

# **The Changing Endpoints and Outcomes in the Oncology Drug Approval Process**

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Recertification

# Disclosure

- **Scott Soefje, PharmD, reports receiving consulting fees from Watson Pharmaceuticals**

# Learning Objectives

After attending the presentation, the participant will be able to:

- Explain the changes in legislation that allow the FDA to use surrogate endpoints and outcomes for accelerated drug approval
- Outline the FDA requirements for accelerated drug approval for oncology products, including post-marketing surveillance
- Compare and contrast surrogate endpoints that have been used for oncology drug approval in recent years to the traditional survival and response rate endpoints
- Describe examples of oncology products that have received accelerated approval, the endpoints used for approval, and the outcomes of the full approval review
- Explain the current FDA opinion on the use of patient reported outcomes in the drug approval process

# Goals

The overall goals of this presentation are to:

- Illustrate the endpoints and outcomes requirements for FDA accelerated approval of oncology drug products
- Compare and contrast the endpoints and outcomes used in oncology drug approvals in the past decade
- Define the role of patient reported outcomes in the oncology drug approval process

# Outline

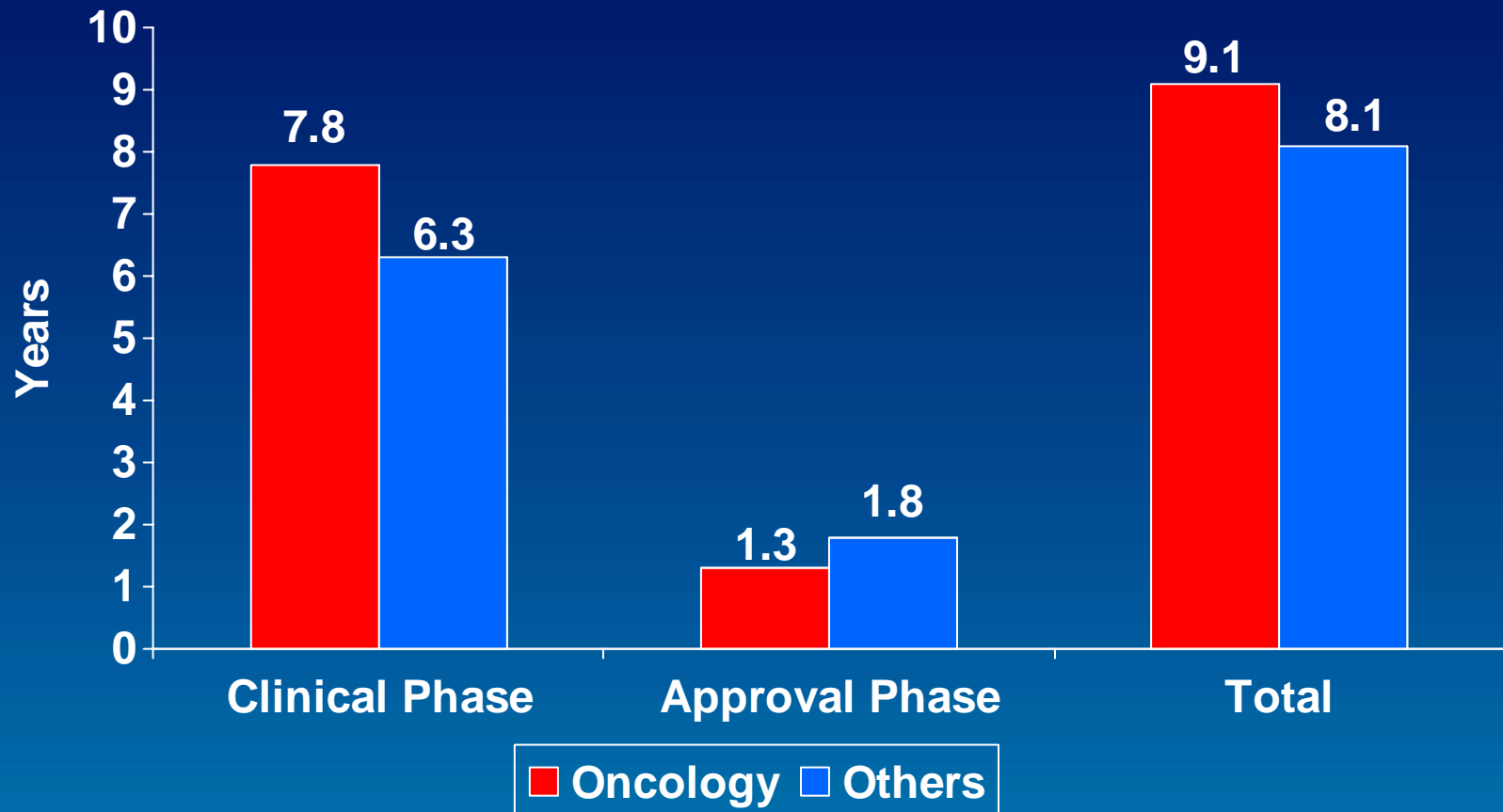
- History of drug approval in the United States
- Endpoints in oncology trials
  - Traditional
  - Accelerated approval
  - Patient reported outcomes
- Examples of accelerated approvals in oncology

