New Drug Review:
2008 Update

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Topics to be covered

- What were your priorities for new drug review in 2008 and how did you do?
- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
- What will be your priorities for new drug review in 2009?

2008 Review Priorities

- Recruitment of new staff
  - Needed to meet the ever growing workload for new drug review program and to implement new provisions of FDAAA
  - Workload/staffing imbalance has been a growing problem through PDUFA II and III with increasing requests for meetings, SPAs, etc.
  - OND and CDER used all tools available to aid recruitment in 2008

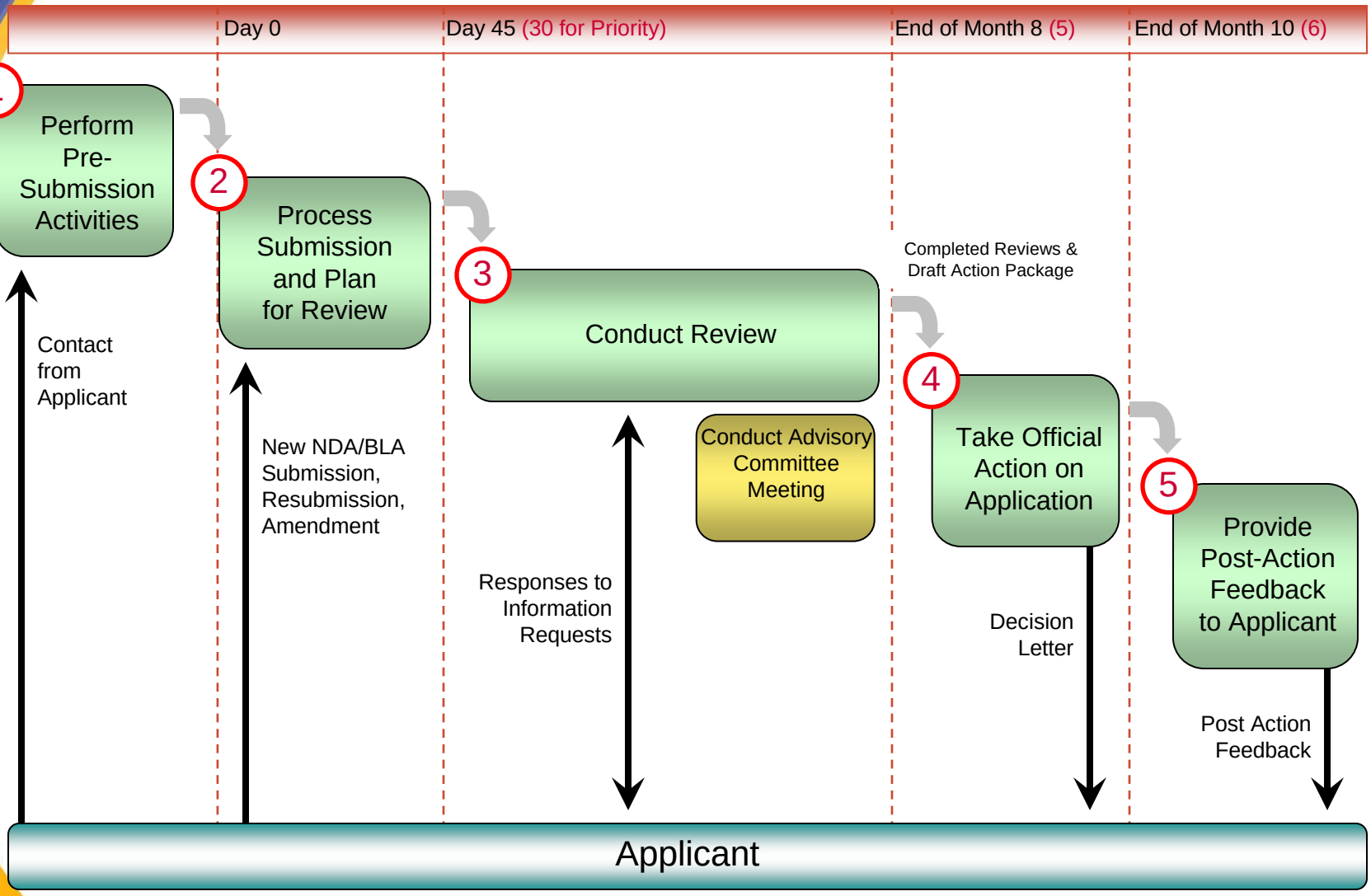
Recruitment Results FY08

	CDER	OND
FY08 FTE Ceiling	2882	890
Onboard 10/1/07 (# under ceiling)	2236 (-646)	731 (-159)
New hires during FY08	663	209
Onboard 9/30/08 (# under ceiling	2632 (-250)	852 (-38)
Net gain FY08	396	121

2008 Review Priorities

- Pilot 21st Century Review Process
  - New review process developed to embed principles of GRMP into our day-to-day review of applications
  - New process emphasizes:
    - Expectation for complete applications at time of submission; sponsors must do their part!!!
    - Review planning and timelines for deliverables
    - Cross-disciplinary teamwork & communication
    - Work distribution throughout the review cycle
    - Involvement of signatory authority early/often
    - Protection of time for end-of-review activities
    - Greater transparency to sponsor during review

