New Drug Review:
An Update and a Look Ahead

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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, Yashika Rahaman, Nelson Cheung and Patrick Frey for their help in conceiving and conducting many of the analyses presented in this talk.

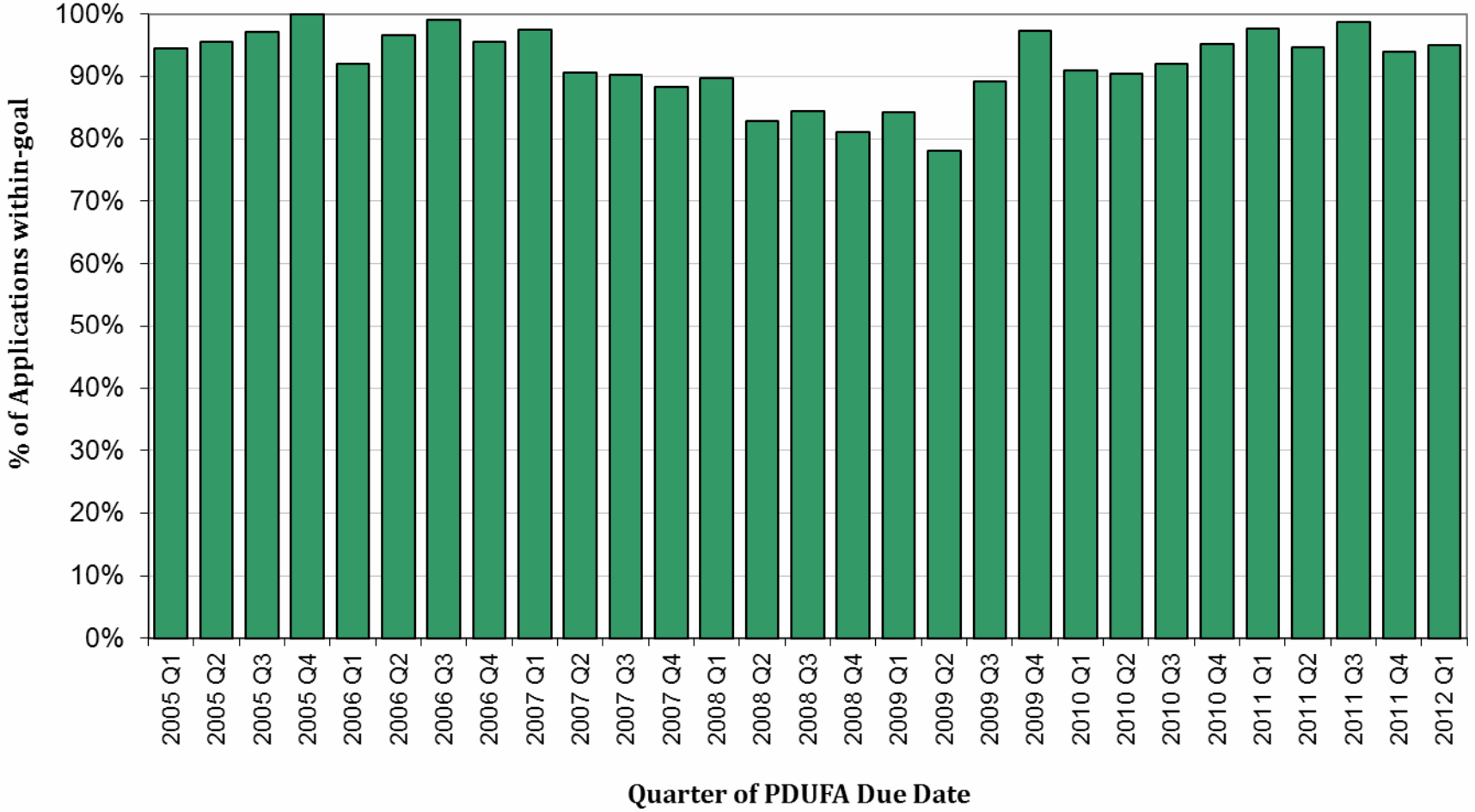
Topics to be covered

- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
- 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
- New workload associated with implementation of the FDA Amendments Act of 2007 had an adverse impact on our ability to meet all of our PDUFA goals in FY08/09
  - Even during this period our application review performance was still in the 80-90% on time range and many of the applications that missed their first-cycle PDUFA goals were approved on the first cycle; i.e., "the wheels did not come off the wagon"
- We are now back on track and meeting/exceeding nearly all of our PDUFA goals for application review

CDER PDUFA Application Review Performance (NDAs, BLAs, Efficacy Supplements) 2005 -2012



•*CDER data as of 03/31/2012. Figures reflect aggregate performance for all NDAs, BLAs, and Efficacy Supplements based on the month of the PDUFA review goal.

