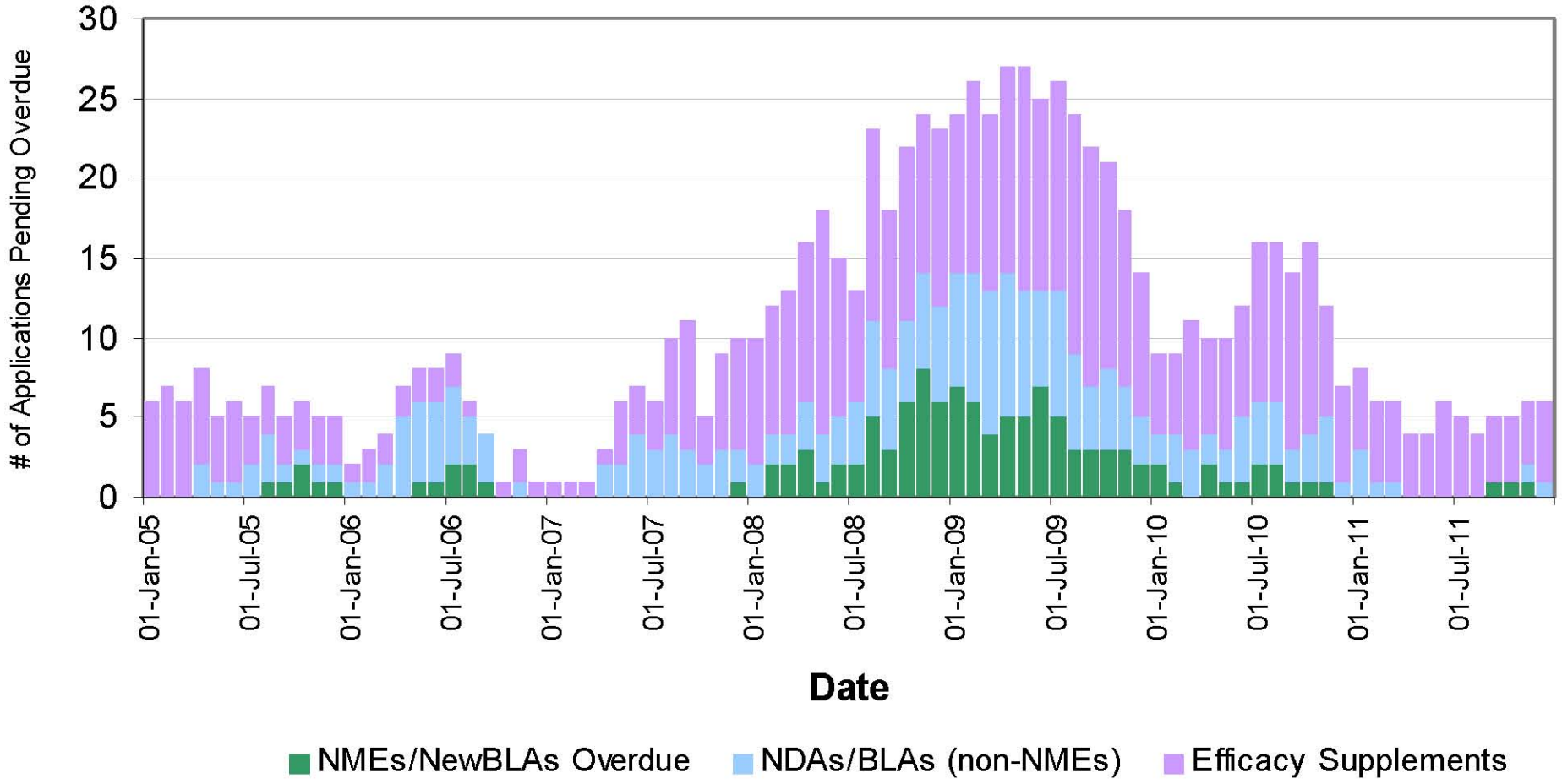
* Many FY2011 submissions are still pending within goal. Potential performance is the highest level that may be achieved if all pending actions are taken within goal.

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.

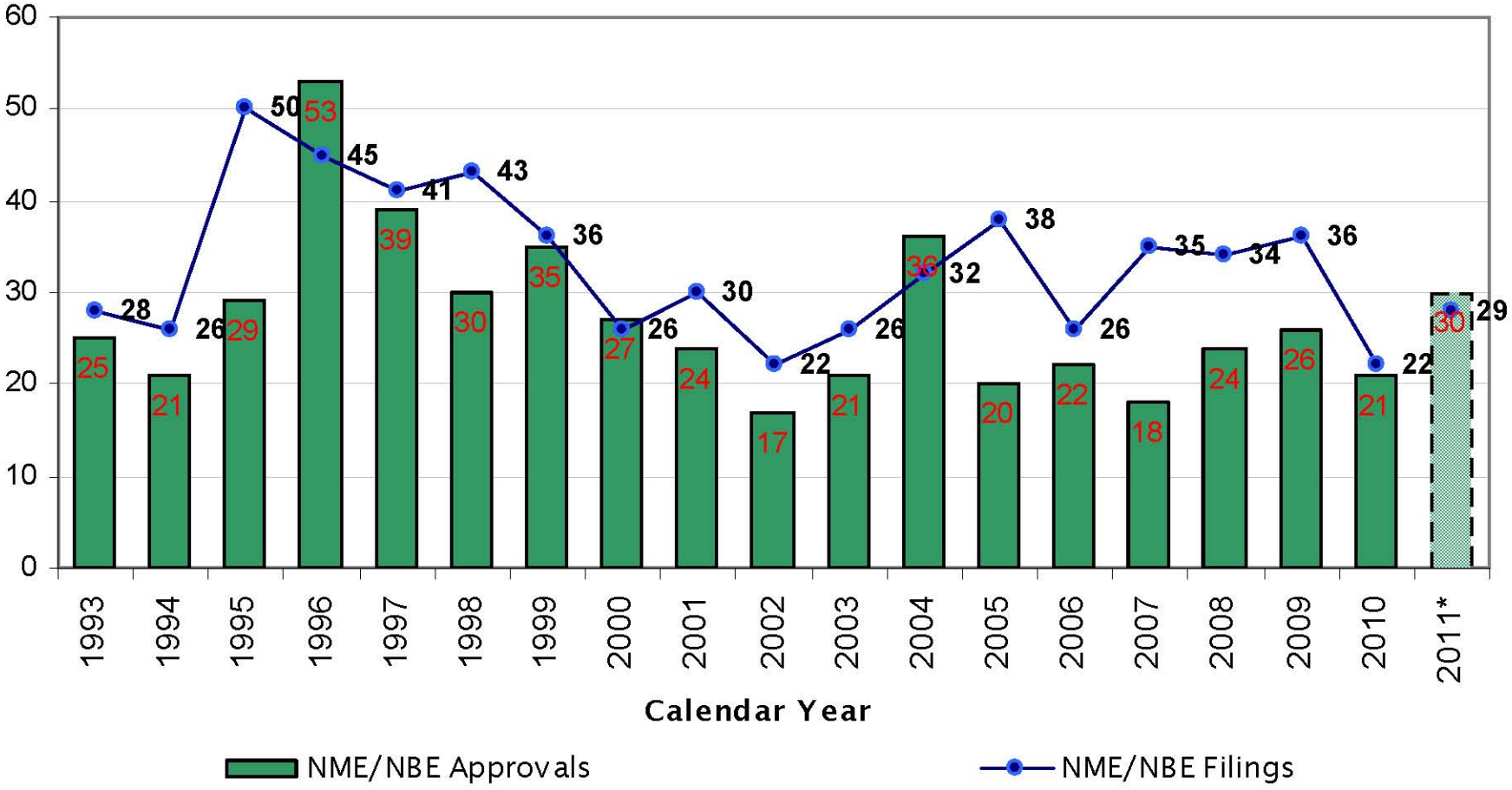
What about new drug approvals?

