CDER Update

Steven K. Galson, MD, MPH

Director, Center for Drug Evaluation and Research

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Priorities for 2007 and Hot Topics

- IOM- Future of Drug Safety Study
- 2006 Application and Approval Wrap-Up
- Modernization of US Drug Regulatory System
  - Improved science, regulatory efficiency, process improvements
- FDA/CMS

2006 Priority drug approvals – Patients remain at the top of our priority list

Vorinostat	solid tumors, lymphoma, leukemia
Noxafil	broad-spectrum antifungal
Duodote	atropine for nerve agent poisoning
Atripla	HIV fixed dose combination
Prezista	HIV new protease inhibitor
Dasatinib	chronic myeloid leukemia
Chantix	smoking cessation
Vivitrol	once a month IV alcoholism treatment
Eraxis	Canidida infections
Sutent	advanced renal cell carcinoma & GI stromal tumor

FDA Request to IOM

- Why did we request the Future of Drug Safety Study?
  - 2004 FDA initiative to strengthen and improve the management of drug safety issues
    - Examine roles of FDA
    - Examine ongoing safety evaluation efforts
    - Evaluate existing tools, organization, and operations and authorities
    - Make recommendations in the areas of organization, legislation, regulation, and resources to improve risk assessment, surveillance, and safe use of drugs

Regulatory Modernization Steps Taken During IOM Study

- Restructure
  - Increase management focus
  - Increase resources and staffing
  - Initiated key process improvement projects – will result in fundamental changes in how groups interact – Dr. Seligman to discuss

Regulatory Modernization Steps Taken During IOM Study

- Restructure
- Physician and patient information
  - Newly designed prescription drug labeling
    - Helps manage the risks of medication
    - Reduce medical errors
  - Public Health Notices
    - Health Care Practitioner and Patient information sheets

Regulatory Modernization Steps Taken During IOM Study

- Restructure
- Physician and patient information
- Electronic drug label
  - New rule mandated more organized, informative labels
  - DailyMed web site provides access to current drug information

Regulatory Modernization Steps Taken During IOM Study

- Restructure
- Physician and patient information
- Electronic drug label
- Drug safety oversight board
  - Provides oversight and advice to FDA leadership on important drug safety issues

Regulatory Modernization Steps Taken During IOM Study

- Restructure
- Physician and patient information
- Electronic drug label
- Drug safety oversight board
- Adverse event reporting system
  - Planning a replacement web-accessible computer system that will include signal detection and tracking tools
  - Developing a standard AE reporting form for all centers and for on-line submission

FDA Perspective on IOM Findings and Recommendations

FDA Perspective

- IOM report provides a significant opportunity to reexamine our approach to drug safety
- Renewed incentive to address tools, resources, and approaches to improve drug safety
- Identified vulnerabilities in the drug safety system
  - Chronic under funding
  - Organizational problems
  - Unclear regulatory authority and insufficiently flexible regulatory tools
  - Inadequate quantity and quality of post-approval data

FDA Perspective

- Five FDA drug safety working groups
  - Randall Lutter, PhD, Associate Commissioner for Policy and Planning provides oversight
  - Mid-January goal
  - FDA cross-center effort to evaluate and consider for implementation IOM's proposed near-term improvements and longer-term proposals
  - Groups to identify and develop specific proposals

FDA Perspective (1/5)

- IOM report provides a significant opportunity to examine CDER structure and organization
  - Support cultural change
  - Incorporate safety goals into PDUFA goals
  - Integrate postmarketing safety staff into drug review process and share post approval authority with drug review staff
  - Incorporate lifecycle approach to risk/benefit
  - Team approach to assessing safety and efficacy

FDA Perspective (2/5)

- IOM report provides a significant opportunity to examine regulatory authority challenges
  - Clarification of agency enforcement authority
    - Labeling change / negotiation
    - Post-approval studies (Phase IV)
  - New enforcement authority

FDA Perspective (3/5)

- IOM report provides a significant opportunity to improve communication about safety
  - Public perceives all approved drugs as safe
    - All drugs have risks and benefits
    - Newly approved drugs have limited safety data

FDA Perspective (4/5)

- IOM report provides a significant opportunity to address resource issues
  - Analyze and develop estimates to support improvements in drug safety and efficacy activities over a product's lifecycle related to prospective increase in both funds and personnel for FDA