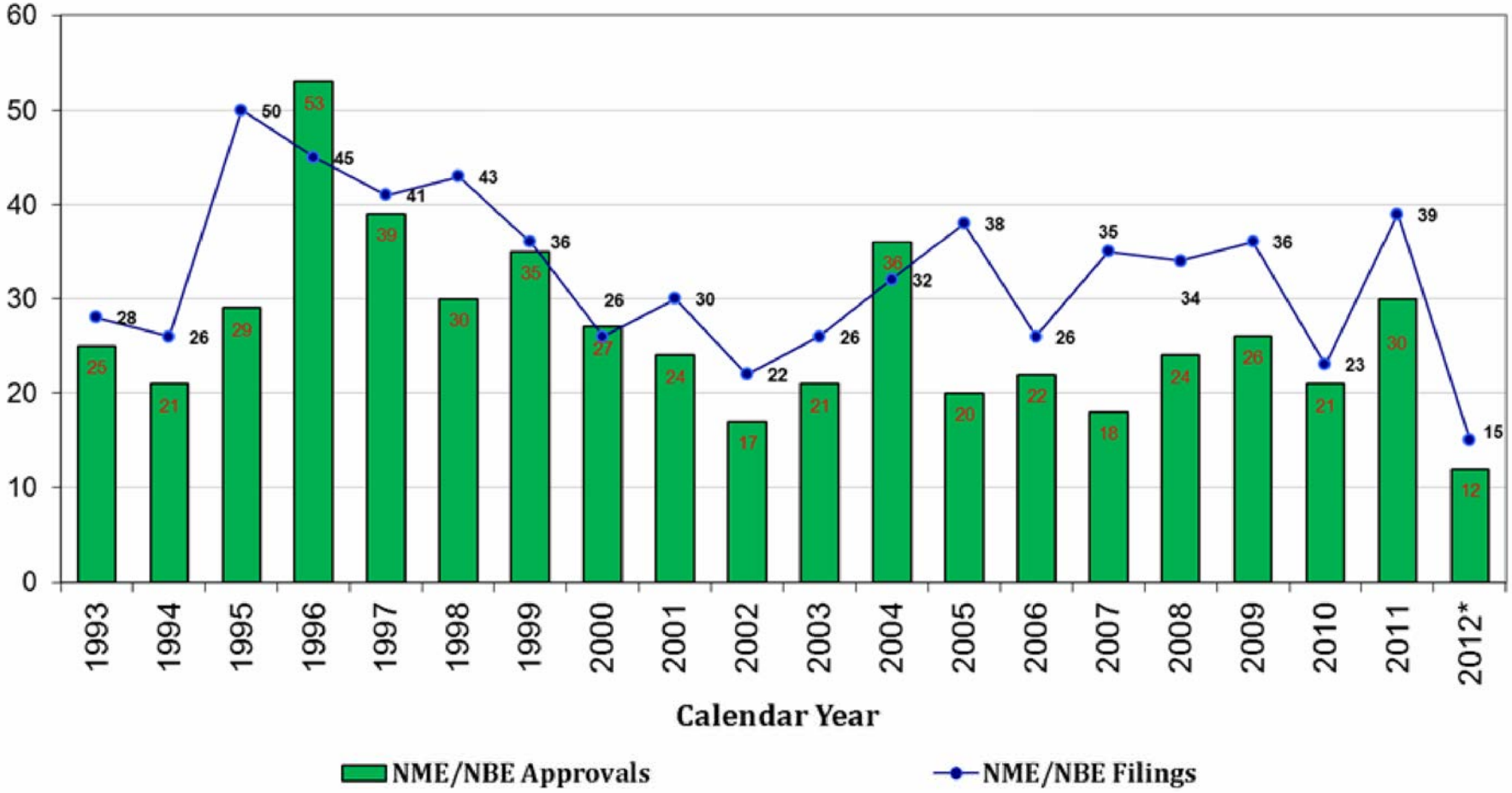
What about new drug approvals?

- 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 2012 the FDA storylines are "innovation," "jobs," "breakthrough therapies," "venture capital drying up," and "streamlining regulation"
- Despite the shifting FDA storylines:
  - In my 20+ 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 (2)?

- In CY11 CDER approved 30 NME applications, the highest number since 2004
  - NME filings in CY11 (39) were higher than the average for recent years (e.g., 30.6/year CY06-10)
- To date in CY12 CDER has approved 12 NME applications and has received 15 NME applications for filing
  - **CAUTION: PDUFA goal dates are not uniformly distributed across a calendar year; projections for full year data based on ½ year data are subject to significant error**
- First-cycle approval rates for NME applications in PDUFA IV are at the highest levels since the start of PDUFA
- Median approval times for NME applications are 10 months, a 47% reduction from CY93
- US leads the world in first introductions of NMEs

CDER New Molecular Entity and New Biologic Entity Filings and Approvals



•*CDER data as of 06/18/2012. New Biologic Entities are included in CDER figures beginning in 2004, when review authority for therapeutic biologic products was transferred from CBER to CDER.

Snapshot of CY 2012 NME Approvals*

Trade Name	Met PDUFA Goal Date	Approved on the First Cycle	Priority Review	Fast Track Designation	First-In-Class Drug	Approved First in the U.S.	Orphan Designation
Voraxaze							
Picato							
Inlyta							
Erivedge							
Kalydeco							
Zioptan							
Surfaxin							
Omontys							
Amyvid							
Elelyso							
Stendra							
Perjeta							

•* Data as of June 18, 2012

Analysis of NME approvals for **rare diseases**

	NMEs and New Biologics	Rare (% of total approvals)
CY 2012*	12	4 (33%)
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%)