- The debate about whether FDA is too fast or too slow in approving new drugs continues
  - In 2007 the FDA storylines were "VIOXX," "Avandia," "drug safety," and "FDAAA"
  - In 2011 the FDA storylines are "innovation", "jobs," "progressive approval," "venture capital drying up," and "FDA reform"
- Despite the shifting FDA storylines:
  - In my 19 ½ years at FDA I have never received or issued an order to "speed up" or "slow down" on drug approvals
- We review each application on its merits and apply our best judgment with regard to the data, the science, and the statutes/regulations
- We do not have goals for numbers of approvals by year, division, etc.

What about new drug approvals (cont)?

- To date, in CY2011 FDA has approved 30 NME applications, the highest number since 2004
- NME filings to date in CY2011 (29) are on track for the average level seen in recent years
- 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

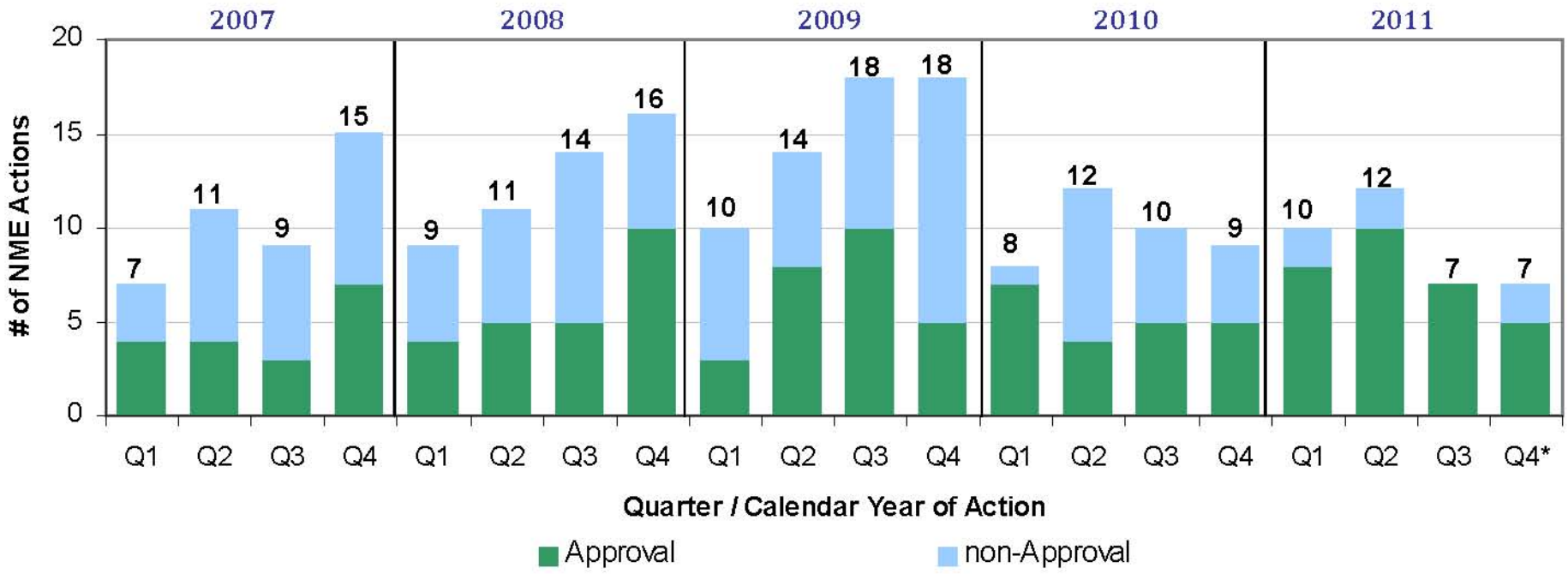


*CDER data as of 11/30/2011. New Biologic Entities are included in CDER figures beginning in 2004, when review authority for therapeutic biologic products was transferred from CBER to CDER.

Why only 30 NMEs?
You approved 20 in the first 6 months!!

- Analysts were predicting 40 NME approvals for CY2011 last summer, so what happened?
  - The average number of NME applications filed by FDA per year between CY2006-2010 was 30.6
  - We cannot approve more NME applications than we receive!!
- NME submissions and PDUFA goal dates are not uniformly distributed across the calendar year
  - In CY2011 CDER took action on 22 NMEs in the first 6 months, but only 14 NMEs in the second 6 months (to date)
  - The percentage of NME actions that were approvals was high and similar between the first and second 6 months
- CDER did not "slow down" NME approvals in the second 6 months of CY2011

CDER NME Actions by CY Quarter

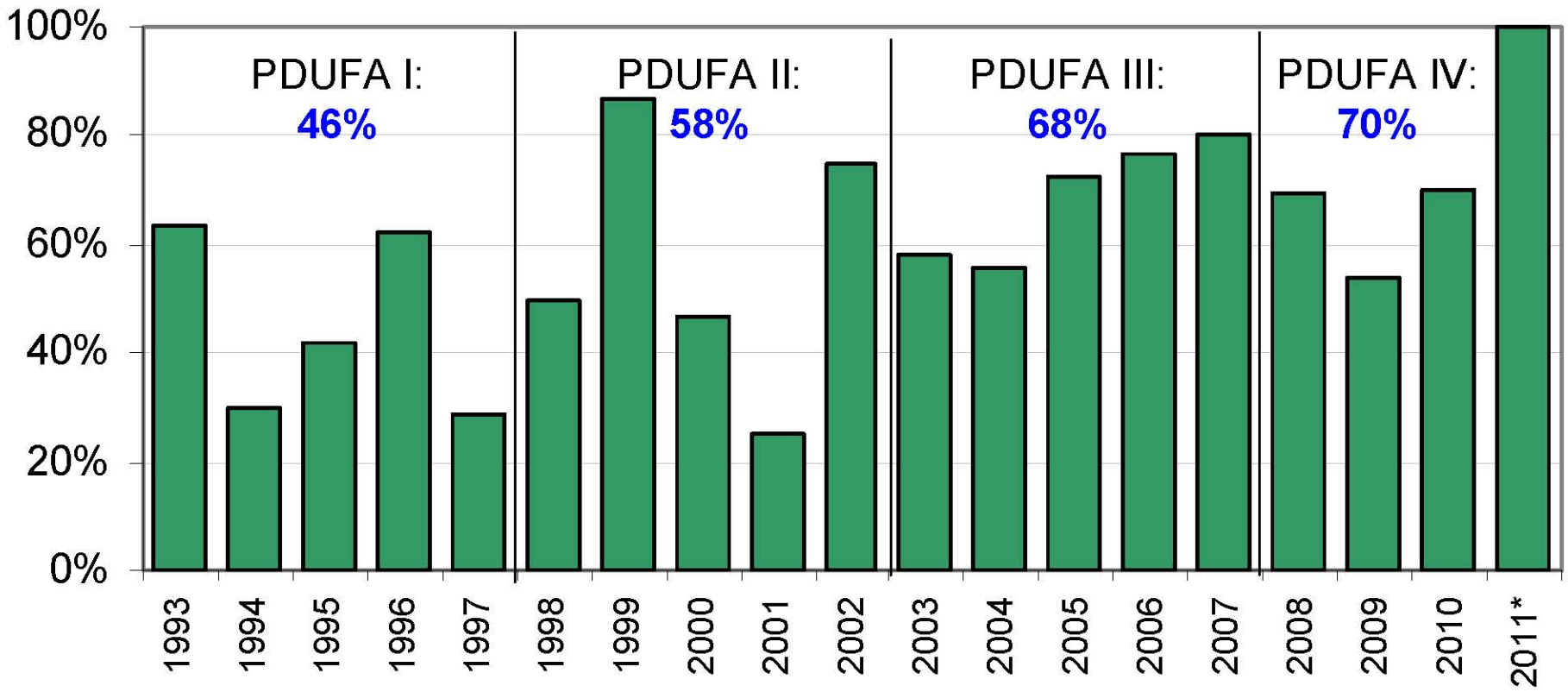


*NME and new-BLA actions and approvals for Q4 2011 through 11/30/2011. Non-approvals also include cases where pending application is withdrawn by the sponsor.