21st Century Review Process



Pilot Status and Plans

- Each OND division applied new review model to one NDA/BLA in FY08 as pilot
- Extensive training of review staff in new process and teamwork skills
- Lessons learned collected and used to make modifications to improve process
- Ongoing training and oversight for implementation rollout
- Applies to all NMEs submitted in FY09
- Will need to continue to modify the process to incorporate FDAAA-related issues

2008 Review Priorities

- "Stand up" Safety First Initiative
  - The goal of Safety First is to bring the same level of priority and project management to postmarketing safety issues that is applied to application review
  - Safety First also ensures that all appropriate disciplines and expertise are applied to review of postmarketing safety issues to ensure sound decisions
  - Safety First continues emphasis on early communication to the public and greater transparency to FDA decisions

Safety First Status

- Dedicated staff in each OND division to manage safety portfolio
  - Deputy Director for Safety and dedicated Safety Project Manager
- Increased interactions and communication between OND and OSE
  - Regular monthly meetings to review portfolio
  - "Equal voice" for OND and OSE in decision making
- New tracking system in place for postmarketing safety issues
  - Includes over 300 active postmarketing safety issues
- Improved project management of reviews
  - Developing formal work plans and goals for each safety issue
- Focus on early communication and follow up communication when issue resolved

2008 Review Priorities

- Implement FDAAA (Title IX)
  - Landmark legislation providing FDA with expanded authorities to manage the entire life-cycle of drugs
    - Ability to require Risk Evaluation and Mitigation Strategies (REMS) to ensure safe and effective use of drugs
    - Ability to require postmarketing studies or trials to assess serious safety issues
    - Ability to order safety related labeling changes
  - Many detailed timelines and deliverables included in the legislation

Title IX Status

- Steering Committee in CDER to oversee implementation
- Working closely with OCC on statute interpretation and implementation
- New processes being developed and standardized to manage FDAAA-related safety actions and to ensure consistency
- Extensive and ongoing training for staff on new authorities and procedures
- “Deemed REMS” notice issued and submissions now under review

CDER FDAAA Title IX Actions

(as of 12/2/08)

Total REMS Approved	21
Medication Guide only REMS (# that updated existing MG)	16 (6)
REMS with communication plan and/or elements to assure safe use	5
Total PMRs (PMRs as part of an approval)	34 (24)
Safety labeling changes ("class" changes counted as one change)	7
Safety labeling orders	1

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
- FDA has been struggling to meet PDUFA goals for the past several years
- In FY08 we made a management decision that we would not be able to meet all PDUFA goals and meet all our other priorities
  - But, all is not lost - we continue to meet most of our PDUFA goals

CDER FY07 Application Review

(applications submitted in FY07, status as of September 30, 2008)

Submission Type	Number Filed*	2007 Performance Goal	Current Performance
NDAs/BLAs			
Standard	84	90% in 10 months	88%
Priority	24	90% in 6 months	90%
NMEs/New BLAs			
Standard	20	90% in 10 months	80%
Priority	10	90% in 6 months	90%
NDA / BLA Resubmissions			
Class 1	23	90% in 2 months	70%
Class 2	48	90% in 6 months	94%
NDA / BLA Efficacy Supplements (ES)			
Standard	136	90% in 10 months	86%
Priority	46	90% in 6 months	89%
NDA / BLA ES Resubmissions			
Class 1	16	90% in 2 months	81%
Class 2	23	90% in 6 months	91%
NDA / BLA Manufacturing Supplements			
Requiring Prior Approval	677	90% in 4 months	92%
CBE	1363	90% in 6 months	98%

CDER FY07 Procedural Goals

(requests submitted in FY07, status as of September 30, 2008)

Type	Number	2007 Performance Goal	Current Performance
IND Complete Response to Hold	138	90% within 30 days	77%
Special Protocols	449	90% within 45 days	88%
Meeting Tracking			
Responses to Meeting Requests	2209	90% within 14 days	83%
Scheduling Meetings:	1885	90% within goal	86%
*Type A**	194	90% within 30 days	80%
Type B	1174	90% within 60 days	85%
Type C	517	90% within 75 days	89%
Meeting Minutes	1484	90% within 30 days	78%
Dispute Resolution	22	90% within 30 days	100%

But, what about FY08 Goals?

- The FY08 cohort is not mature enough to report accurate performance data
  - Many applications are under review and have not reached their first PDUFA goal date
  - Based on current data, our potential performance is generally in line with the FY07 data
- Reasons for missed PDUFA goal dates in past year include:
  - FDAAA-related issues (e.g., REMS, PMRs)
  - Workload/competing priorities
  - Pending citizen petitions
  - Inspectional issues (clinical and/or manufacturing)
  - Advisory committee scheduling (FDAAA provision for NMEs)

Missed Goals, a closer look

Data from 1/1/08 through 10/31/08	NDAs/ BLAs	ES
Total PDUFA goals	159	190
PDUFA goals missed (% of total)	32 (20%)	19 (10%)
Actions on overdue applications (% of overdue actions)	20 (63%)	15 (79%)
AP actions for overdue appl. (% of actions on overdue appl.)	12 (60%)	11 (73%)

What about new drug approvals?