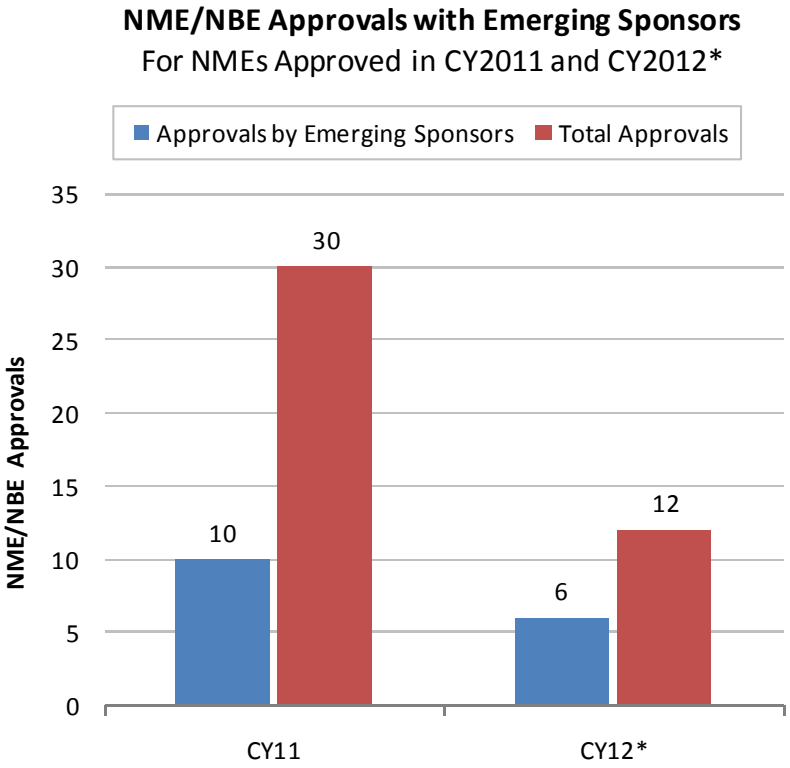
- *Data as of June 18, 2012

CDER NME/NBE Rare Disease Drug Approval CY 2011-2012

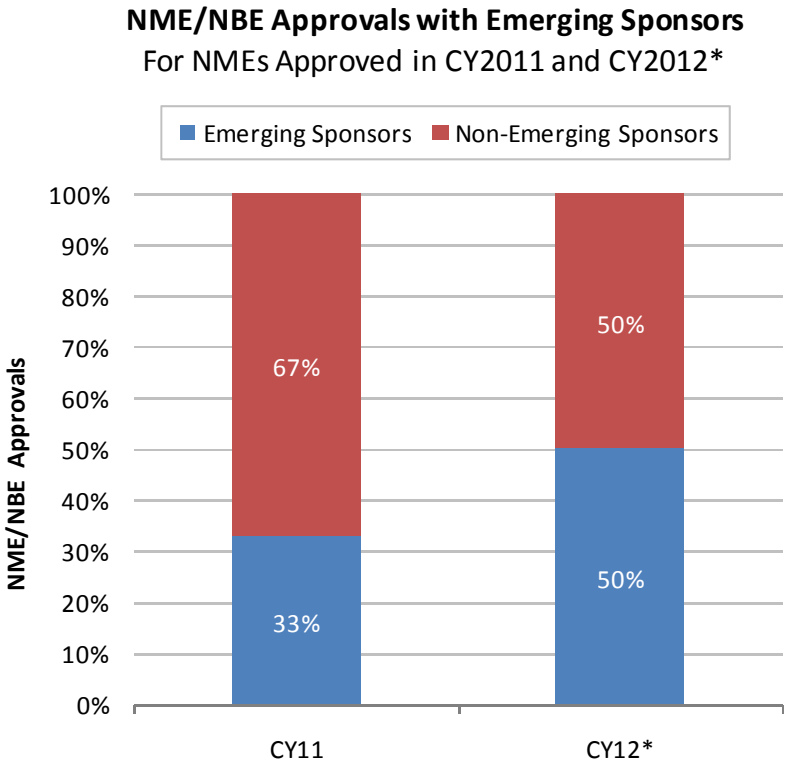
- 2011, n=11 (12 indications)
  - Ipilimumab (melanoma)
  - Vandetinib (med. thyroid CA)
  - Belatacept (organ rejec, kdny tx, EBV+)
  - Brentuximab (Hodgkins)
  - Brentuximab (anapl. lge cell lymphoma)
  - Vemurafenib (melanoma BRAF+)
  - Crizotinib (NSCLC ALK+)
  - Icatibant (HAE)
  - Asparaginase (ALL)
  - Deferiprone (transfus. Fe overload due to thalassemias)
  - Clobazam (Lennox-Gastaut)
  - Ruxolitinib (Myelofibrosis)
- 2012, n = 4*
  - Glucarpidase (MTX toxicity)
  - Ivacaftor (CF)
  - Lucinactant (RDS preemies)
  - Taliglucerase (Gaucher)