Looking beyond the *quantity* of NMEs

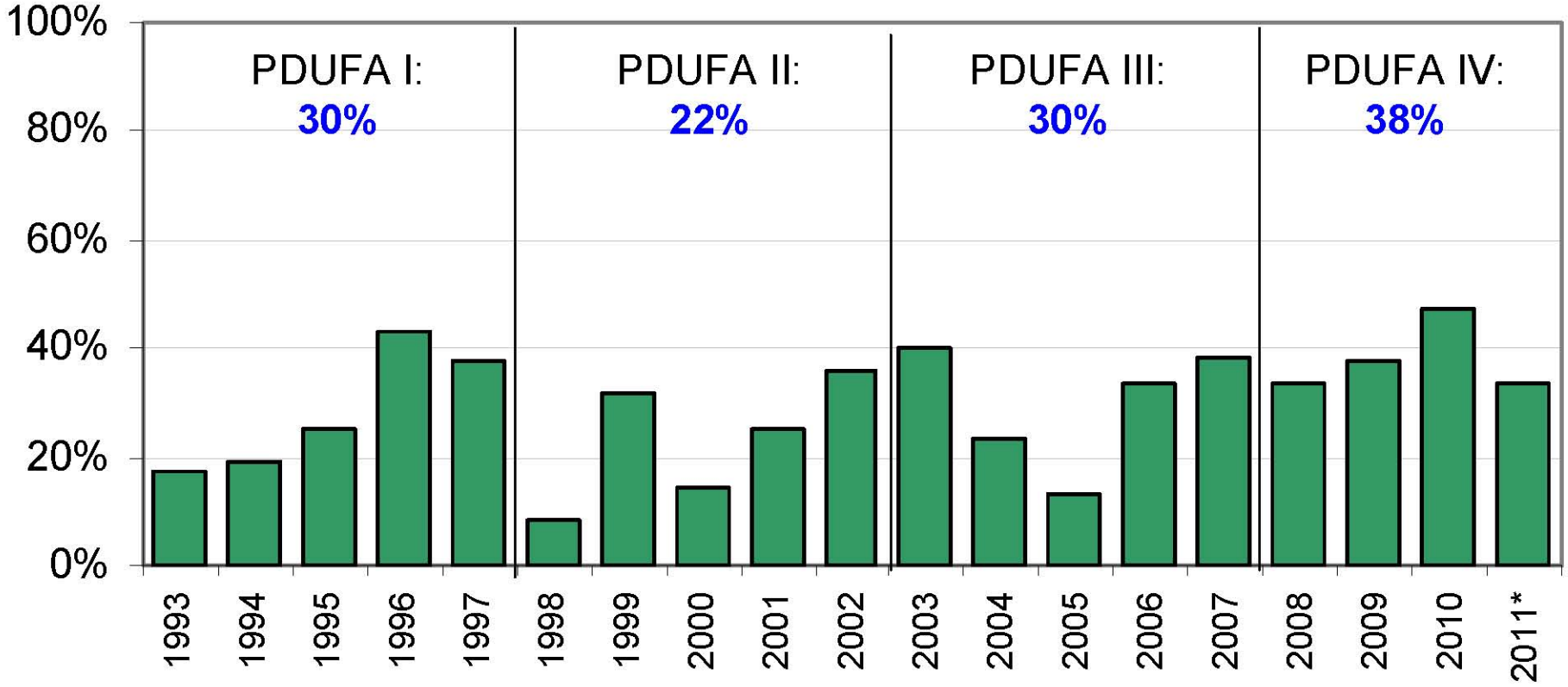
- Many of the NMEs approved in CY2011 were "breakthrough" therapies for patients and represent a significant advance for patients and public health
- 12 of the 30 NMEs were the first drugs approved in their therapeutic class
- Two are novel targeted cancer drugs based on predictive biomarkers with concurrently 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



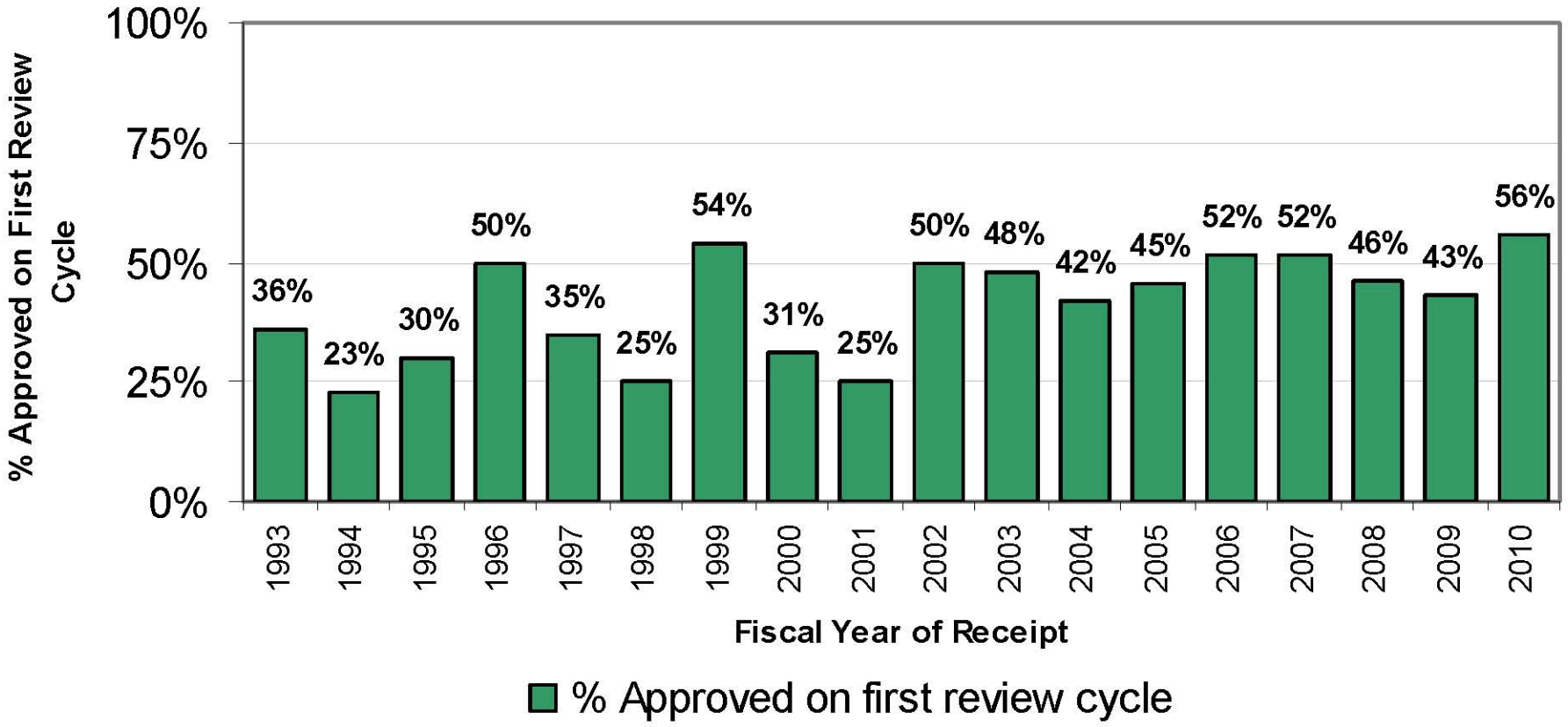
*CDER NME and new BLA actions as of 11/30/2011. Ten FY 2011 priority NMEs/NBEs have reached a regulatory action to date, with four currently pending first-cycle review.

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.