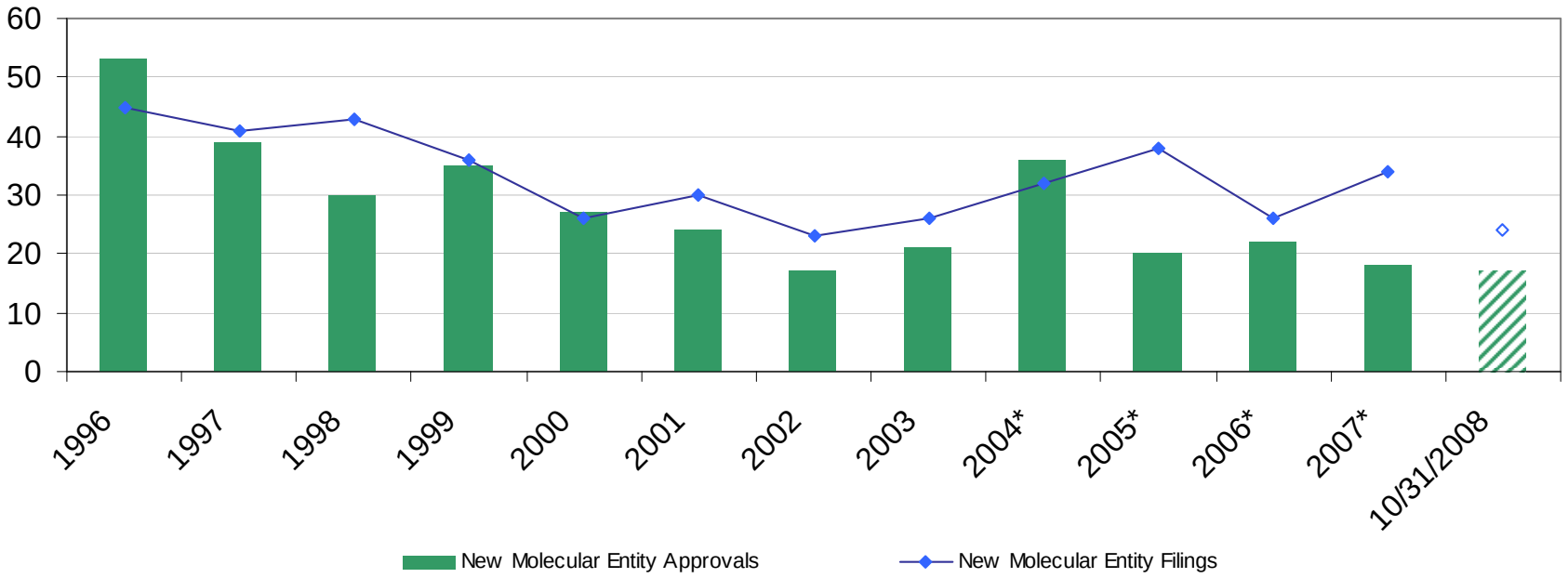
- The never ending debate about whether FDA is too fast or too slow in approving new drugs continues to rage
  - In fact, we hear complaints from both sides of the issue at the same time!!
- In my 16 ½ years at FDA I have never received or issued an order to “speed up” or “slow down”
- We review each application on its merits and apply our best judgment with regard to the data, the science, and the regulations
- We do not have goals for numbers of approvals by year, division, etc.
  - Drugs that meet the standards for approval are approved
  - Drugs that do not meet the standards are not approved

What metric to follow for trends?

- We believe the most appropriate metrics are those based on submission cohorts; i.e., by FY
  - Unfortunately, submission cohorts take time to mature; analysts and the media are impatient for results
- Approval cohorts; i.e., by CY, provide more timely information
  - Unfortunately these analyses are analogous to averaging apples and oranges