•* Data as of June 18, 2012

Comparison of Emerging Sponsor Approvals CY2011-CY2012



Source: FDA DBAR, Orange Book



Source: FDA DBAR, Orange Book

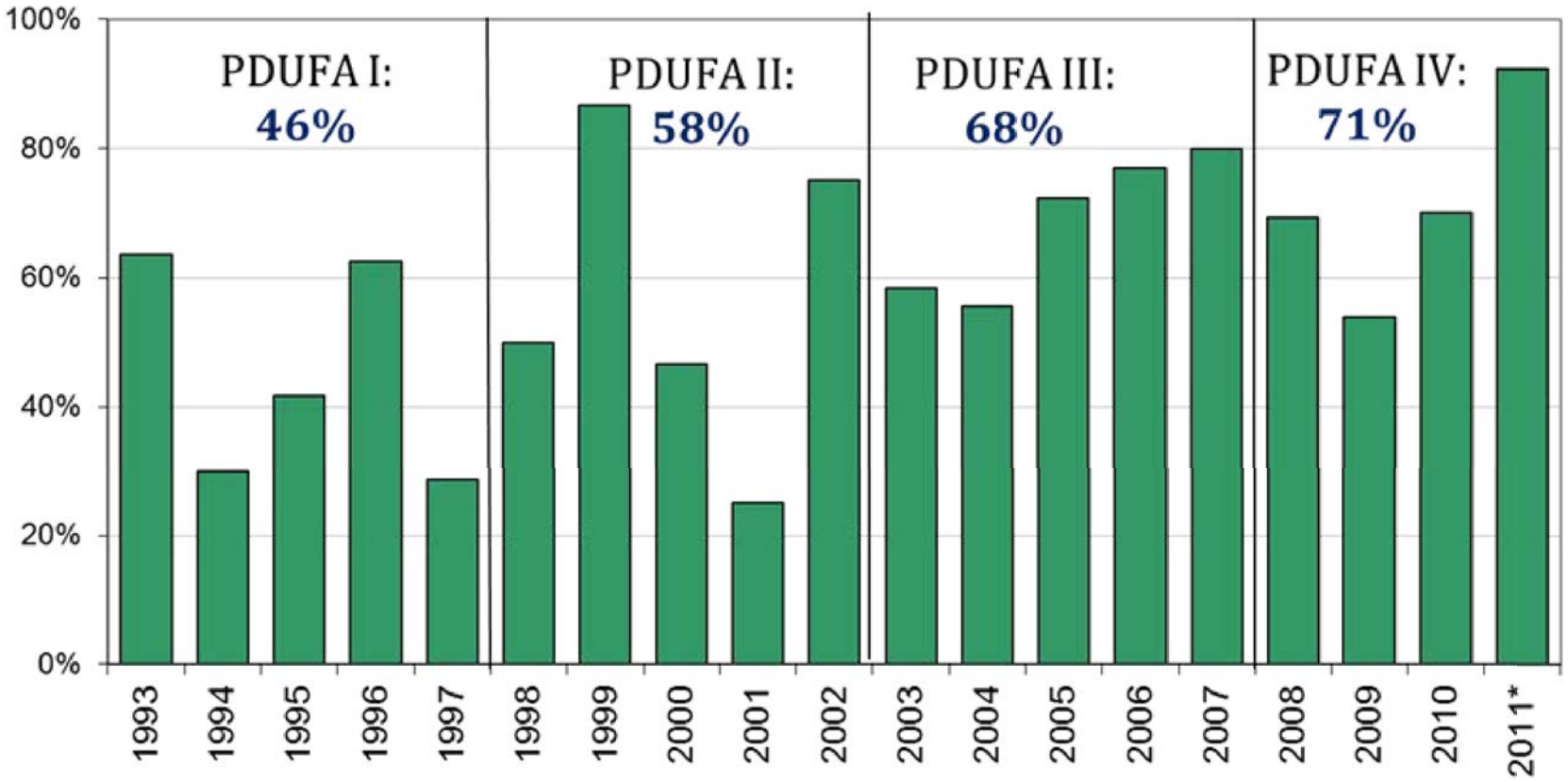
**2012 data as of June 18, 2012*

NME/NBE Approvals with Emerging Sponsors CY2012

PATHWAY	ACTIVE INGREDIENT	TRADE NAME	DOSAGE FORM	APPLICANT	REVIEW TYPE	APPROVAL DATE	EMERGING SPONSOR?
BLA	GLUCARPIDASE	VORAXAZE	INJECTABLE; INJECTION	BTG INTERNATIONAL INC	STANDARD	17-Jan-12	YES
NDA	LUCINACTANT	SURFAXIN	SUSPENSION; INTRATRACHEAL	DISCOVERY LABS	STANDARD	6-Mar-12	YES
NDA	PEGINESATIDE ACETATE	OMONTYS	SOLUTION; INTRAVENOUS, SUBCUTANEOUS	AFFYMAX	STANDARD	27-Mar-12	YES
NDA	FLORBETAPIR F 18	AMYVID	SOLUTION; INTRAVENOUS	AVID RADIOPHARMS INC	STANDARD	6-Apr-12	YES
NDA	AVANAFIL	STENDRA	TABLET; ORAL	VIVUS	STANDARD	27-Apr-12	YES
NDA	TALIGLUCERASE ALFA	ELELYSO	INJECTABLE; INJECTION	PROTALIX LTD	STANDARD	1-May-12	YES