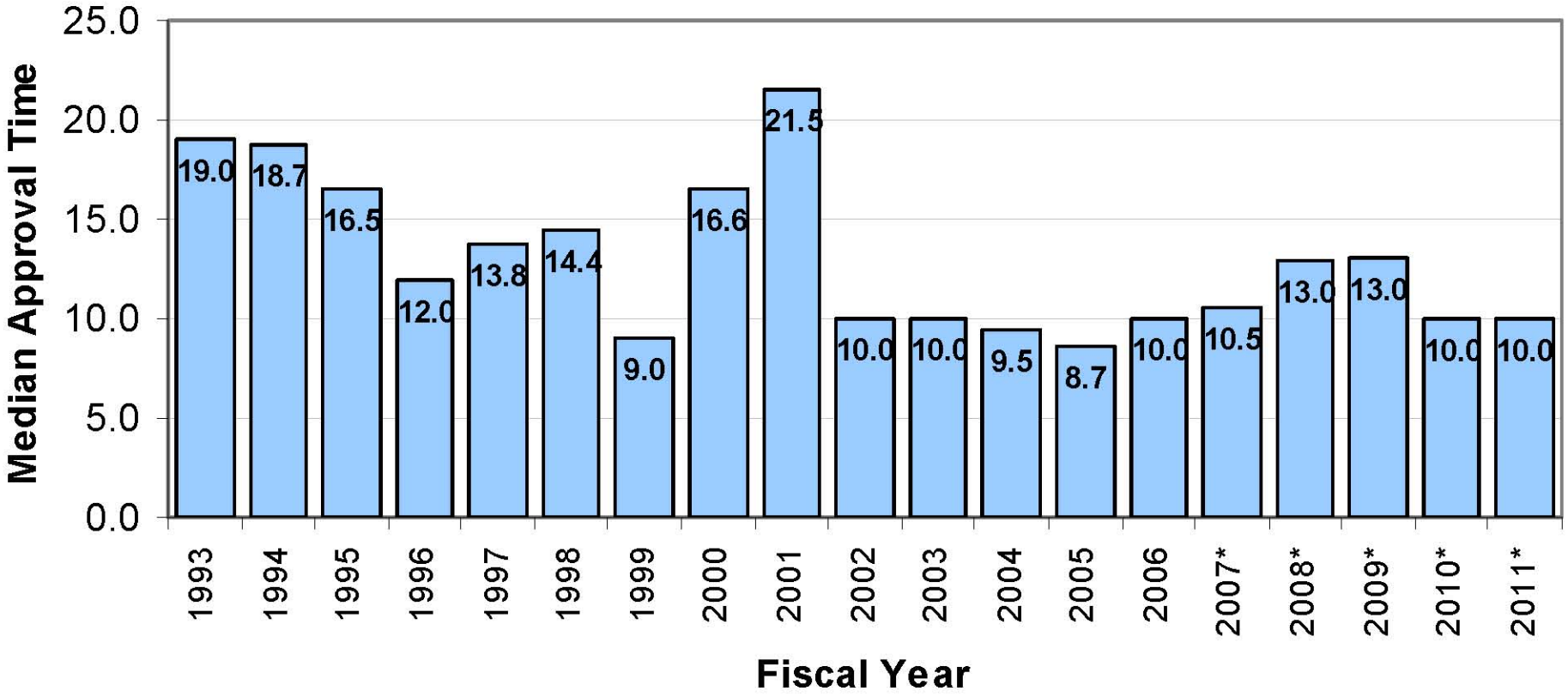
CDER NME/NBEs First Cycle Approval Rate
(by fiscal year of receipt)



*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.

CDER NME/NBE Median Approval Times

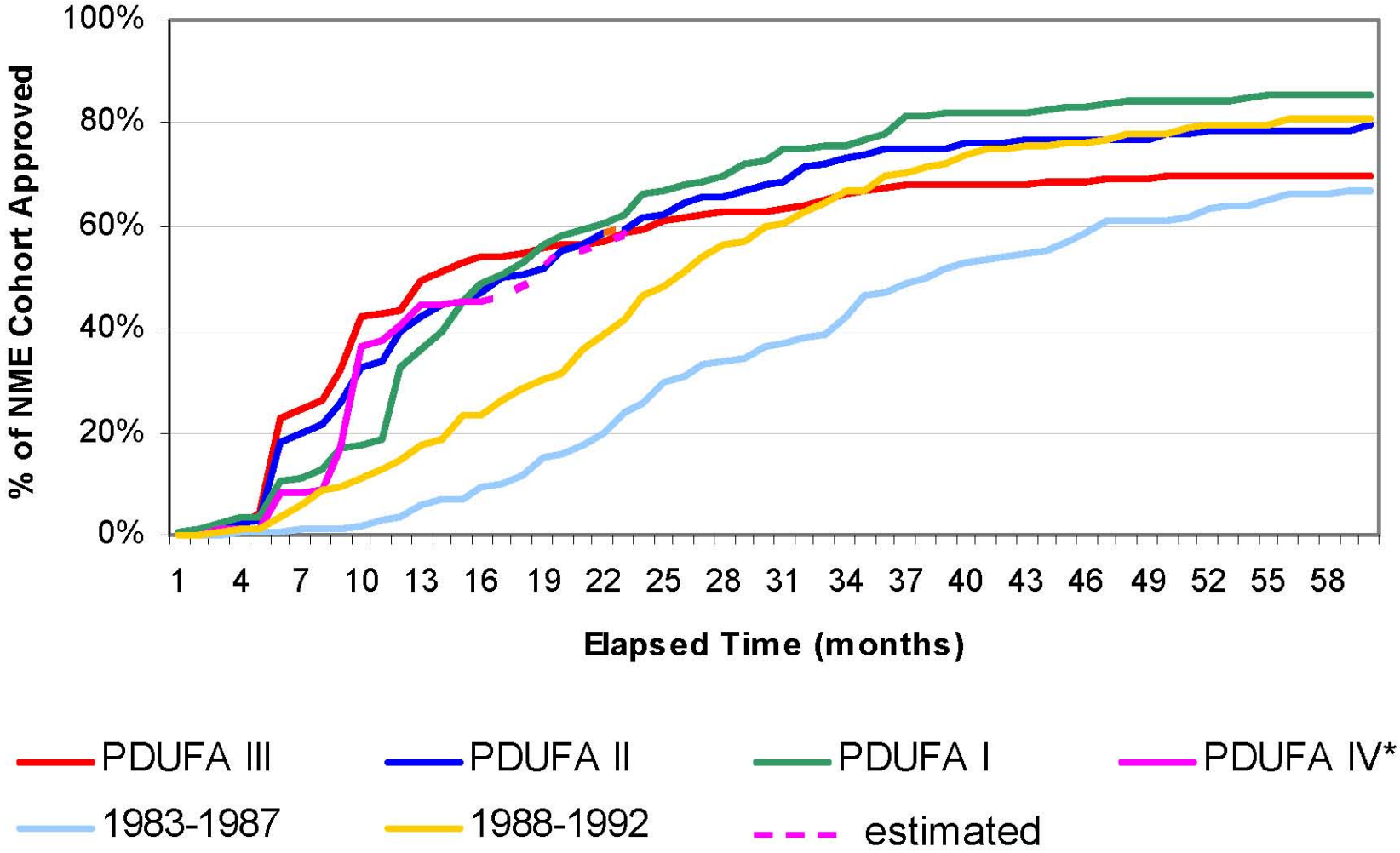
(by fiscal year of receipt)



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.