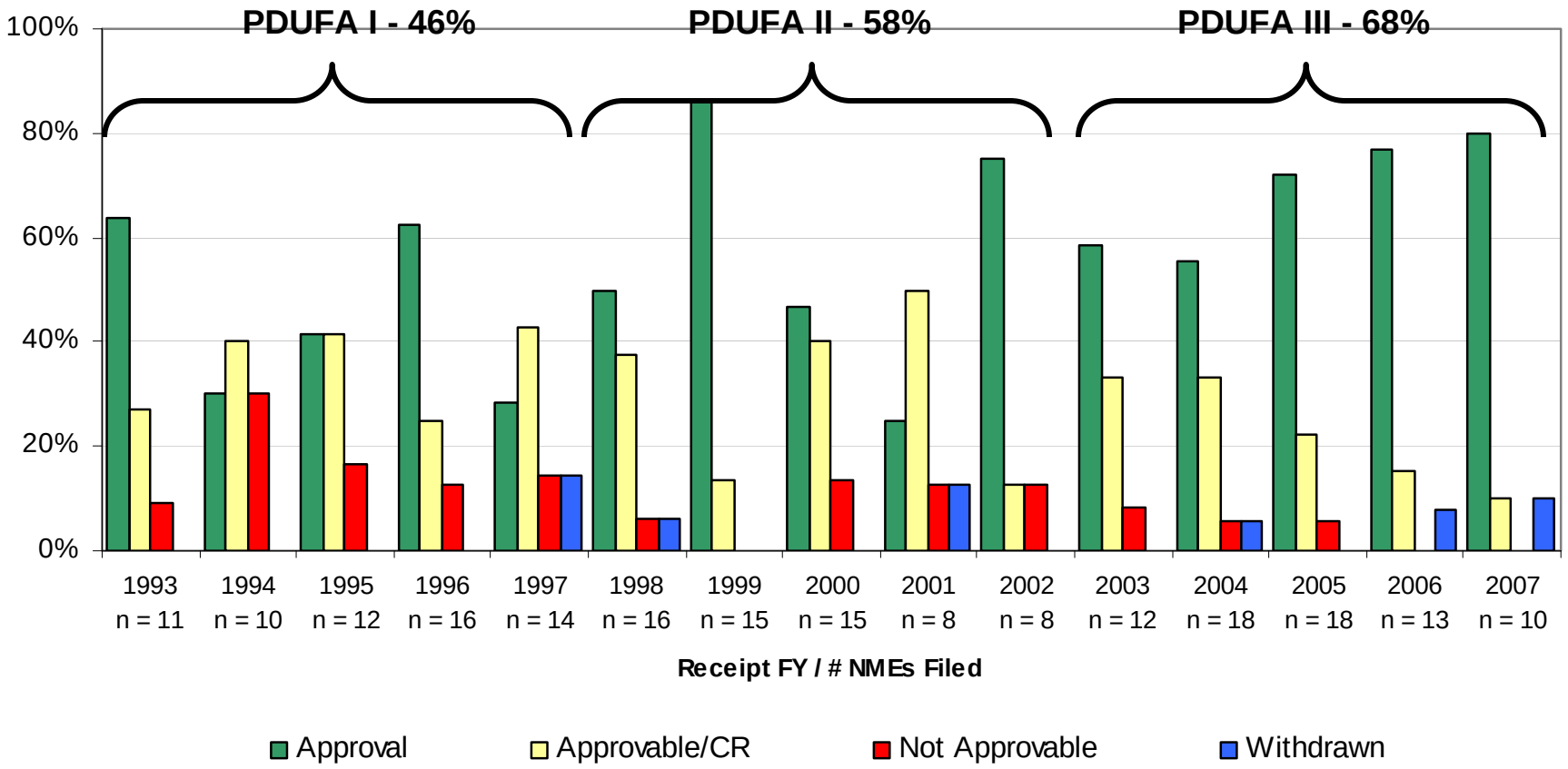
CDER CY New Molecular Filings and Approvals

(1996 - 2007)