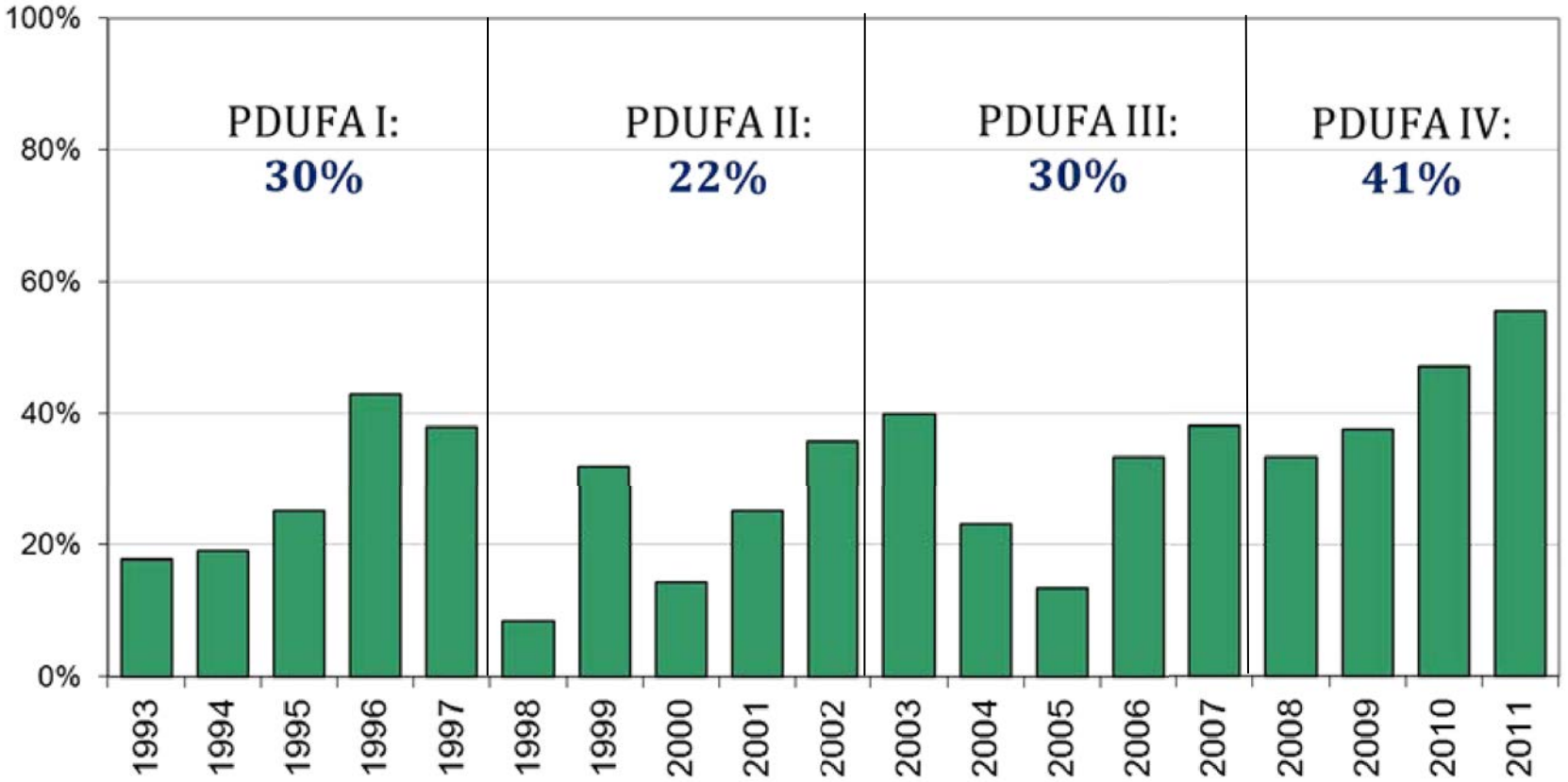
**2012 data as of June 18, 2012*

CDER First Action Approval Rates for Priority NMEs/NBEs



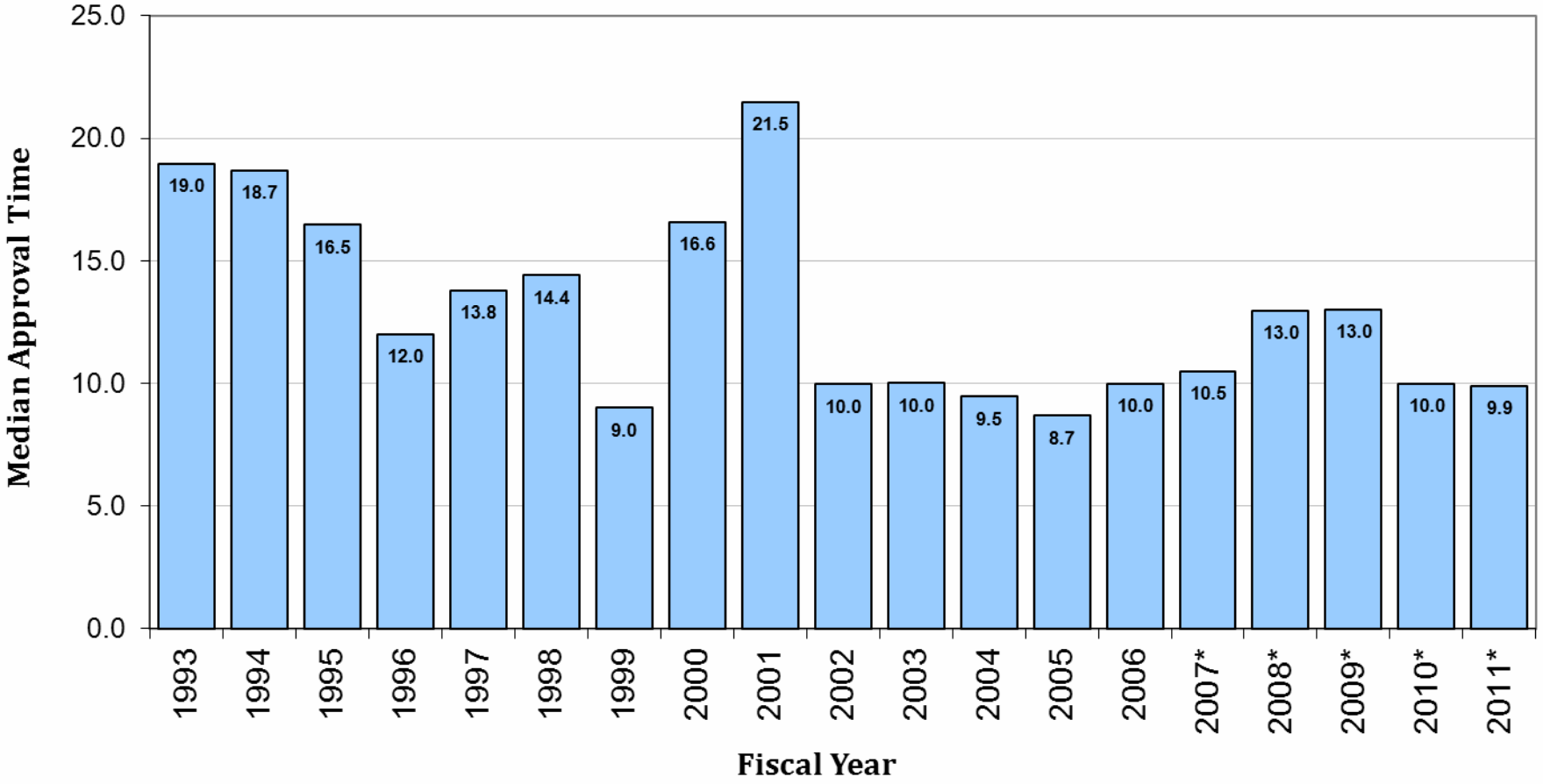
- * FY '11 have pending applications awaiting first cycle decision.
- CDER NME and new BLA actions data as of 06/18/2012. New Biologic Entities are included in CDER figures beginning in 2004, when review authority for therapeutic biologic products was transferred from CBER to CDER.

CDER First Action Approval Rates for Standard NMEs/NBEs



•*CDER NME and new BLA actions data as of 06/18/2012. New Biologic Entities are included in CDER figures beginning in 2004, when review authority for therapeutic biologic products was transferred from CBER to CDER.

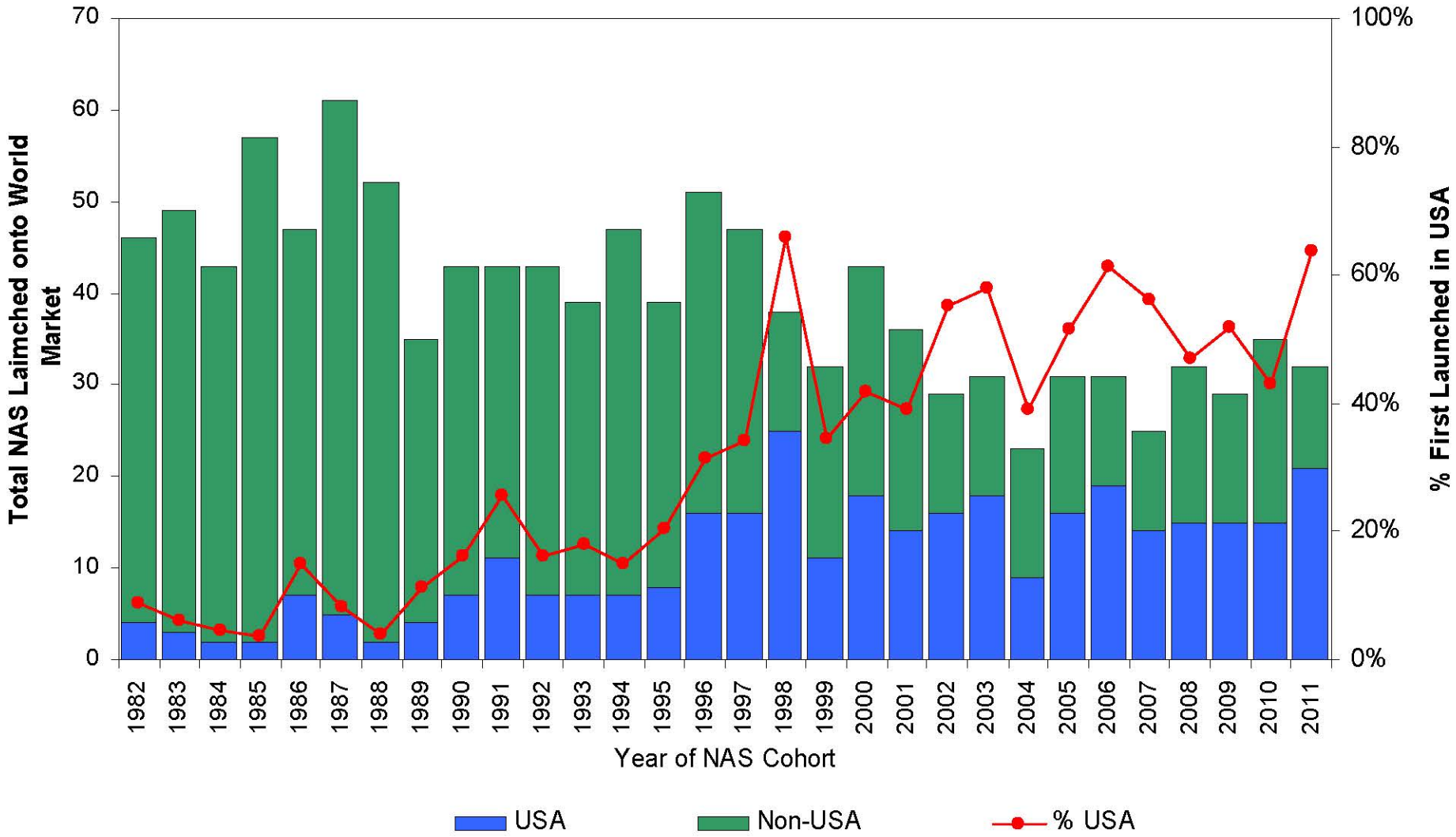
CDER NME/NBE Median Approval Times (by fiscal year of receipt)