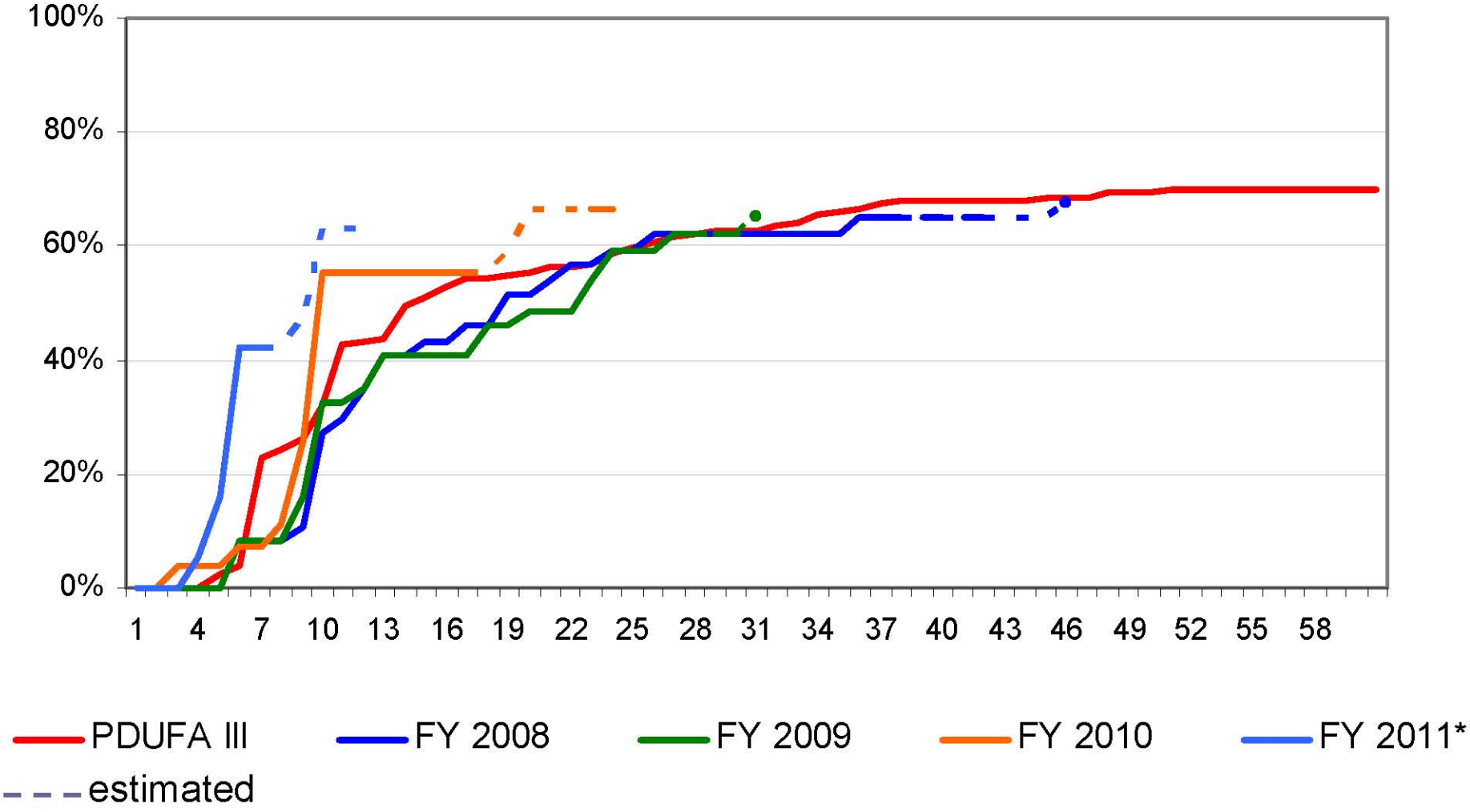
PDUFA NME Approval Rates



*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

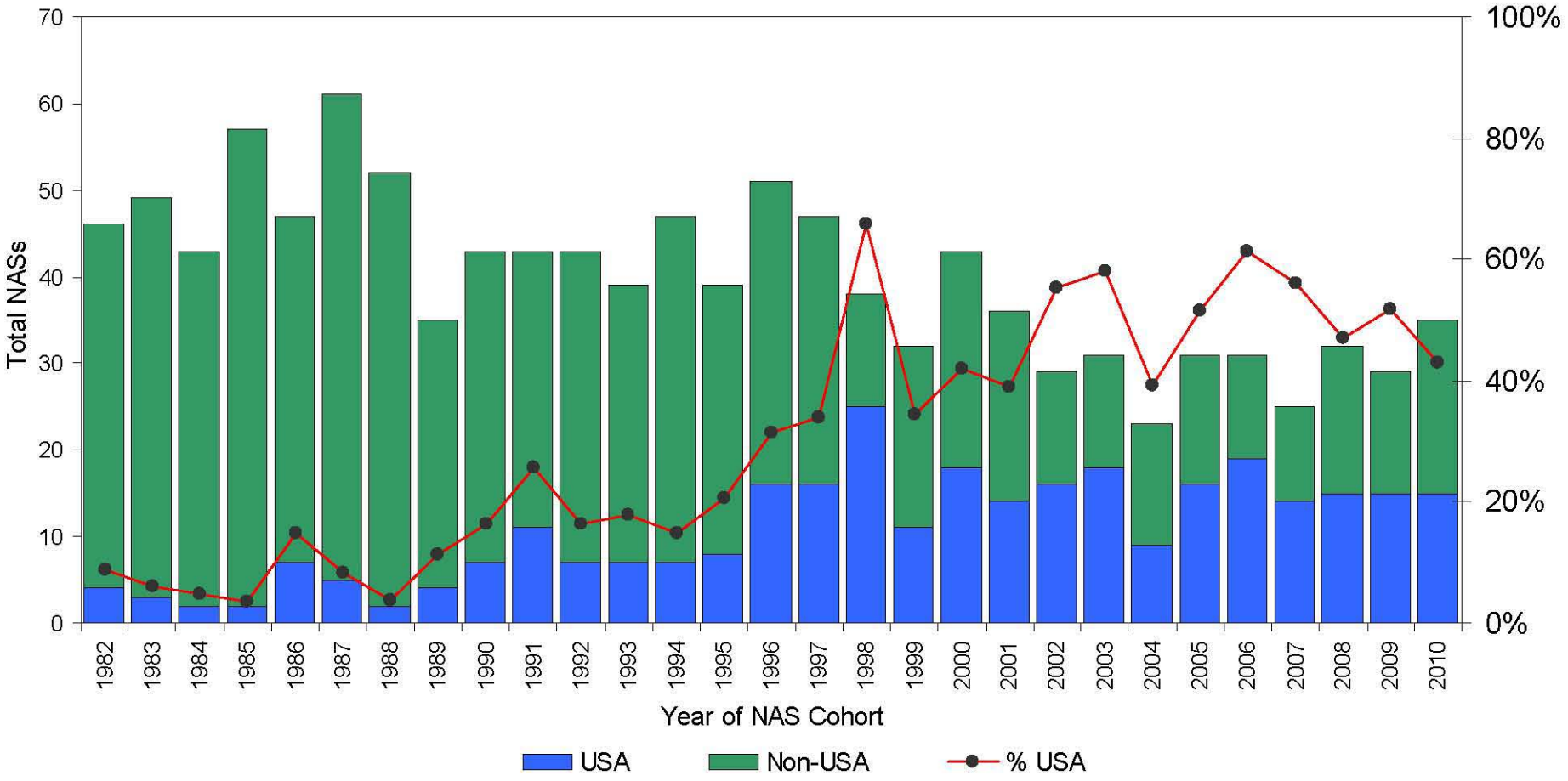
PDUFA IV NME Approval Rates for Individual Years

(by Fiscal Year of receipt)