# New Drug Approval: The Numbers

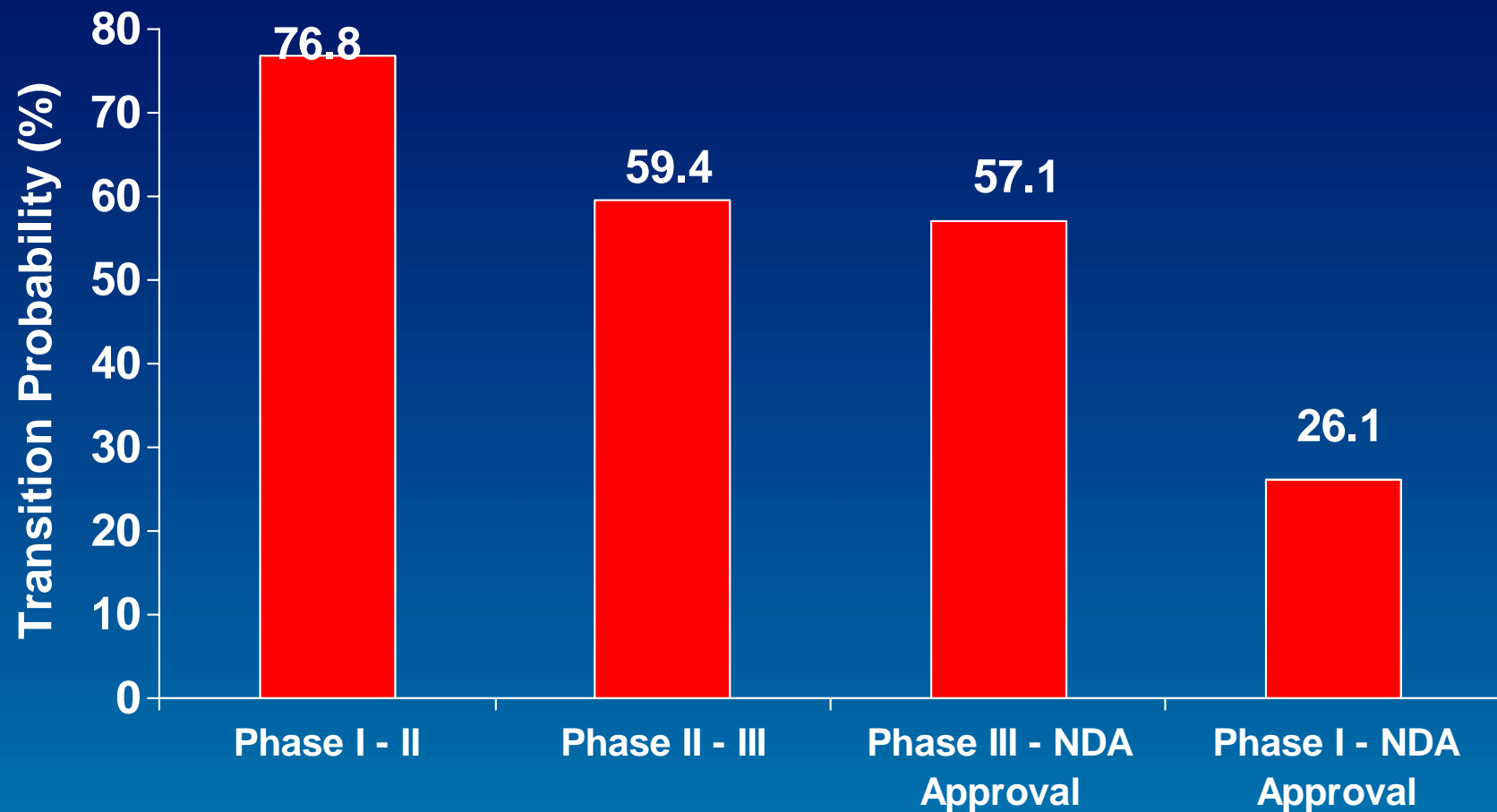
- Estimated to take 10 years from discovery to approval
- Cost: \$800 million
- Pharmaceutical investments in R&D have increased 40% in the past 10 years