•CDER data as of 06/18/2012

•*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.

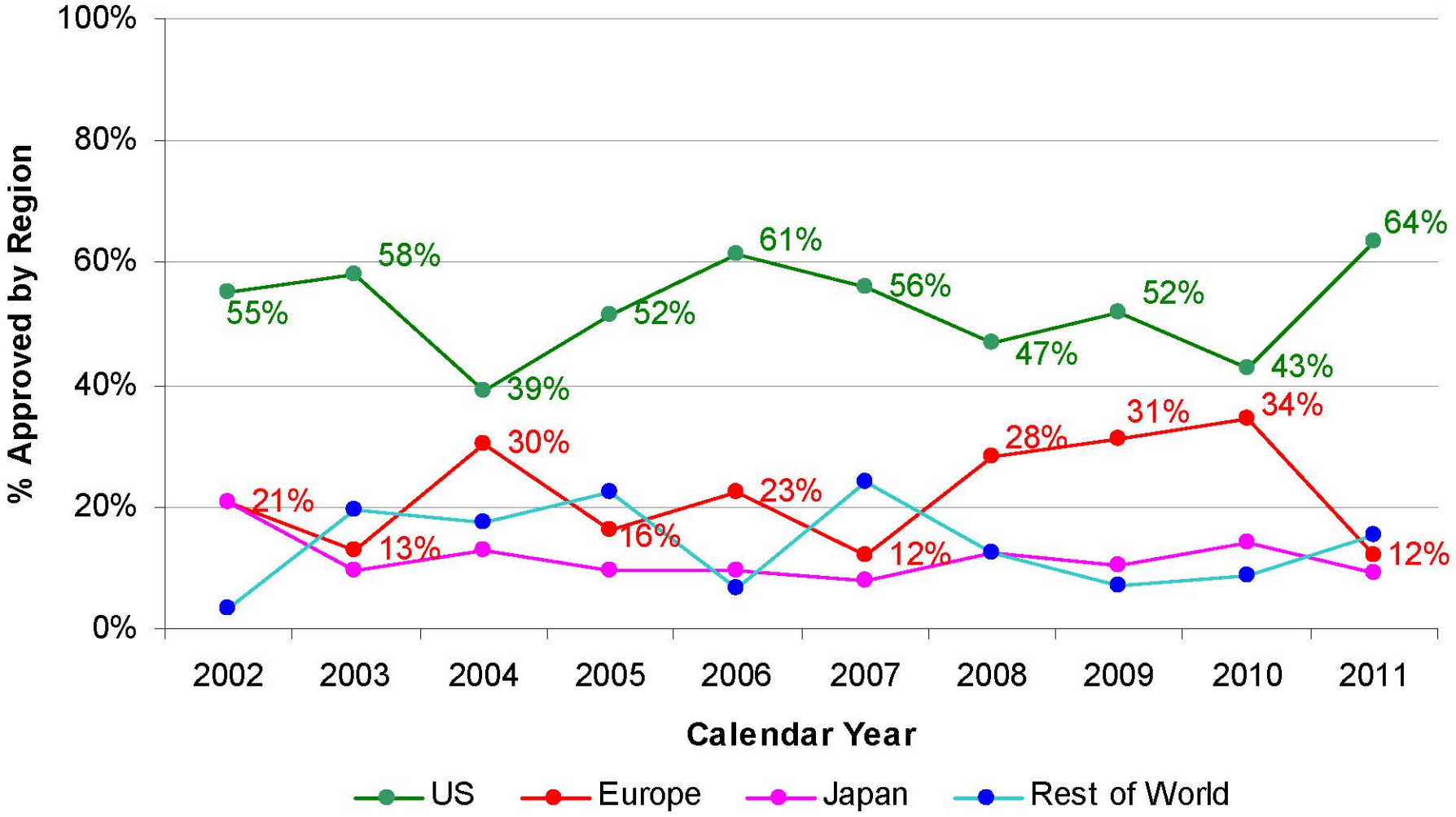
USA Share of New Active Substances First on World Market



Source: Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 - 2005), PharmaProjects/Citeline (2006 -2011) *www.citeline.com*

Global New Active Substance First Launches by Region

2002 - 2011



Source: Scrip Magazine (Feb 2003, Feb 2004, Feb 2005), Pharmaprojects (2006, 2007), Pharmaprojects R&D Annual Review (May 2008, May 2009, May 2010), Citeline Pharma R&D Annual Review (May 2011, May 2012)

www.citeline.com

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 agreement on enhancements in several areas:

- 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

PDUFA V "Program" for NME review

- Overall goal is to improve first-cycle approval rates for NMEs **without** altering the standards for approval
  - 60-day filing review period "off the PDUFA clock" provides FDA staff with more time to address added complexity of modern application review (e.g., advisory committee meetings, REMS, PMRs) and time to complete additional tasks added as part of the new review process (e.g., late-cycle meeting with applicant)
  - Mid-cycle communication to applicant and late-cycle meeting between applicant and review team will improve transparency during review and may provide an opportunity to address deficiencies identified by the review team in the first cycle
- The "Program" will test the hypothesis that the review process changes can further increase first-cycle approvals

Key elements of the "Program"