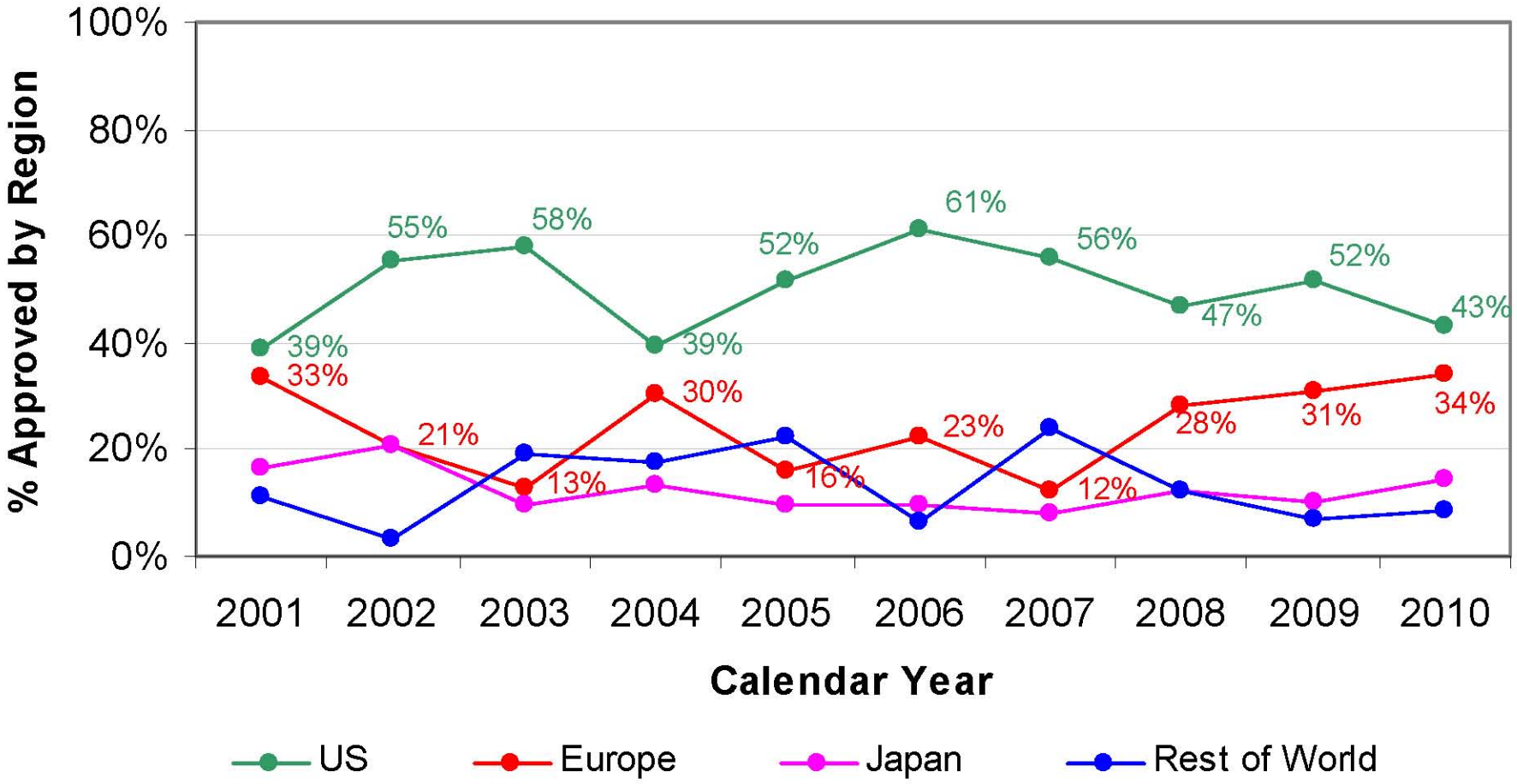
*CDER data as of 11/30/2011 and includes NMEs and NBEs filed by CDER. PDUFA IV (in progress) includes NMEs filed in FY 2008 – June 30, 2011. Estimates are based on approvals to date, elapsed time of pending applications, and historic approval rates for NMEs

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)

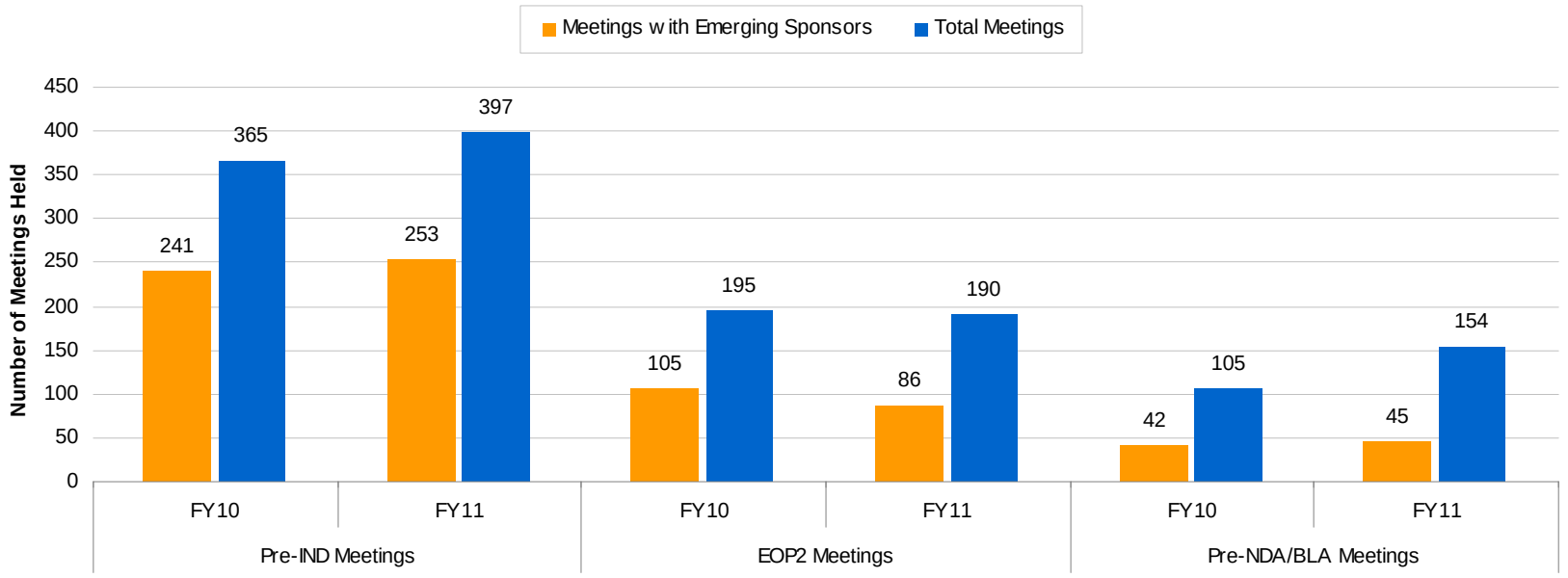
Emerging role of emerging sponsors

- The new drug research and development paradigm is shifting rapidly from traditional big pharma to venture capital backed small companies
- Good news is that some small companies are successfully bringing innovative new products to market; e.g.,
  - Seattle Genetics and brentuximab for Hodgkins Disease and anaplastic large cell lymphoma
  - Shire Orphan and icatibant for hereditary angioedema
  - Incyte and ruxolitinib for myelofibrosis

Emerging role of emerging sponsors (cont)

- New paradigm impacts on CDER's workload and interactions with sponsors; we are working to catch up to the new model
  - Inexperienced sponsors need more advice and meetings with FDA and require greater clarity from us in the advice provided
    - "That will be a review issue" is often interpreted as "that will be just fine"
  - VC backed sponsors tend to be more "transparent" in sharing information with the public about interactions with FDA
    - "Drug development by press release"
    - Public statements are often overly optimistic/do not capture nuance of FDA advice; we are constrained in monitoring/responding to statements
    - Late failure of programs is often characterized to the public as "FDA moved the bar;" we have limited ability to provide our perspective on unapproved drugs
  - Small companies are more likely to submit formal dispute resolution requests
    - FDRR route is quicker, less expensive, and more "promising" than conducting new trials, but success rate is low