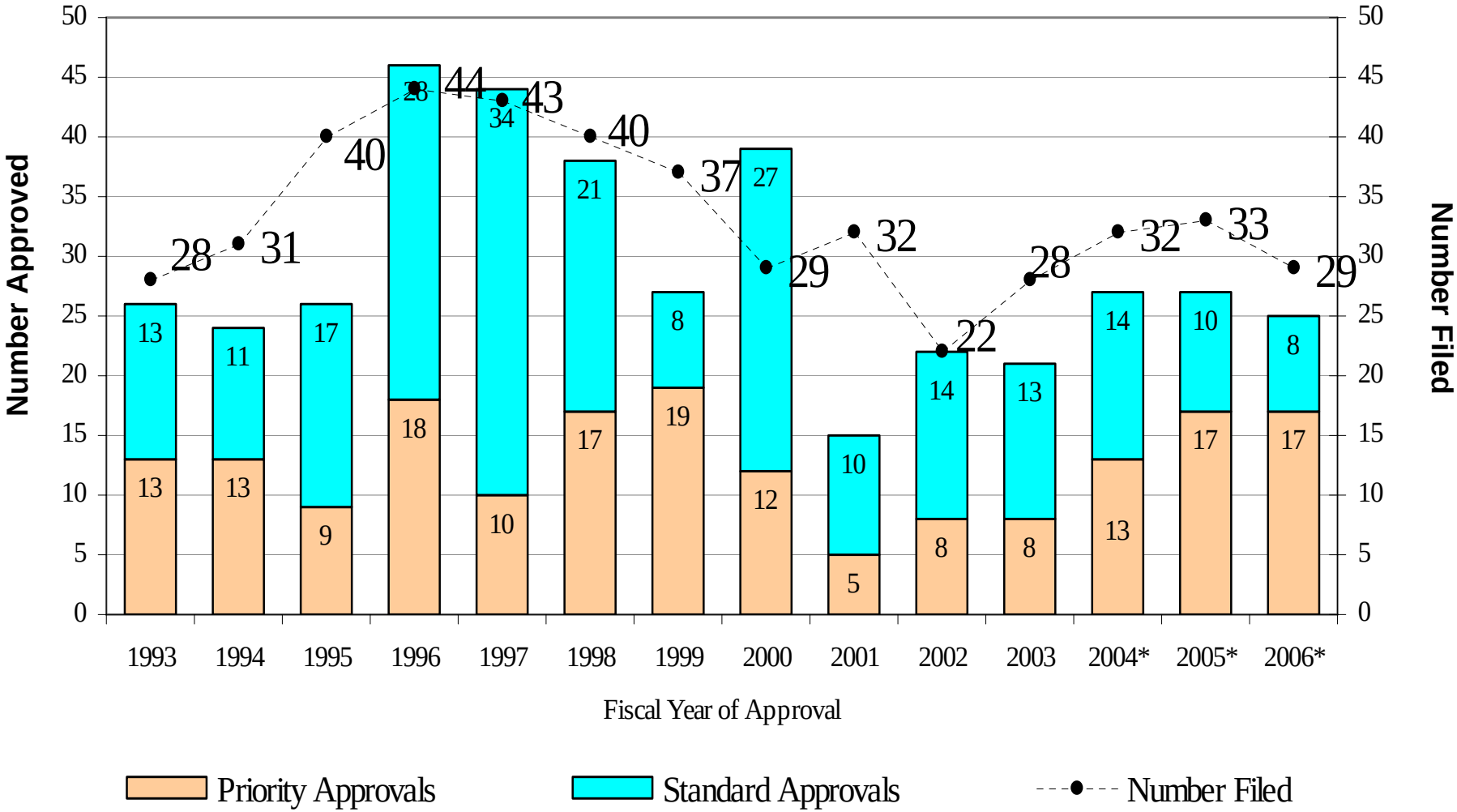
FDA Perspective (5/5)

- IOM report provides a significant opportunity to address the science of drug safety
  - Limited scientific capabilities and resources in epidemiology and informatics
  - Limited role for advisory committees, and lack of epidemiology expertise on committees
  - More public disclosure of drug information
  - Improved signal detection
  - Testing of safety hypotheses