# New Drug Approval Times



# Phase Transition of Oncology Agents (1993–2002)



# Drug Approval History: A Cycle of Crisis – Legislation – Adaption

- 1906 – Pure Food and Drug Act
  - Adulterated food and medicine
- 1938 – Food, Drug and Cosmetic Act
  - Elixir sulfanilamide incident
- 1951 – Durham-Humphrey Amendments
  - Defined prescription drugs
- 1962 – Kefauver-Harris Amendments
  - Thalidomide incident



# Requirements for Approval

- Remember, FDA does not approve the drug, they approve the label, which is the claim about the use of the drug
- Requires substantial evidence of benefit
  - Adequate and well-controlled trials that demonstrate safety and efficacy
  - Evidence of benefit
  - Favorable risk-benefit profile
- FDA must be able to generate a product label

# Requirements for Approval

- Specific criteria for oncology
  - Improved survival
  - Palliation of symptoms with no decrease in survival
  - Reduction in the risk of developing a malignancy
- Approval is based upon the sum of all the data presented
- FDA typically relied on Oncology Drug Advisory Committee (ODAC) advice

# Drug Approval History

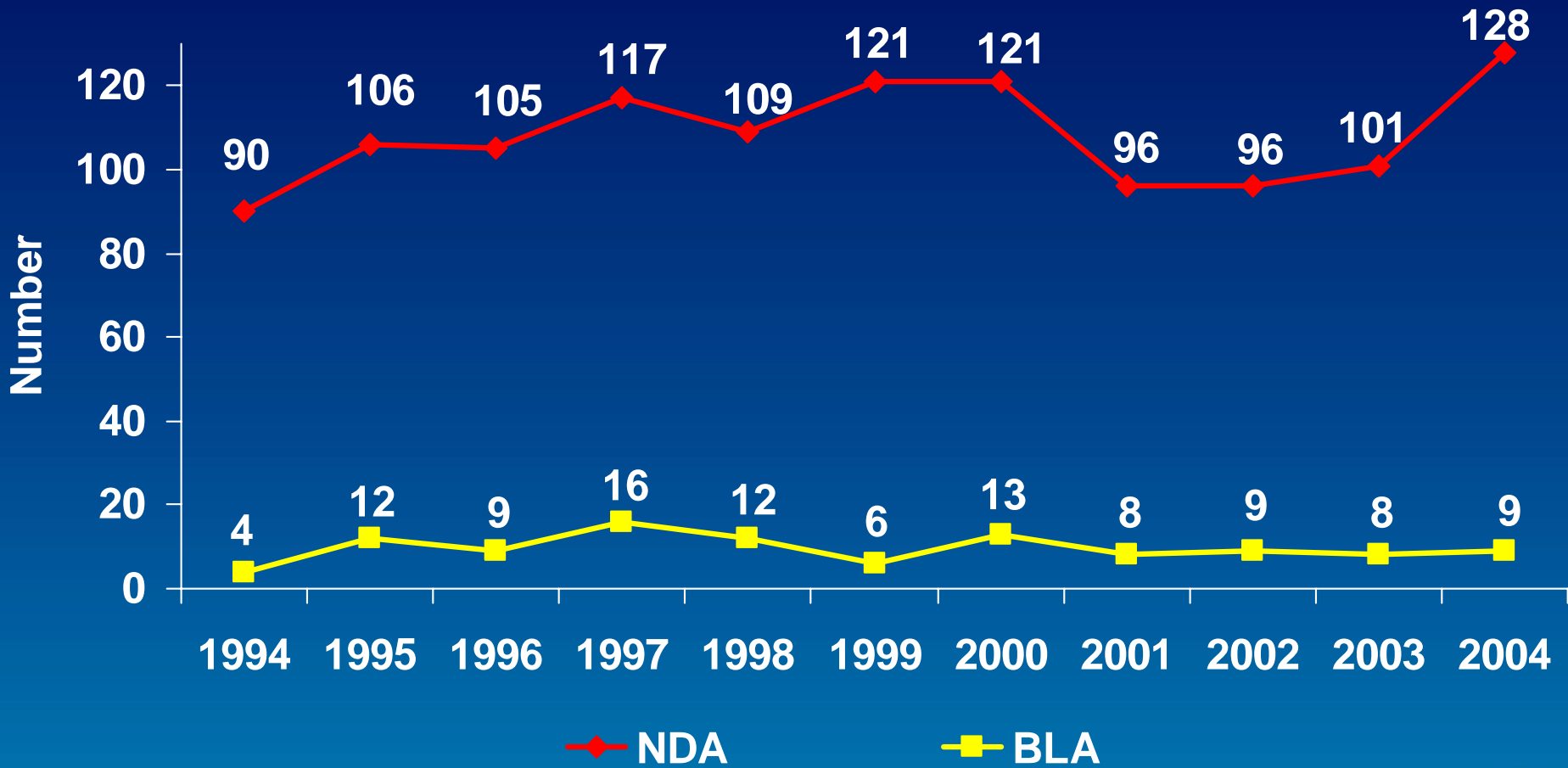
- 1992 – Prescription Drug User Fee Act (PDUFA)
- 1997 – FDA Modernization Act (FDAMA)  
(PDUFA II)
- 2002 – PDUFA III
- 2007 – FDA Amendments Act (PDUFA IV)