*beginning in 2004 these figures include BLAs for therapuetic biologics

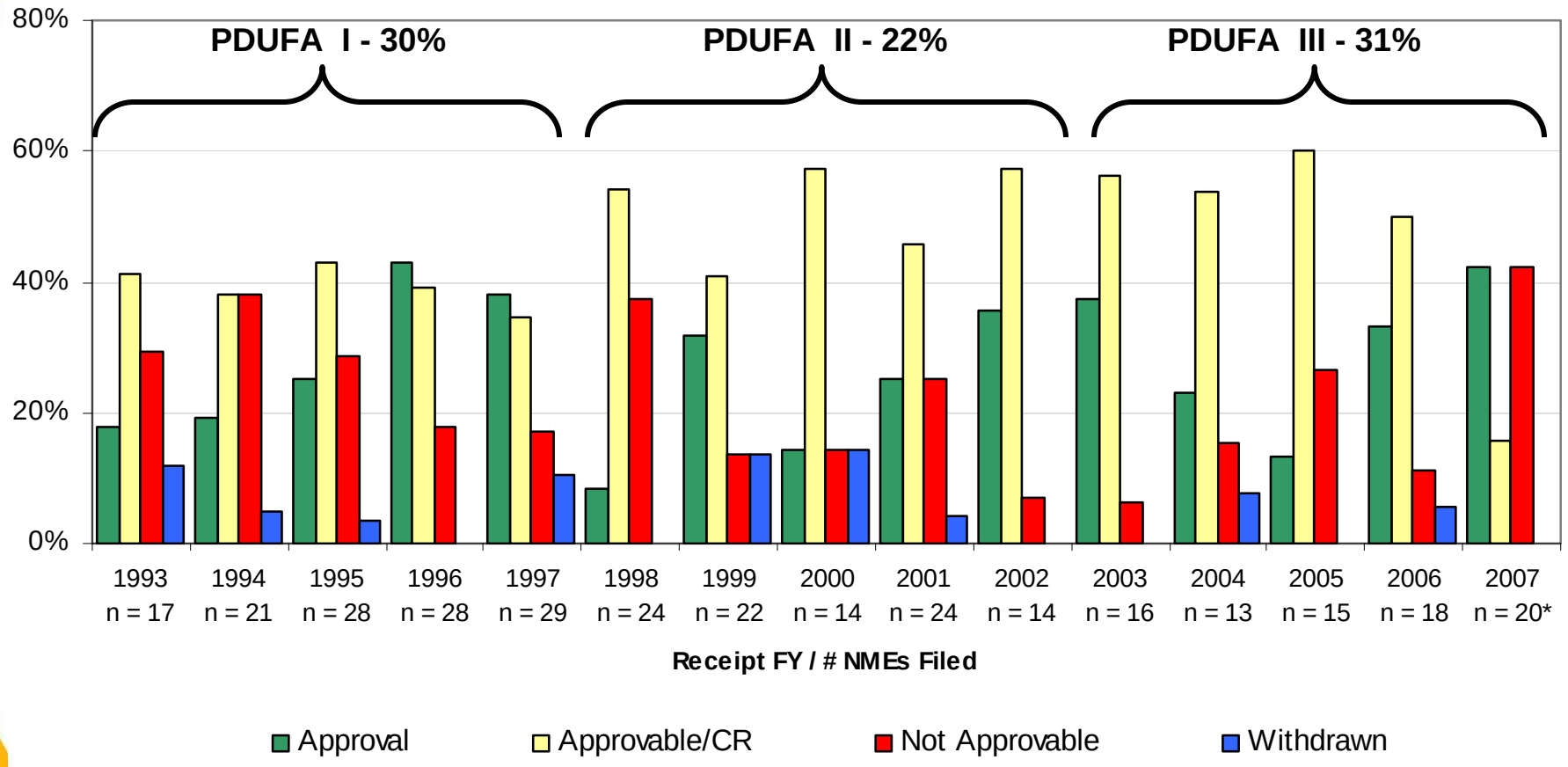
First Action Approval Rates for Priority New Molecular Entities



Data as of 31-Oct-2008.

*Includes the therapeutic biologic products transferred from CBER to CDER beginning in FY 2004.

First Action Approval Rates for Standard New Molecular Entities



Data as of 31-Oct-2008.