2006 Application and Approval Wrap-Up

- Estimated end-of-year data as of 12/1/2006:
  - Number priority drugs approved – 10, down 5 from 2005
    - Median FDA review time – unchanged from 2005 at 6.0 months
  - Standard – 13, up from 5 in 2005
    - Median review time – 13.0 months, down from 15.8 months in 2005

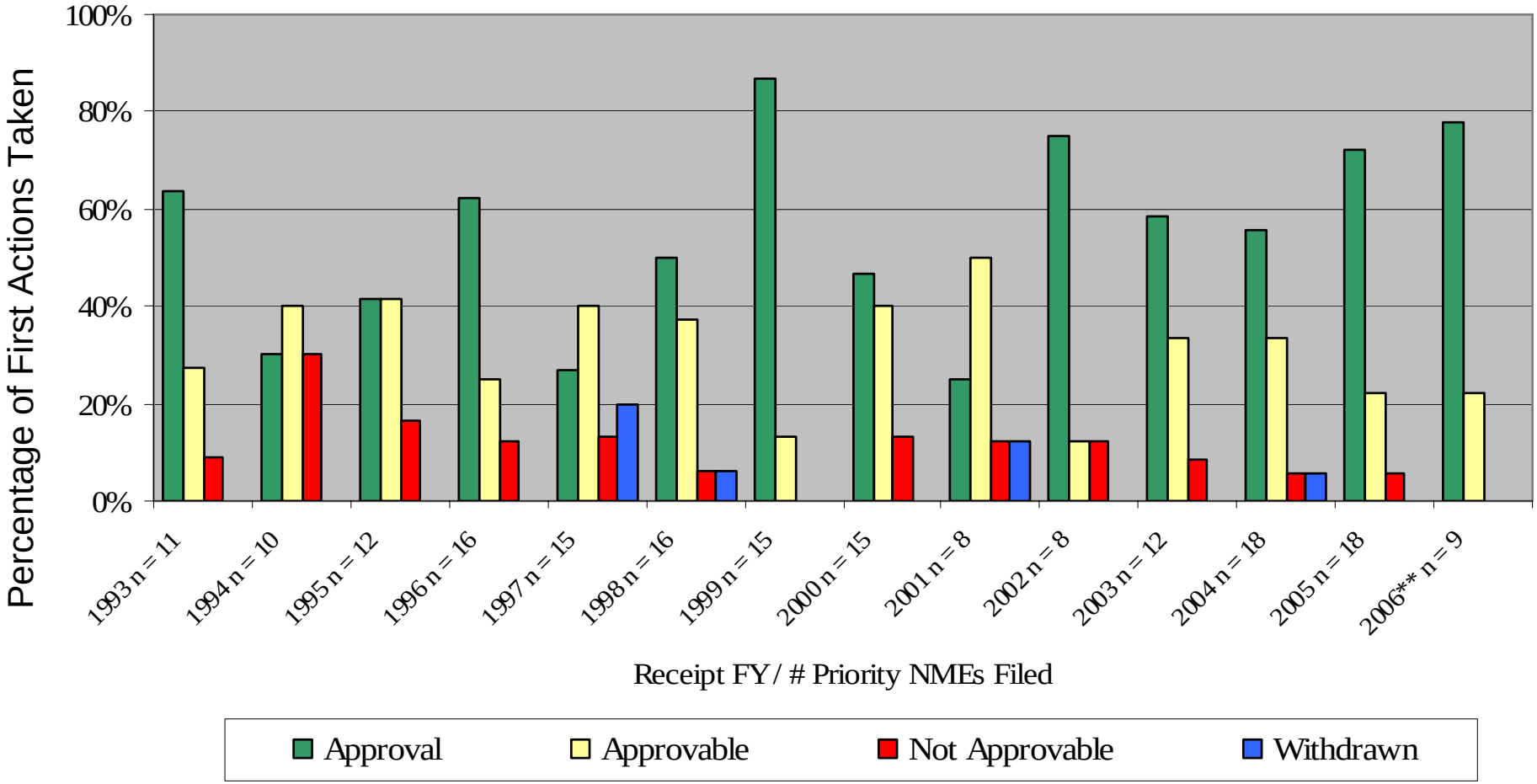
CDER New Molecular Entity and New BLA Approvals by Fiscal Year



As of 30-Sep-06

*Includes the therapeutic biologic products transferred from CBER to CDER effective 10/1/2003.