All are attempts to speed up and/or improve the drug approval process

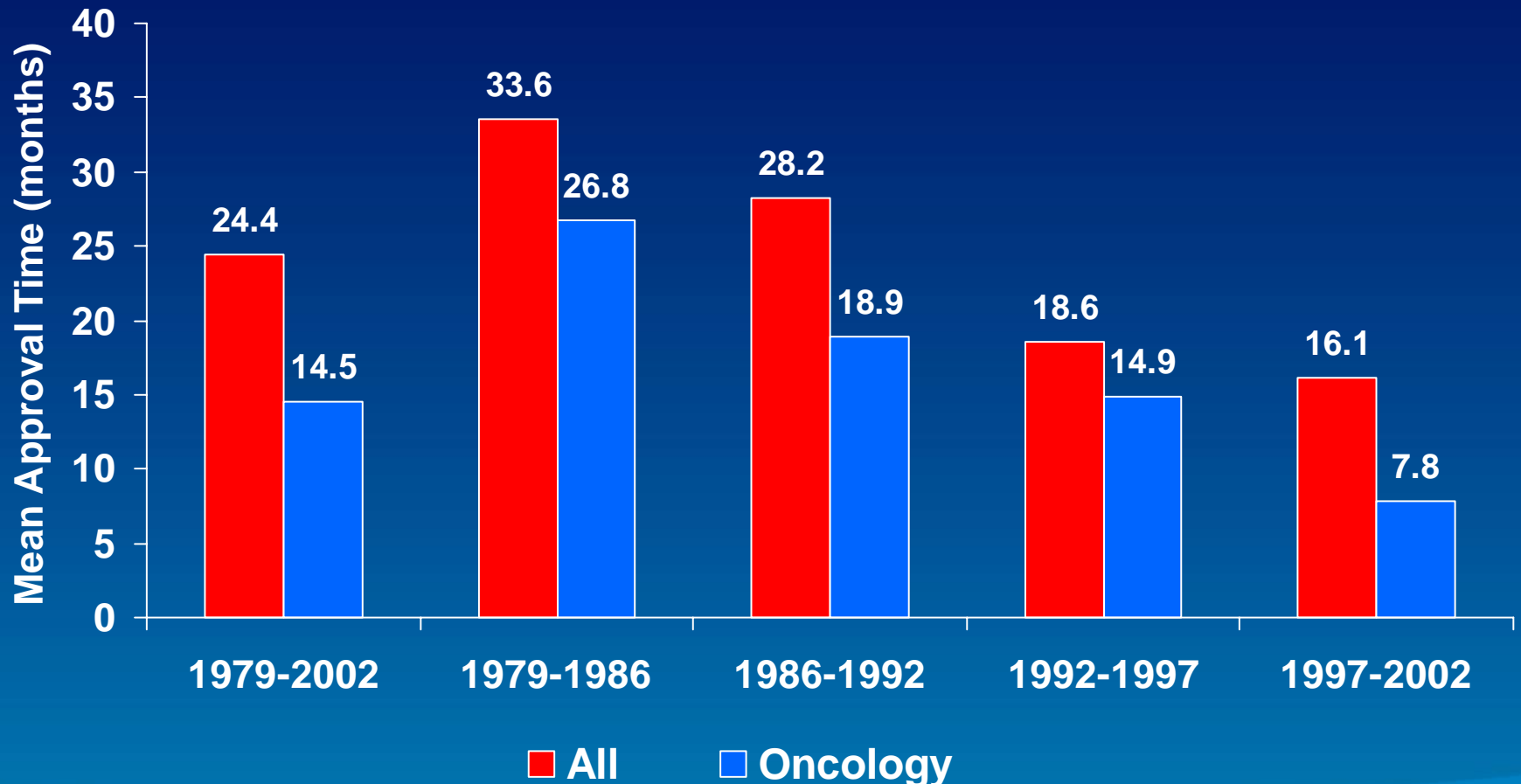
# Prescription Drug User Fee Act: 1992

- FDA was perceived to not have enough staff to handle the increased demands for drug approval
- Believed that Congress was unlikely to appropriate additional funds to increase staff
- FDA negotiated a plan with PHARMA to have the drug manufacturers pay a user fee for each drug review
- FDA was to make submission decisions within a fixed time frame
  - Standard review – 12 months
  - Priority review – 9 months