*FY 2007 percentages based on the 19 standard NME actions to date. There is one FY 2007 standard NME awaiting a first action decision.
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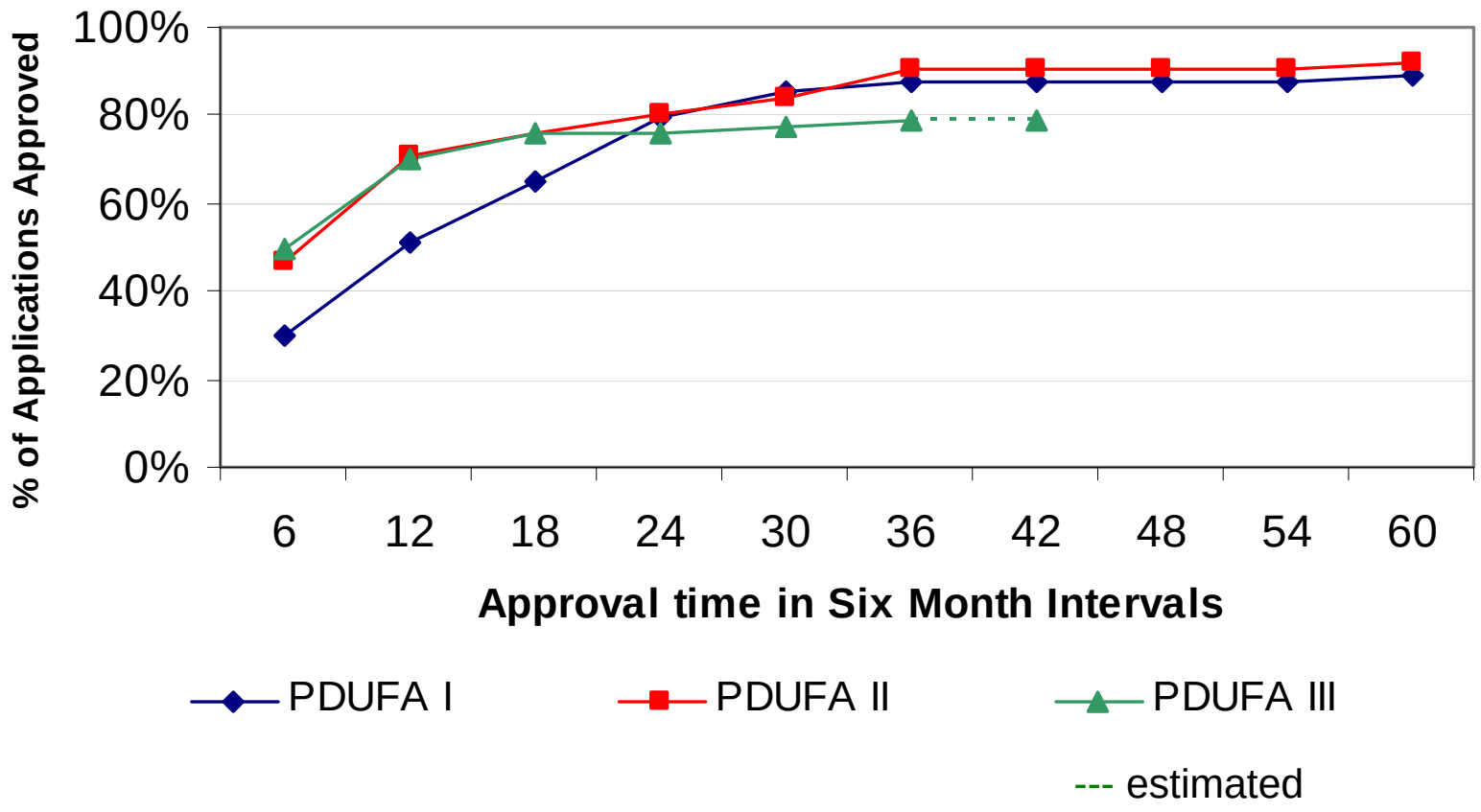
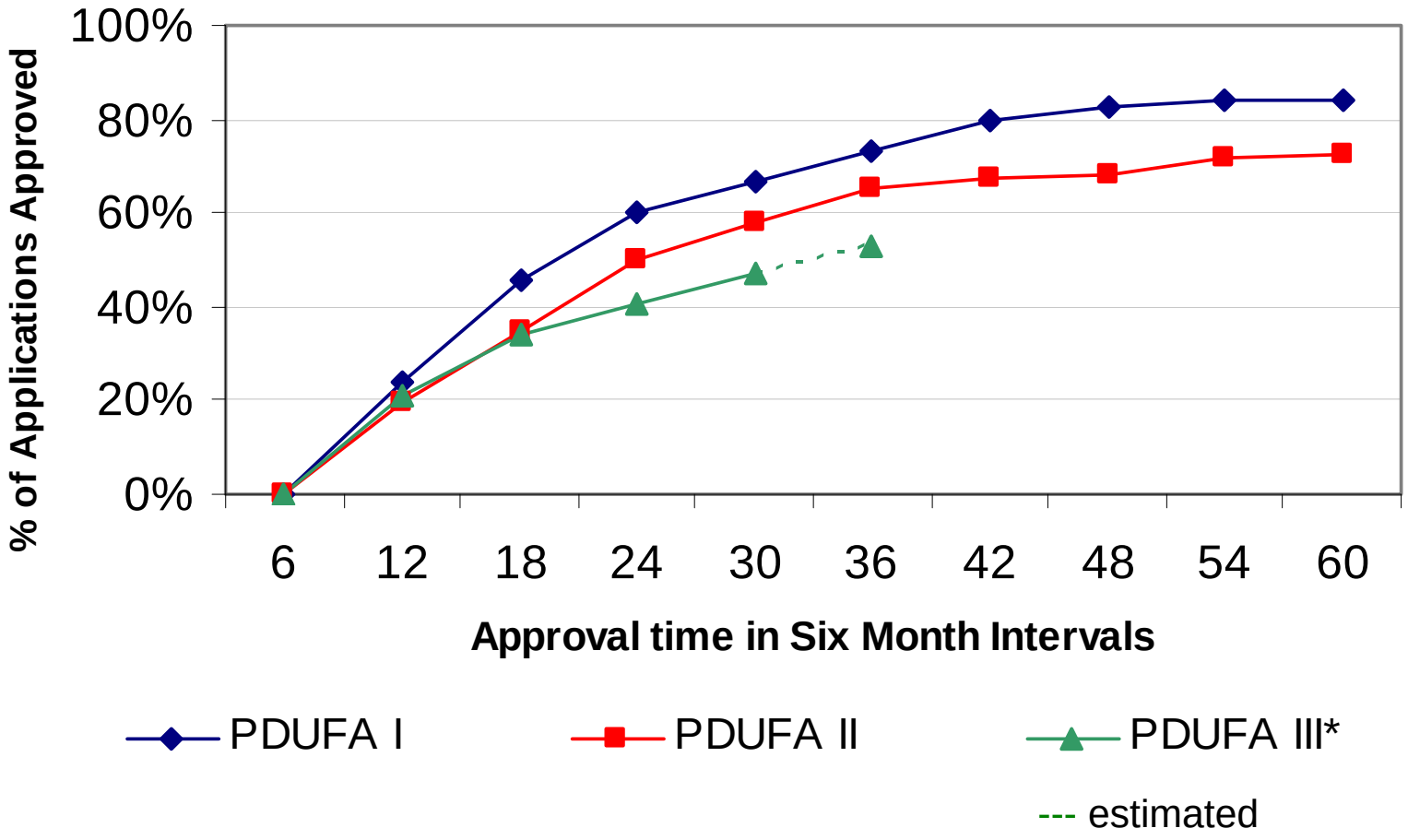
Time to Approval for Priority New Molecular Entities