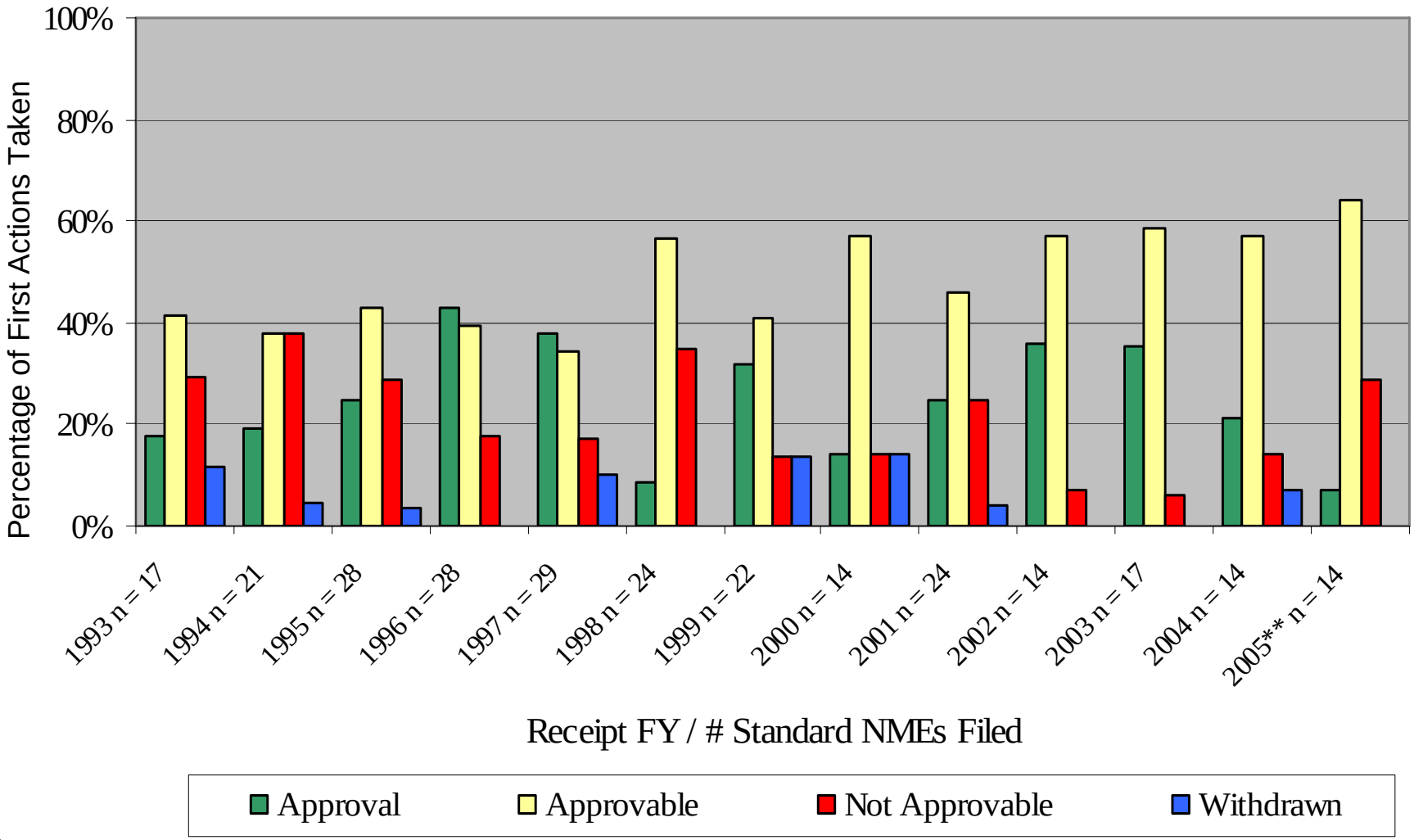
First Action Percentages for CDER Priority NMEs and New BLAs by Fiscal Year of Receipt



As of 30-Sep-06

** Percentages based on 9 priority NME (3 New BLA) first actions to date; one NME and 2 Priority New BLAs are pending a first action decision.