# PDUFA: Impact on Drug Applications

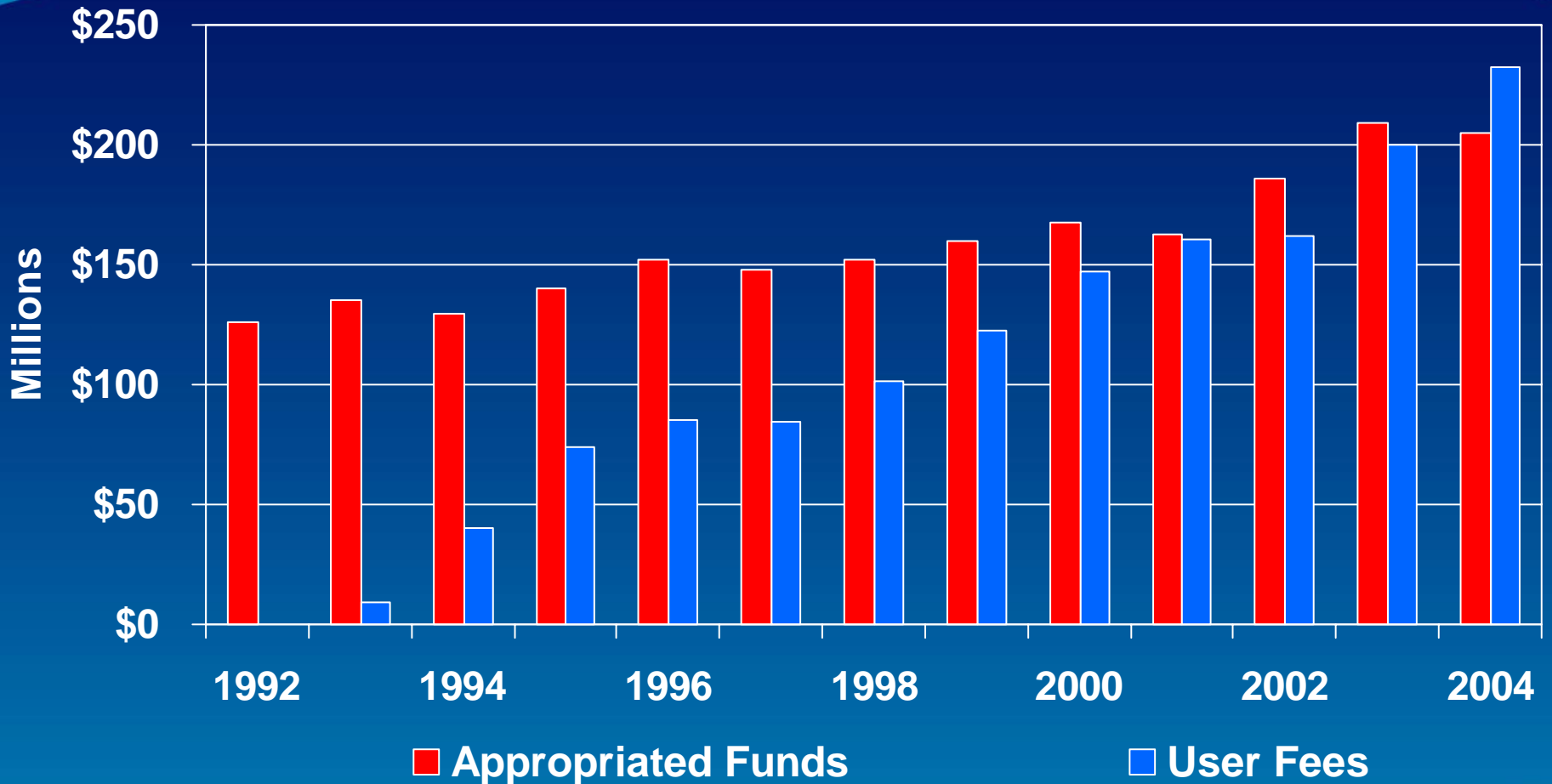


# Approval Times for New Molecular Entities



Adapted from Berndt ER, et al. *Nat Rev Drug Discov.* 2005;4:545-54. Reprinted by permission from Macmillan Publishers Ltd. Copyright 2005.

# PDUFA Impact on FDA Budget



# FDA Modernization Act: 1997

- Goal was to streamline drug development
- Reauthorized PDUFA for 5 years
- Established rules for fast track designation
- Guidance for industry on serious or life-threatening diseases
- Defined post-marketing requirements
- Addressed pediatric studies



# FDA Amendments: 2007

- Extended PDUFA for 5 years
- Expanded pediatric research
- Created Reagan-Urdall foundation with the goals to:
  - Modernize product development
  - Accelerate innovation
  - Enhance product safety
- Enhanced authority for post-marketing surveillance

# FDA Approval Types

- Under FDAMA, the FDA has the following approval routes for drug products
  - Standard – FDA must respond to sponsor within 10 months of filing
  - Priority – FDA must respond to sponsor within 6 months of filing
  - Accelerated (21 CFR 314 – Subpart H) – For life-threatening illness that allows surrogate endpoints for approval

# FDA Fast Track

- Fast track is designed to expedite development and review of new drugs for serious or life-threatening illnesses
- Is intended for the combination of a product and a claim that addresses an unmet medical need
- Independent of priority review and accelerated approval