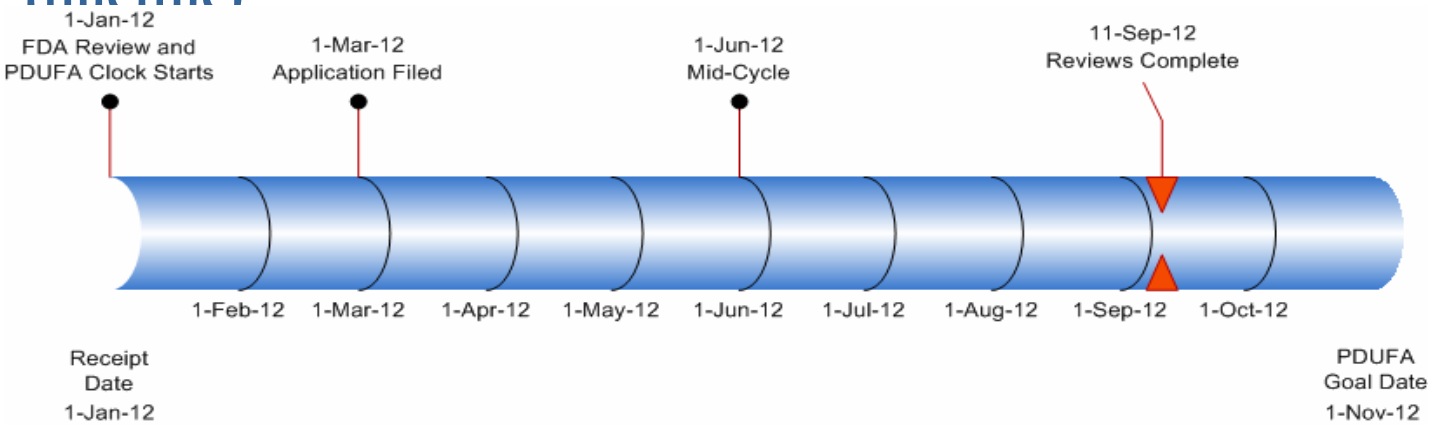
- **Complete** applications at the time of submission
  - Enforces a core principle of the PDUFA program that has been honored in the breech by applicants (and FDA) for 20 years
  - Allows FDA team to plan its review and stay on track without the disruption of unsolicited late amendments
- 60-day filing review period "off the clock"
  - PDUFA clock starts when application is filed, not when submitted, effectively adding 2 months to time for review completion
  - In our review process this extra time will be added "at the end" to provide more time to address issues before the action is taken (e.g., inspection findings, REMS, labeling, PMRs)
- Mid-cycle communication
  - Conference call after internal mid-cycle meeting to share updates with applicant and plan for remainder of review

Key elements of the "Program" (2)

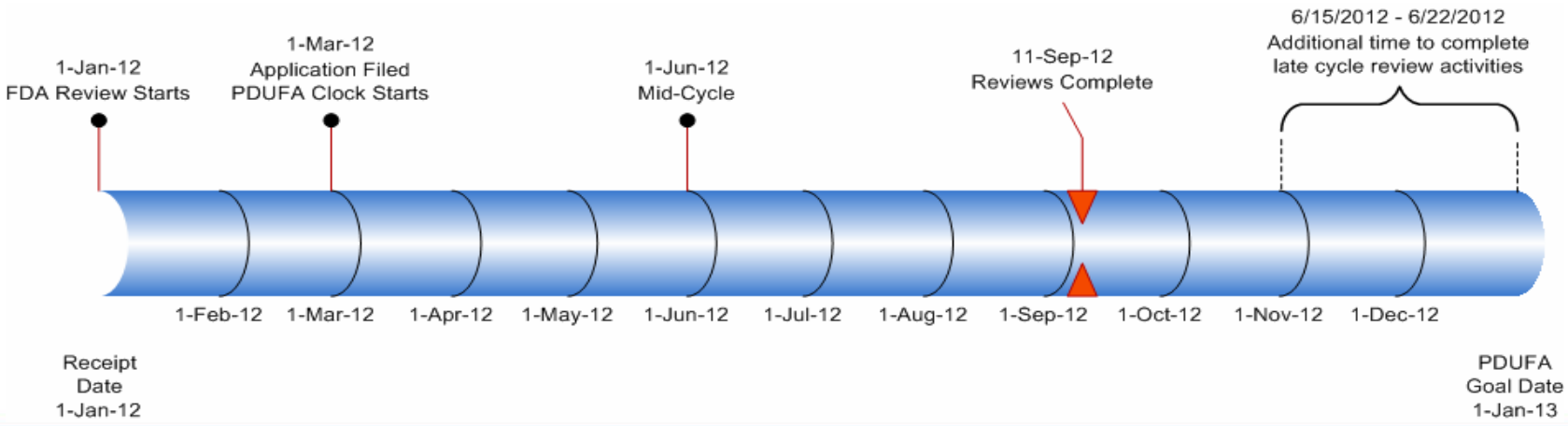
- Discipline review letters
  - Issued following completion of primary/secondary review by discipline to alert applicant to potential deficiencies
- Late-cycle meeting
  - Face-to-face meeting between review team and applicant to discuss review findings to date and plan for AC and remainder of review
  - **NOT** a decisional meeting on planned action, but may facilitate addressing issues in first cycle and avoid need for CR letter
    - Applicant and review team can discuss new analyses/data that may be available and whether to submit/review in current cycle, which may prompt 3-month extension of PDUFA goal date
  - Planning for AC meeting will avoid redundancy of applicant/FDA presentations in areas of agreement and allow focus on areas of disagreement or need for committee input