First Action Percentages for CDER Standard NMEs and New BLAs by Fiscal Year of Receipt

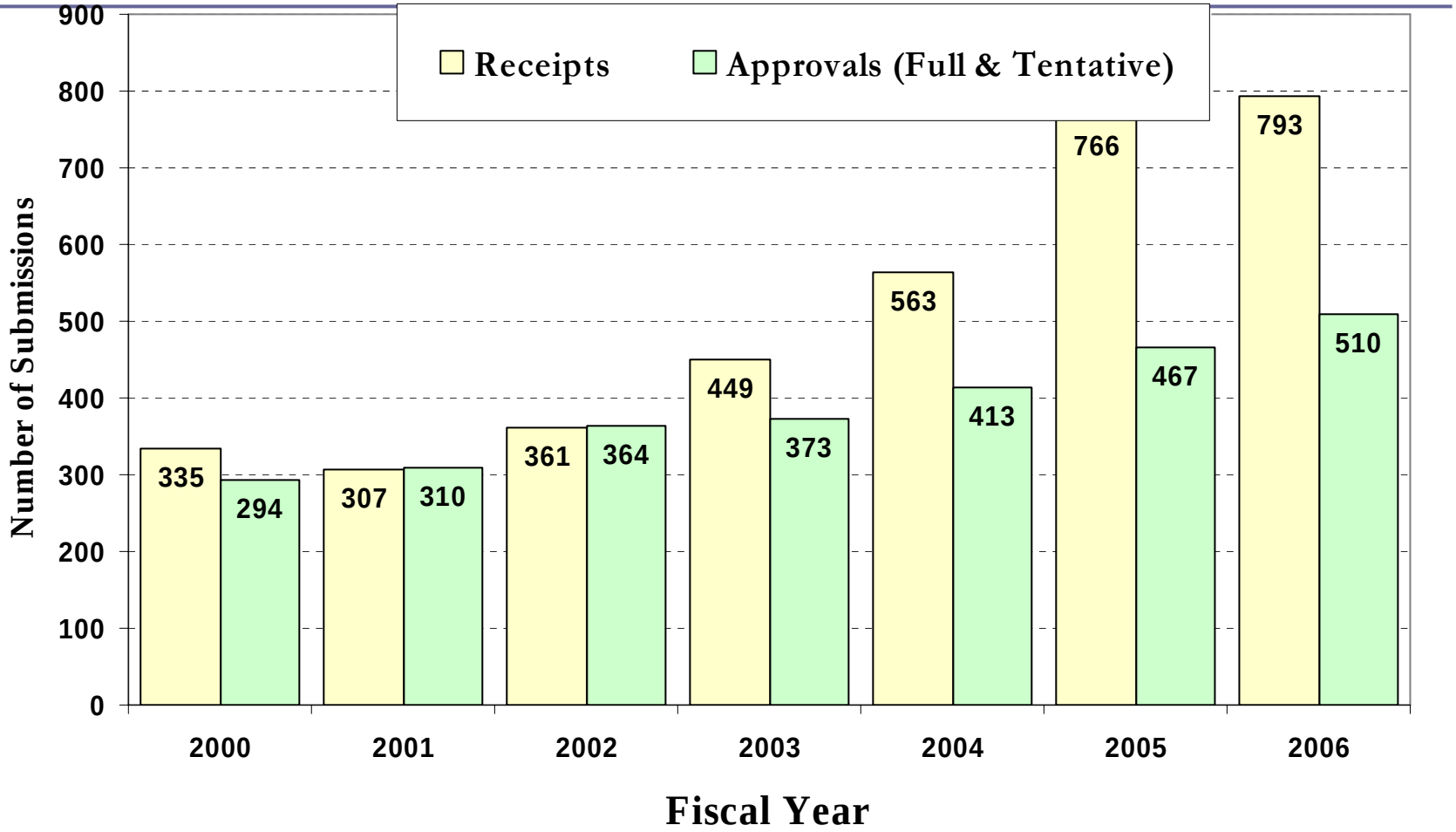


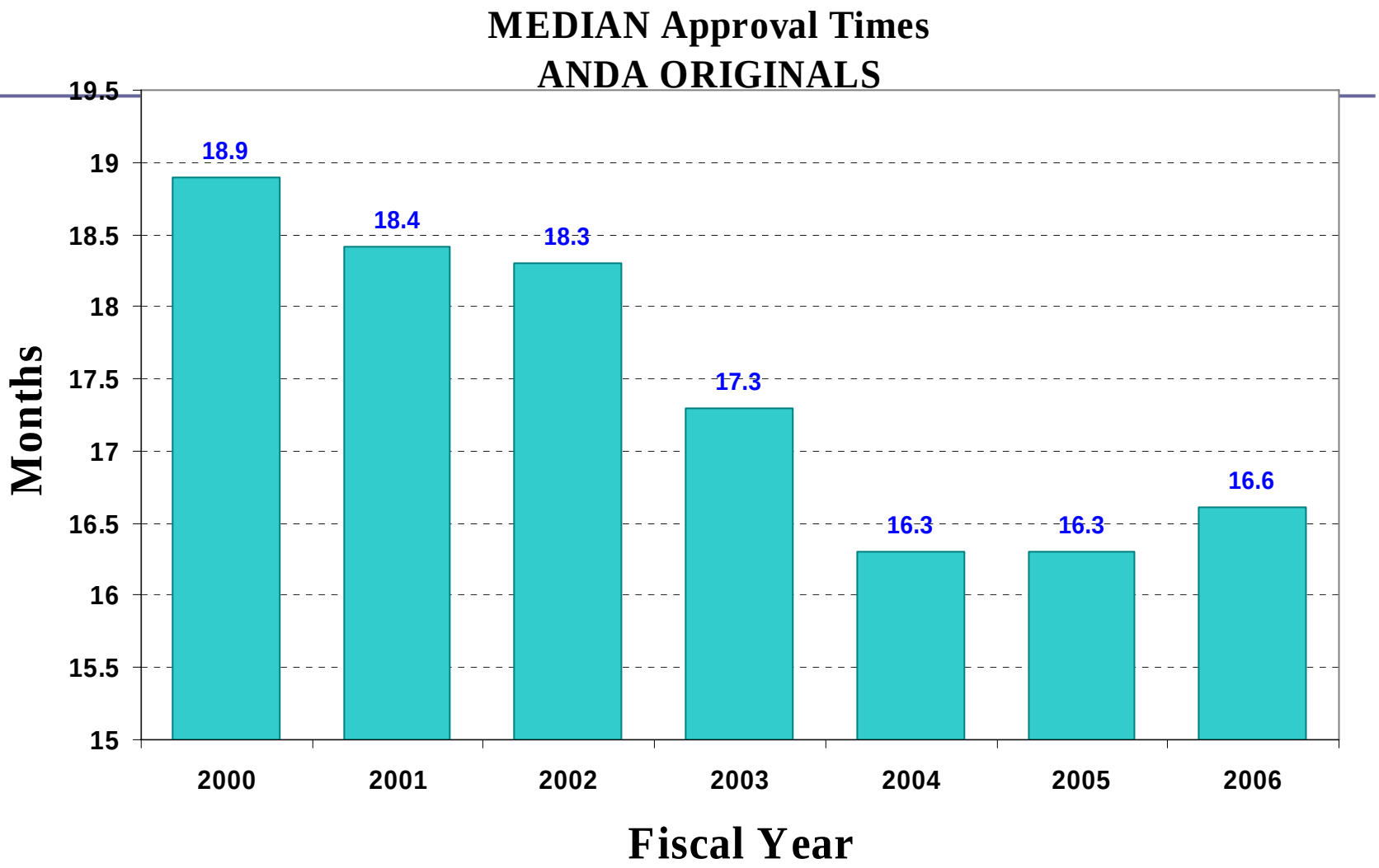
* As of 30-Sep-06

** One standard FY 2005 NME is pending a first action

Includes the therapeutic biologic products transferred from CBER to CDER effective 10/1/2003.