# Benefits of Fast Track

- Scheduled meetings to seek FDA input into development plans
- The option of submitting a New Drug Application in sections rather than all components simultaneously
- The option of requesting evaluation of studies using surrogate endpoints

# Accelerated Approval

- Allow the use of surrogate endpoints for drug approval
- For products intended to treat serious or life-threatening illnesses:
  - When better than current treatments
  - When no treatment exists
- Approved on condition that manufacturer conducts additional studies to verify clinical benefit

# Accelerated Approval

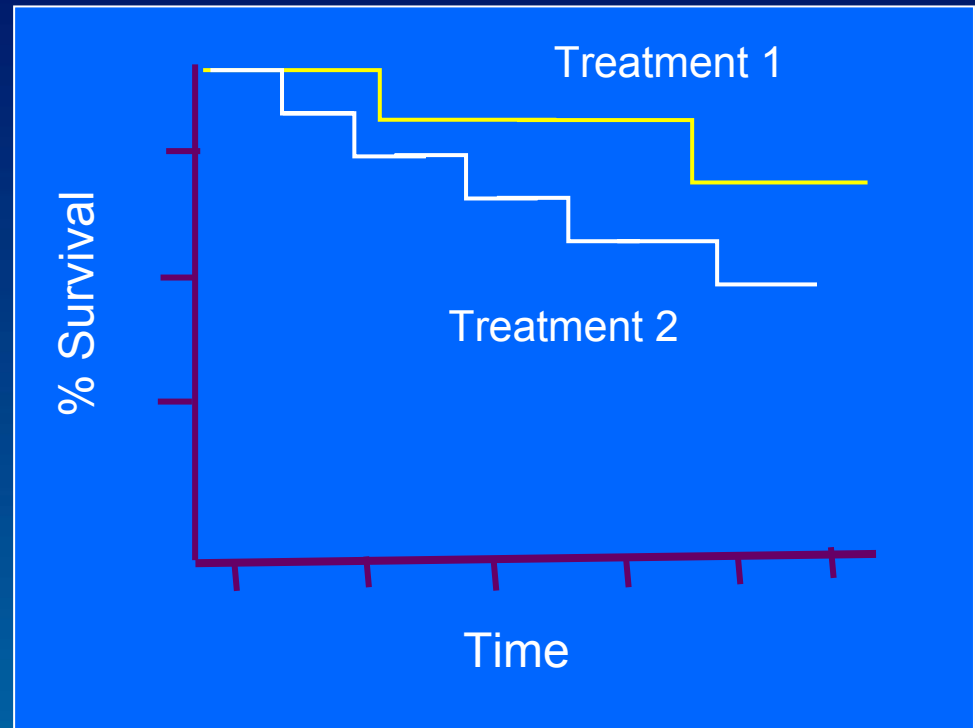
- Surrogate endpoints
  - Endpoint that is “reasonably likely” to predict clinical benefit
  - “Based upon epidemiologic, therapeutic, pathophysiologic, or other evidence”
- In non-oncology settings, more established surrogates have been used
  - Blood pressure
  - Cholesterol levels

# Substantial Evidence

- “Adequate and well-controlled investigations”
- Usually more than one trial is expected
- FDAMA (1997) allows for a single trial, plus other supportive evidence
- Evidence for effectiveness:
  - Large and multicenter trial
  - Statistically strong evidence
  - Demonstrates an important clinical benefit
  - Results so persuasive – additional trials not ethical

# Traditional Endpoints

- Overall survival
- Response rate (RR)
- Symptomatic improvement



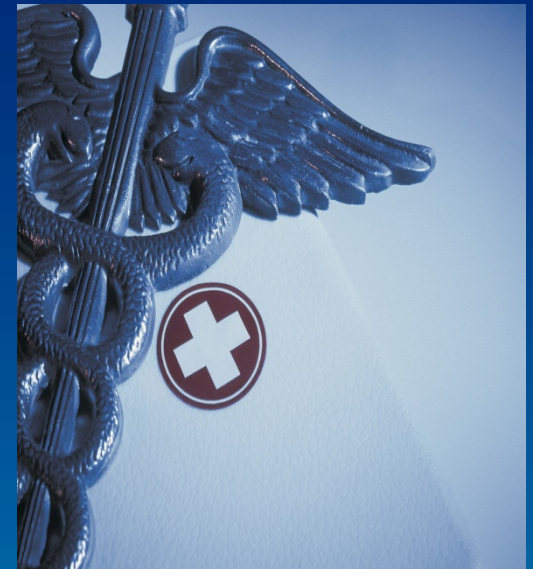
# Surrogate Endpoints Used for Accelerated Approvals