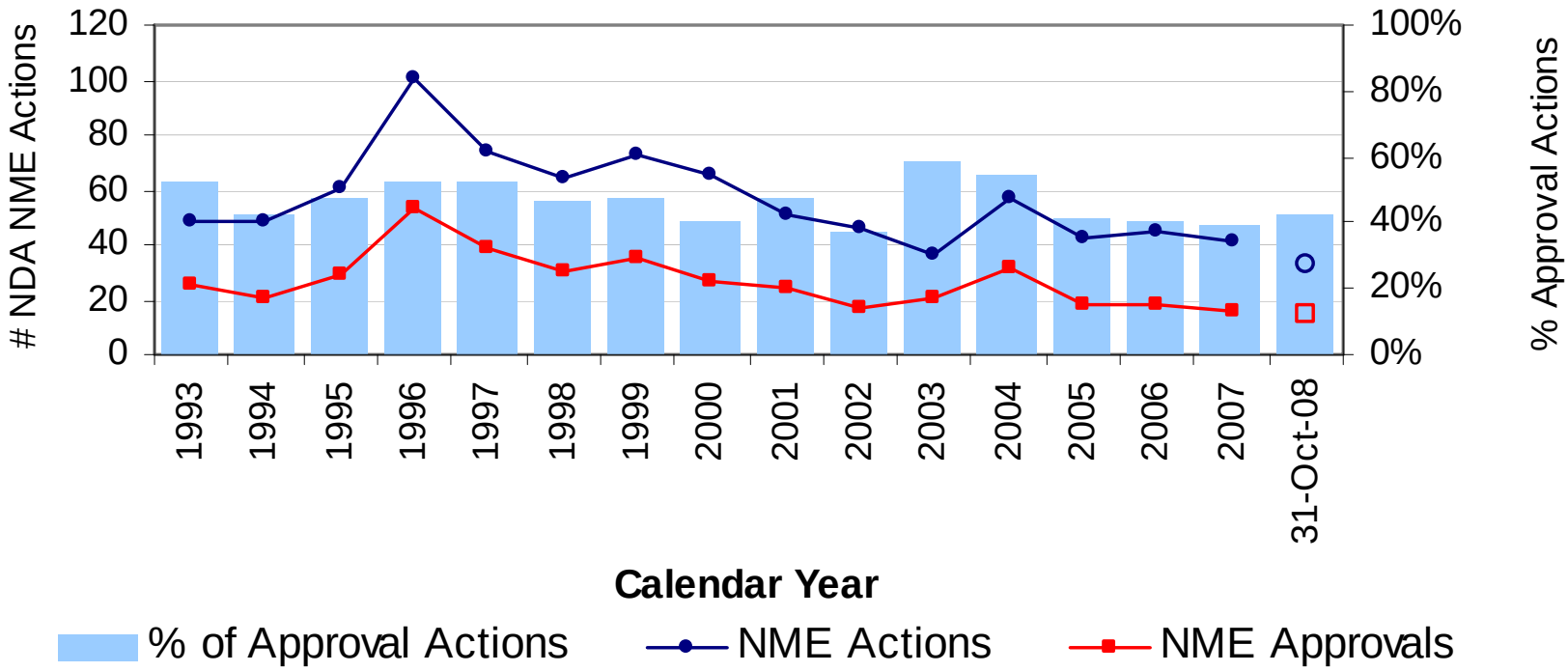


Time to Approval for Standard New Molecular Entities



* PDUFA III includes FY2003 – 2006 only. It is too early to provide long term approval rates for FY 2007.

NDA NME Actions and Approvals



*2008 figures as of 31-Oct-2008. These data include only NME NDAs and do not include therapeutic biologic products submitted under BLAs

So, why are there fewer NMEs?

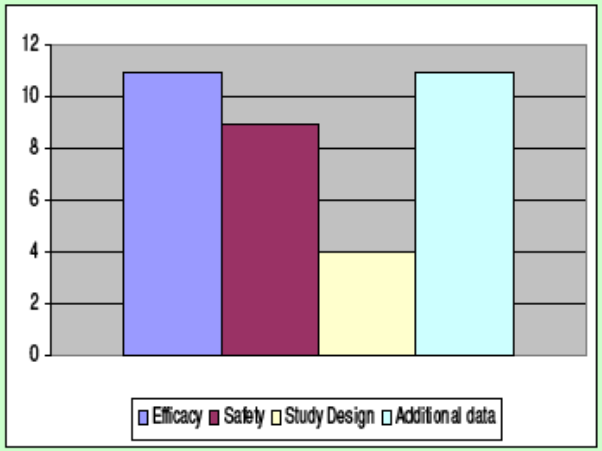
- The biggest factor driving the fall off in the number of new NMEs approved by FDA each year is the number of NMEs submitted for FDA review
  - We cannot approve what we don't have to review!
- There are many possible explanations for the decrease in the number of NMEs submitted for FDA review
  - We believe a major driver is a fall off in the number of "me-too" NMEs submitted (sometimes called "me-too late")

But, isn't EMEA faster and less "conservative"?