PDUFA V Timeline Comparison

- **Non-"Program" Standard Application (Current PDUFA IV timeline)**



- **"Program" Standard Application**



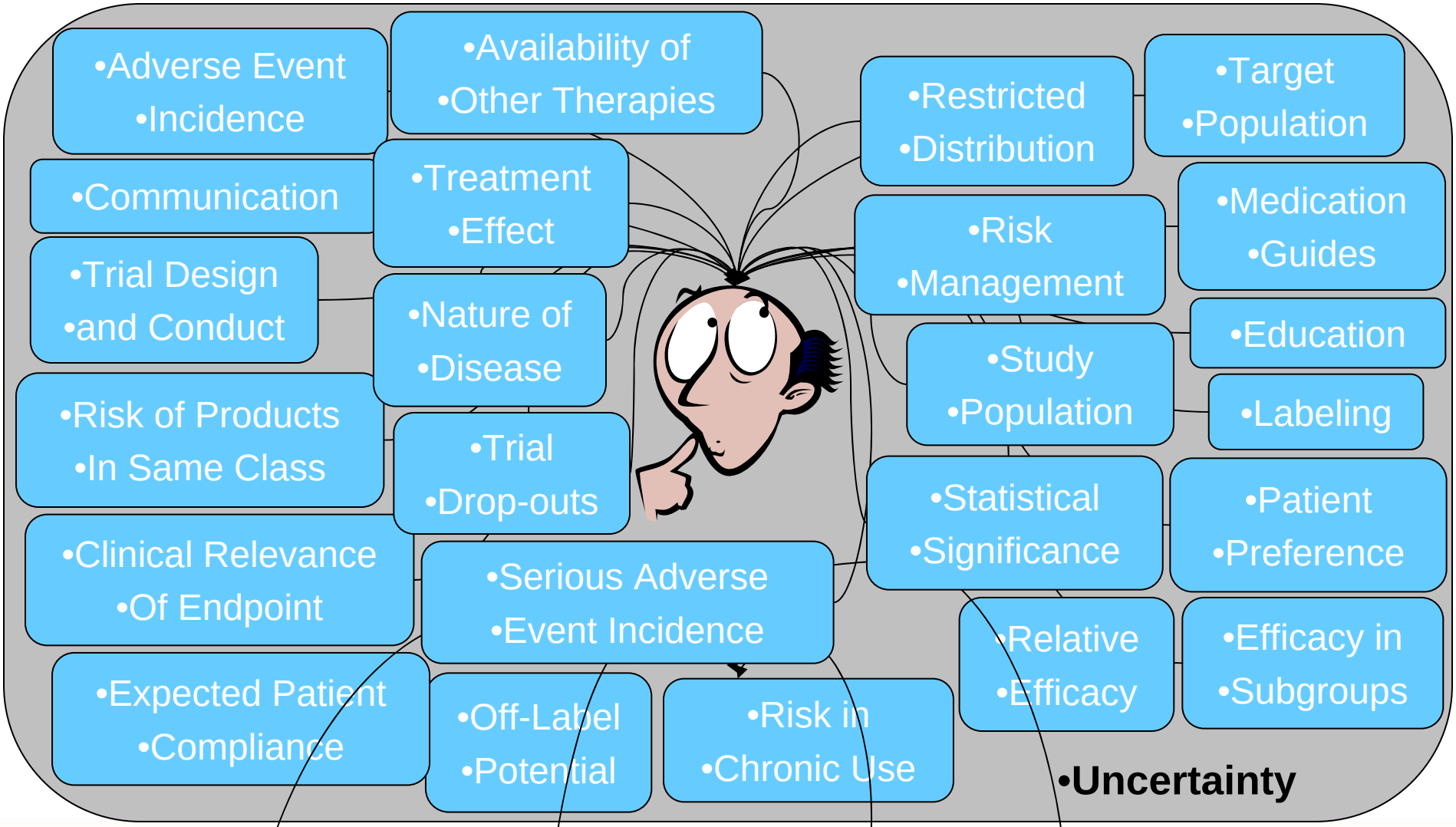
The "Program" and investors

- Discipline review letters and late-cycle meeting will provide applicants greater transparency into the FDA review findings well before action on the application
- Information shared could "signal" the outcome of the review on that cycle, but the reliability of the "signal" may be poor given the ongoing nature of the review
  - An application that looks "positive" at the late-cycle meeting may not be approved based on more senior (e.g., Office Director) review of the issues, unacceptable late inspection results (GCP, GMP), etc.
  - An application that looks "negative" at the late-cycle meeting may be approved with additional review and as issues are resolved
- ? Impact on requirements for disclosure by applicant to investors and public

Development of benefit/risk framework

- Goal is to better standardize our decision-making process and improve transparency in communicating our decisions internally and externally
- Work on project began in CDER in 2009 and is currently being pilot tested using 6 NME applications (one per OND review office)
- Will be incorporated into review templates, decision memo templates, and CDER SOPs as appropriate during PDUFA V

What's on the regulator's mind?



CDER Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

Sample Framework Questions: Therapeutic Area

- Analysis of condition
  - Describe the condition that is treated or prevented by the drug
  - What are the clinical manifestations of the condition, what is known about its natural history, and how does severity vary across sub-populations?
- Unmet medical need
  - Describe the other therapies used to treat the condition, including approved and off label pharmacological therapies and non-pharmacological therapies
  - How effective and well-tolerated are these alternatives, and what evidence is available to support these conclusions?

Sample Framework Questions: Product Specific

- Benefit
  - Describe the trials (including strengths and weaknesses) that were conducted to establish safety and efficacy
  - What endpoints were evaluated and are they clinically meaningful? How did benefits vary across sub-populations of responders?
- Risk
  - Characterize safety concerns identified from trials. What was the incidence of the risk and did it vary by sub-population? Did risk change with continued exposure; is it reversible when treatment is stopped?
  - How might the incidence change in the post-market setting? Is additional work needed to further characterize the risk?

Sample Framework Questions: Product Specific (2)

- Risk Management
  - What risks (if any) require mitigation or further characterization? What tools are recommended to address the risks, and what is the expected contribution of each tool to the overall risk management?
  - What would constitute a successful risk management plan, how might it be measured, and if the desired impact is now achieved, at what point should the risk management plan be re-evaluated?

CDER New Drug Review: 2012 Summary

- CDER is meeting or exceeding nearly all PDUFA application review goals
- 30 NME approvals in CY11 was highest total since 2004, 12 NME approvals to date in CY12
- Rate of submission of NME applications remains flat
- NME first cycle approval rates for PDUFA IV at all time high
  - ≈50% overall first cycle approval rate for NMEs still leaves room for improvement given eventual ≈75% NME approval rate
- U.S. continues to lead the world in first approval of new active substances; U.S. patients benefit from early access
- 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

CDER New Drug Review: 2012 Looking Ahead

- Reauthorization of PDUFA has broad stakeholder support and Congressional bi-partisan support
- Enhancements in PDUFA V are designed to further improve efficiency of the FDA review process and to enhance regulatory science to improve application quality and the chances of success for innovative products
- Development of benefit/risk framework will improve quality, transparency, and communication of FDA decisions
- PDUFA V program provides appropriate balance to address the needs of the divergent stakeholders and to provide framework to build on a 20-year track record of success

Questions