CDER Meetings with Emerging Sponsors

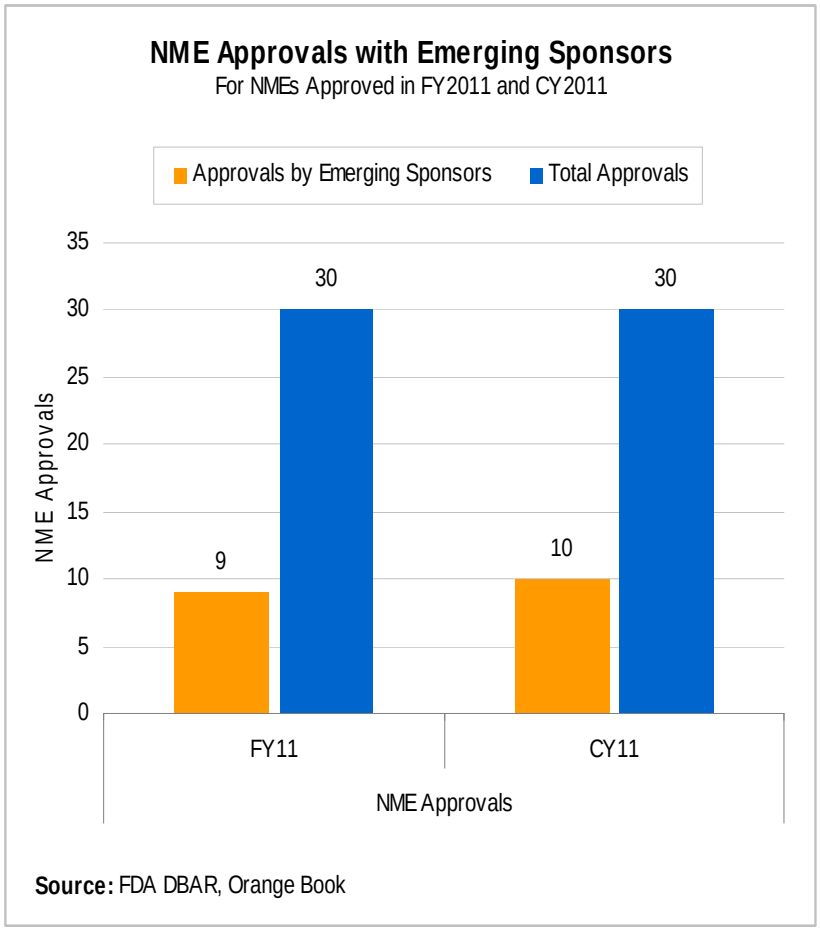


Source: FDA DBAR, Orange Book

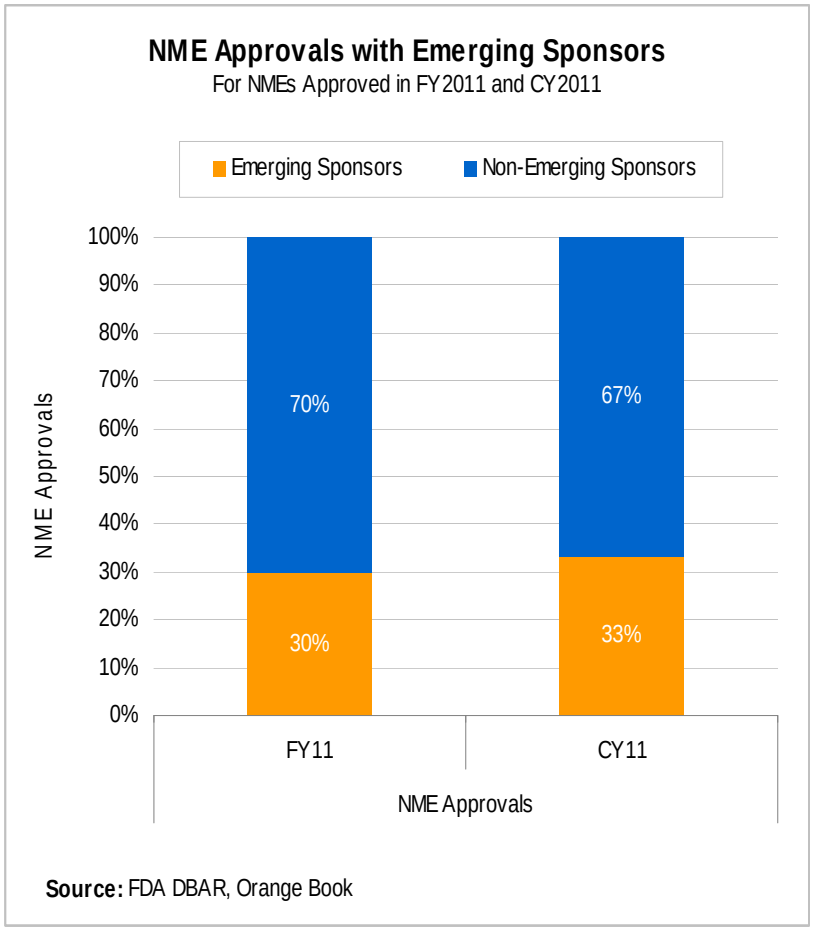
Analytical Methods

- Analysis compared two data sets:
  - Pre-IND, EOP2, and Pre-NDA/BLA meetings held from DARRTS for FYs 2010 & 2011
  - Orange Book data as of September 30, 2011
- Meetings held categorized as those from "emerging" or "non-emerging" sponsors
  - An emerging sponsor is defined as a sponsor who, at the time of meeting request, was not a holder of an approved application in the Orange Book
  - This is the same emerging sponsor definition used in PDUFA V discussions to inform the potential workload of the emerging sponsor IND communication proposal
- This approach involves some imputation of sponsor name since the same sponsor can appear in multiple ways both in DARRTS and in the Orange Book

NME Approvals with Emerging Sponsors



Source: FDA DBAR, Orange Book



Source: FDA DBAR, Orange Book

NME Approvals with Emerging Sponsors

REG_PATHWAY	APPL_NO	ACTIVE_INGREDIENT	TRADE_NAME	DOSAGE_FORM	APPLICANT	CLASSIFICATION	APPROVAL_DATE	APPROVAL_CY	APPROVAL_FY	Emerging Sponsor Flag
NDA	200327	CEFTAROLINE FOSAMIL	TEFLARO	POWDER	CEREXA, INC.	1-S	29-Oct-10	2010	2011	TRUE
NDA	22505	TESAMORELIN ACETATE	EGRIFTA	POWDER	THERATECHNOLOGIES INC.	1-S	10-Nov-10	2010	2011	TRUE
NDA	22408	SPINOSAD	NATROBA	TOPICAL SUSPENSION	PARAPRO	1-S	18-Jan-11	2011	2011	TRUE
NDA	22567	VILAZODONE HYDROCHLORIDE	VIIBRYD	TABLET	TROVIS PHARMACEUTICALS	1-S	21-Jan-11	2011	2011	TRUE
BLA	125370	BELIMUMAB	BENLYSTA	INJECTION	HUMAN GENOME SCIENCES	1-P	9-Mar-11	2011	2011	TRUE
NDA	201917	TELAPREVIR	INCIVEK	TABLET	VERTEX	1-P	23-May-11	2011	2011	TRUE
NDA	201699	FIDAXOMICIN	DIFICID	TABLET	OPTIMER PHARMACEUTICALS	1-P	27-May-11	2011	2011	TRUE
BLA	125388	BRENTUXIMAB VEDOTIN	ADCETRIS	INJECTION	SEATTLE GENETICS	1-P	19-Aug-11	2011	2011	TRUE
NDA	22150	ICATIBANT	FIRAZYR	INJECTION	SHIRE ORPHAN	1-P	25-Aug-11	2011	2011	TRUE
NDA	21825	DEFERIPRONE	FERRIPROX	TABLET	APOPHARMA	1-S	14-Oct-11	2011	2012	TRUE
NDA	202192	RUXOLITINIB	JAKAFI	TABLET	INCYTE	1-P	16-Nov-11	2011	2012	TRUE
BLA	125387	AFLIBERCEPT	EYLEA	INJECTION	REGENERON	1-P	18-Nov-11	2011	2012	TRUE

Analysis of NME approvals for rare diseases

	NMEs and New Biologics	Rare (%)
CY 2011*	30	11 (37)
CY 2010	21	7 (33)
CY 2009	26	9 (35)
CY 2008	24	8 (33)
CY 2007	18	6 (33)
CY 2006	22	6 (29)