- The FDA and EMEA approval systems are very different, but often work in "parallel"
  - Most NMEs are submitted to both agencies
  - Submission timing is generally within 6-12 months between the agencies
- Some sponsors and analysts have stated that FDA has become too "conservative" and that EMEA is approving drugs faster than FDA

Analysis of FDA and EU Approvals – Presented by Paul Huckle of GSK at CMR Meeting on Predictable Outcomes, Fall 2008

Divergent outcomes in EU and USA 1995-2007



EU rejected 26 applications that were approved by the FDA

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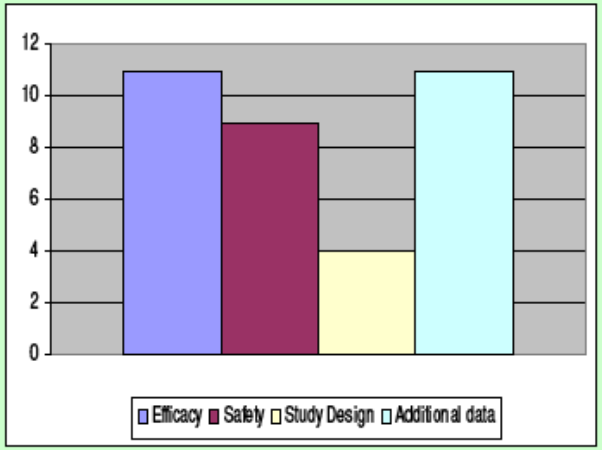
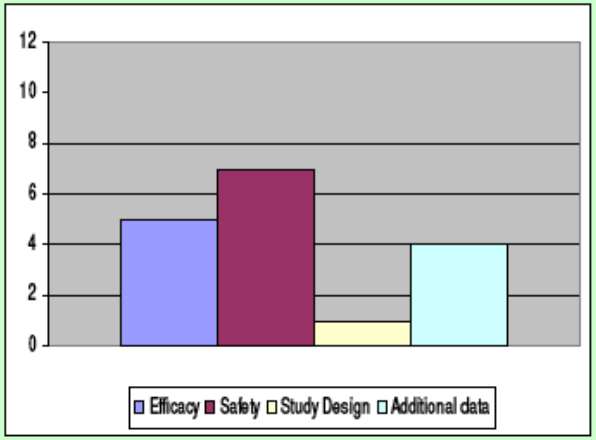


EU rejected 26 applications that were approved by the FDA

FDA rejected 14 applications that were approved by EMEA



Comparison of New Molecular Entity Outcomes for FDA and EMEA**

(Jan 2006 – October 2008)

	# of NMEs Reaching First Regulatory Action[a]	Approval Outcome[b]	Non-Approval Outcome	% Approved during timeframe
FDA	83	53	30	**64%**
EMEA	92	62	30	**67%**

** Preliminary FDA analysis

[a] FDA figures do not include resubmissions of NDAs that were first acted on prior to 2006.

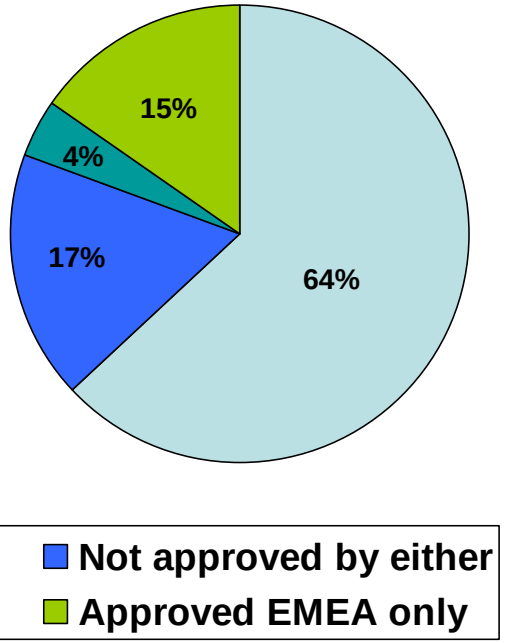
[b] Approval outcomes include approval following NDA resubmission to FDA or revised opinion following re-examination by CHMP during this timeframe.

Source: FDA data and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP Monthly Plenary Meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for New Molecular Entities.

New Molecular Entities Having Outcomes in ***both*** FDA and EMEA**

(Jan 2006 – October 2008) *n = 46*

Regulatory Outcome	#
Approved by both Authorities	29
Not Approved by either Authority	8
Approved by FDA only	2
Approved by EMEA only	7



** Preliminary FDA analyses

Source: FDA data and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP Monthly Plenary Meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for New Molecular Entities.

Priorities for 2009

- Continue to recruit and train new staff
- Apply 21st Century Review process to NMEs, continue to refine the process
- Continue "stand up" of Safety First program; enhance early communication
- Better integrate new FDAAA procedures into review process
- Continue to meet PDUFA goals whenever possible; work back to 90%

Questions?