Comparison of Receipts and Approvals of ANDA Applications




MEDIAN Approval Times
ANDA ORIGINALS
Months
19.5
19
18.5
18
17.5
17
16.5
16
15.5
15
18.9
18.4
18.3
17.3
16.3
16.3
16.6
2000
2001
2002
2003
2004
2005
2006
Fiscal Year

Regulatory Modernization Efforts

- Across CDER programs
  - Regardless of budget challenges in FY2007, these activities will continue
    - Progress in
      - Electronic application receipt, processing, posting labels
      - Paperless adverse event receipt
      - Reforms in chemistry and manufacturing data required under GMP initiative means fewer supplemental applications for small chemistry changes
      - Advisory Committee management –
        - best practices effort
        - reform of member selection process

Regulatory Modernization Efforts

- Implementing quality systems across the Center
  - Phase 4 commitments
  - Industry meeting minutes
- Lessons learned - withdrawals
- Generic drug review process improvements to improve efficiency
- Improved operations of Drug Safety Oversight Board
- Beginning today – OSE new system to manage safety reviews and consults – project management approach
  - Increased efficiency and prioritization

Traditional vs. CMC Pilot NDAs - Submission

Traditional NDA

- Brief Quality Overall Summary (QOS)
- Limited Pharmaceutical Development (PD) section
  - Traditional approach to PD
    - Formulation studies limited to excipient selection and compatibility
    - Little or no process development information
    - No risk analysis on impact of material and process on quality
- Executed batch record

CMC Pilot NDA

- More comprehensive QOS
- More expanded PD section
  - More scientific information
  - Elements of quality-by-design (QbD) applied, e.g.,
    - Critical quality attributes (CQA) affecting product performance identified
    - Product and process supported by experimental designs
    - Impact of material and process on CQAs understood
    - Sources of variability in material and process identified and controlled; design space formed
- No executed batch record

Traditional vs. CMC Pilot NDAs - Review

Traditional NDA

- QOS not used or reviewed
- PD used but not always assessed
- Review focused on product characterization, process reproducibility, specification setting, stability/shelf life setting
- Traditional review approach
- Mostly a single chemistry reviewer
- Process managed and overseen jointly by ONDQA and OND
- PAI participated by reviewers on as needed and infrequent basis
- Typically pre-NDA meetings and a few telecons during review

CMC Pilot NDA

- QOS used as a review document
- PD reviewed and assessed
- Review focused on product and process understanding, process robustness, overall control strategy
- Risk-based review
- Team review, typically 3 members with complimentary expertise and experience (Chemist, Pharmacist and Engineer)
- Process managed and overseen by ONDQA IO
- Integrated review/inspection team
- Frequent meetings with applicant before submission, during review, and after approval

Traditional vs. CMC Pilot NDAs - Regulatory Outcome

Traditional NDA

- Product quality controlled primarily by intermediate and end product testing
- Product specification based on regulatory expectations and batch data available at and during submission
- Impact of changes in material supplier or grade unknown until batch failures occur, resulting in rejects, recalls, or supplements
- Process fixed; changes outside operating ranges need supplement

CMC Pilot NDA

- Quality controls shifted upstream with flexible regulatory approaches, e.g.,
  - In-process testing for identification and assay using NIR, in lieu of end-product testing using HPLC
  - In-process testing for dose uniformity by weight variation
  - PAT for certain unit operations
  - Real-time release using PAT
- Product specification based on desired product performance with relevant supportive data
- Post-approval material and process changes within design space need no supplement

FDA/CMS Initiatives

- **FDA/AHRQ/CMS Research Project**

  "Data Development for Patient Safety - A Pilot Study Using Medicare Part B Data“

  --goal is to develop data structures and methodologies for identifying and analyzing ADEs from Medicare claims

  --Agreement for the research was signed in July 2006

  --CDER will be providing CMS training to help epidemiologists interpret and use CMS data

FDA/CMS Initiatives

- Patients age ≥65 more likely to experience serious or fatal ADEs than younger individuals
  - generally poorer health
  - multiple medications on a chronic basis
  - With Medicare prescription drug benefit, CMS now has access to important information on drug use in this population.

FDA/CMS Initiatives

- Medicare Part D data
  - goal of identifying unsafe or suboptimal patterns of use in elderly, either with respect to the particular types of drugs being used or with respect to the dose or duration of use of these drug products.
  - Formal epidemiologic studies
    - examine the nature and magnitude of risk conferred by particular medications,
    - identify risk factors for adverse event occurrence,
    - assess the effect of risk management programs intended to reduce prescription drug risks.

Questions?

steven.galson@fda.hhs.gov