*As of December 7, 2011

NME Approvals FY and CY 2011

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Trade Name	Active Ingredient	Applicant	Priority	Fast Track	Accelerated Approval	First in Class	Orphan	Emerging Sponsor	Approval Date	CY	FY
Pradaxa	Dabigatran etexilate mesylate	Boehringer Ingelheim	√						19-Oct-10	2010	2011
Latuda	Lurasidone hydrochloride	Sunovion Pharmaceuticals							28-Oct-10	2010	2011
Teflaro	Ceftaroline fosamil	Cerexa		√				√	29-Oct-10	2010	2011
Egrifta	Tesamorilin	Theratechnologies						√	10-Nov-10	2010	2011
Halaven	Eribulin mesylate	Eisai	√	√					15-Nov-10	2010	2011
DaTscan	Ioflupane I-123	GE Healthcare	√						14-Jan-11	2011	2011
Natroba	Spinosad	Parapro						√	18-Jan-11	2011	2011
Viibryd	Vilazodone	Trovis Pharmaceuticals						√	21-Jan-11	2011	2011
Edarbi	Azilsartan medoxomil	Takeda							25-Feb-11	2011	2011
Dailresp	Roflumilast	Forest				√			28-Feb-11	2011	2011
Benlysta	Belimumab	Human Genome Sciences	√	√		√		√	09-Mar-11	2011	2011
Gadavist	Gadobutrol	Bayer HealthCare							14-Mar-11	2011	2011
Yervoy	Ipilimumab	Bristol Myers Squibb	√	√		√	√		25-Mar-11	2011	2011
Caprelsa	Vandetanib	AstraZeneca	√	√			√		06-Apr-11	2011	2011
Horizant	Gabapentin Enacarbil	GlaxoSmithKline							06-Apr-11	2011	2011
Zytiga	Abiraterone Acetate	Johnson & Johnson	√			√			28-Apr-11	2011	2011
Tradjenta	Linagliptin	Boehringer Ingelheim							02-May-11	2011	2011
Victrelis	Boceprevir	Schering	√	√		√			13-May-11	2011	2011
Edurant	Rilpivirine	Tibotec							20-May-11	2011	2011

NME Approvals FY and CY 2011

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Trade Name	Active Ingredient	Applicant	Priority	Fast Track	Accelerated Approval	First in Class	Orphan	Emerging Sponsor	Approval Date	CY	FY
Incivek	Telaprevir	Vertex	√	√				√	23-May-11	2011	2011
Dificid	Fidaxomicin	Optimer Pharmaceuticals	√	√				√	27-May-11	2011	2011
Potiga	Ezogabine	Valeant Pharmaceuticals				√			10-Jun-11	2011	2011
Nulojix	Belatacept	Bristol-Myers Squibb		√		√	√		15-Jun-11	2011	2011
Arcapta	Indacaterol	Novartis							01-Jul-11	2011	2011
Xarelto	Rivaroxaban	Johnson & Johnson							01-Jul-11	2011	2011
Brilinta	Ticagrelor	AstraZeneca							20-Jul-11	2011	2011
Zelboraf	Vemurafenib	Roche	√	√		√	√		17-Aug-11	2011	2011
Adcetris	Brentuximab vedotin	Seattle Genetics	√	√	√	√	√	√	19-Aug-11	2011	2011
Firazyr	Icatibant	Shire Orphan	√	√		√	√	√	25-Aug-11	2011	2011
Xalkori	Crizotinib	Pfizer	√	√	√	√	√		26-Aug-11	2011	2011
Ferriprox	Deferiprone	ApoPharma		√	√		√	√	14-Oct-11	2011	2012
Onfi	Clobazam	Lundbeck					√		21-Oct-11	2011	2012
Jakafi	Ruxolitinib	Incyte	√	√		√	√	√	16-Nov-11	2011	2012
Erwinaze	Erwinia L-asparaginase	EUSA Pharma	√	√			√		18-Nov-11	2011	2012
Eylea	Aflibercept	Regeneron	√					√	18-Nov-11	2011	2012

NME Approvals CY2011

- Datscan (ioflupan I-123) (P)
- Natroba (spinosad) (E)
- Viibyrd (vilazodone HCl) (E)
- Edarbi (azilsartan)
- Daliresp (roflumilast) (FC)
- Benlysta (belimumab) (FT, P, E,FC)
- Gadavist (gadobutrol)
- Yervoy (ipilimumab) (O, FT, P, FC)
- Caprelsa (vandetanib) (O, FT, P)
- Horizant (gabapentin enacarbil)
- Zytiga (albiraterone) (P, FC)
- Tradjenta (linagliptin)
- Victrelis (boceprevir) (FT, P, FC)
- Edurant (rilpivirine)
- Incivek (telaprevir) (FT, P, E)
- Dificid (fidaxomicin) (FT, P, E)
- Potiga (ezogabine) (FC)
- Nulojix (belatacept) (O, FT, FC)
- Arcapta (indacaterol)
- Xarelto (rivaroxaban)
- Brilinta (ticagrelor)
- Zelboraf (vemuranfenib) (O, FT, P, FC)
- Adcetris (brentuximab) (O, FT, P, E, FC, AA)
- Firazyr (icatibant) (O, FT, P, E, FC)
- Xalkori (crizotinib) (O, FT, P, C, FC, AA)
- Ferriprox (deferiprone) (O, FT, E, AA)
- Onfi (clobazam) (O)
- Jakafi (ruxolitinib) (O, FT, P, E, C, FC)
- Erwinaze (erwinia L-asparaginase) (O, FT, P)
- Eylea (aflibercept) (P, E)

O=Orphan, FT=Fast Track, P=Priority Review, E=Emerging Sponsor, C=Companion Diagnostic, FC=First in Class, AA=Accelerated Approval

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

PDUFA Stakeholder Concerns Heard in April 2010 Public Meeting

Patient Advocate Perspectives

- Speed drug development through greater focus on regulatory science
- Support development of innovative trial designs
- Advance development of drugs for rare diseases
- Provide clear information on benefits and risks
- Obtain patient input on REMS design
- Ensure REMS don't unduly limit patient access

Consumer Advocate Perspectives

- Strengthen system for oversight and audit of clinical trials
- Provide patient-friendly information on drug safety and effectiveness
- Provide for easier Adverse Event reporting

PDUFA Stakeholder Concerns Heard in April 2010 Public Meeting (cont.)

Health Care Professional Perspectives

- Consider written information for patients that is more effective than current MedGuides
- Make REMS more standardized; establish metrics to evaluate success of REMS
- Assess REMS burden on healthcare system
- Obtain pharmacist input on REMS design

Regulated Industry Perspectives

- Develop more efficient process to deal with post-FDAAA review challenges
- Ensure offices work seamlessly
- Establish more transparent benefit-risk standards
- Ensure greater process consistency across review divisions
- Establish more predictable timeframe for REMS requests

Reauthorization discussions yielded proposed recommendations:

- 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

Next Steps

- November – December 2011
  - Analyze public comments on proposed recommendations and revise recommendations as needed
- January 2012
  - Provide briefings on public meeting findings and final proposed recommendations
  - Transmit final recommendations to Congress
- Program must be reauthorized by Congress by September 30, 2012

CDER New Drug Review: 2011 Summary

- CDER is meeting or exceeding nearly all PDUFA application review goals
- 30 NME approvals in 2011 is highest total since 2004
- Rate of submission of NME applications remains flat
- CDER has approved many important new drugs this year that will positively impact patients and public health
  - Approvals reflect broad use of existing mechanisms to expedite drug development and review
- NME first cycle approval rates for PDUFA IV at all time high
  - ≈50% first cycle approval rate still leaves room for improvement
- Time to 50% approval of NME cohort by FY of submission reduced from 2.5-3 yrs pre-PDUFA to ≈1.5 yrs today

CDER New Drug Review: 2011 Summary (cont.)

- U.S. continues to lead the world in first approval of new active substances; U.S. patients benefit from early access
- Shift from big pharma to small company paradigm is rapidly changing the dynamic of drug development and review
  - Encouraging evidence for success of new model in some cases
  - All stakeholders need to adjust to this new paradigm
- PDUFA V proposals include programs to build on the success of the past 20 years and to adjust to new realities in drug development, science, and regulation
  - Broad support from recent public meeting for speedy reauthorization of this critical and highly successful program
- CDER/FDA track record on new approvals not always fairly communicated to the public
  - Data do not support many of the current claims re: FDA performance