- Response rate
- Disease-free survival (DFS)
- Progression-free survival (PFS)
- Time to progression (TTP)
- Biomarkers
- Quality of life (QoL)



# Overall Survival

- Randomized study is required
- Advantages
  - Universally accepted
  - Easily and precisely measured
- Disadvantages
  - Large studies
  - Affected by crossover
  - Includes non-cancer deaths



# Symptomatic Improvement

- Randomized, blinded study usually required
- Advantages
  - Patient perspective
- Disadvantages
  - Blinding difficult
  - Missing/incomplete data
  - Multiple analysis
  - Lack of validated instruments



# Response Rate – Objective and Complete

- Single arm study can be used, blinding preferred
- Advantages
  - Single arm studies, smaller studies can be used
  - Early effects measured
  - Effects attributed to drug, rarely affected by natural history of the disease
- Disadvantages
  - Activity vs benefit
  - Translate into survival advantage?

# Disease-Free Survival

- Randomized trial essential, blinding preferred
- Advantages
  - Smaller sample size than overall survival
  - Shorter follow-up
- Disadvantages
  - Not validated in all settings
  - Not precisely measured
  - Subject to assessment bias
  - Varying definitions between studies

# Progression-Free Survival

- Randomized trial essential, blinding preferred
- Advantages
  - Smaller sample sizes, shorter follow-up, not affected by crossover
  - Includes stable disease
- Disadvantages
  - Not validated in all settings
  - Not precisely measured, varying definitions
  - Frequent radiology and balanced timing of assessments
  - Includes non-cancer deaths

# Time to Progression

- Randomized trial essential, blinding preferred
- Advantages
  - Smaller sample sizes, shorter follow-up, not affected by crossover
  - Includes stable disease
  - Deaths before progression censored
- Disadvantages
  - Not validated in all settings
  - Not precisely measured, varying definitions
  - Frequent radiology and balanced timing of assessments

# Biomarkers

- Quantifiable measurements of normal to provide a framework to predict what is abnormal
- Exist in many different forms
  - Physiologic – Performance status
  - Imaging – Positron emission tomography (PET)/computed tomography (CT) scans
  - Molecular – Prostate specific antigen (PSA)
  - Cell-based markers – Tumor cells, receptor markers
  - Genetic alterations – Breast cancer gene (BRCA) mutation
  - Gene profiles

# Biomarkers

## ■ Benefits

- Disease prevention
- Prediction of response
- New drug development targets

## ■ Disadvantages

- No direct correlation between biomarkers and clinical endpoints
- Drug affects biomarker, but not disease
- Drug affects biomarker and disease, but to different extents

# Patient Report Outcomes (PRO)

- Measurement of any aspect of health that comes directly from the patient
  - Symptoms
  - Activity of daily living
  - Health-related quality of life (HRQoL) (multidimensional)
- Data can provide evidence from the patient perspective

# Patient Reported Outcomes (PRO)

- Advantage
  - Patient's perspective on treatment
- Disadvantage
  - Blinding is essential, but difficult to do
  - Careful serial assessments
    - Missing data makes interpretation problematic
    - Multiple endpoints and comparisons to baseline must be adjusted in the statistical analysis plan
  - Clinical significance of score changes may be unclear
  - Is additional information gained, compared with a careful recording of toxicity/symptom data?

# FDA Stance on PRO

- PRO claims need to have (where possible)
  - Blinded, randomized trial
  - Minimization of missing data points
  - Prospectively identified hypothesis
- Requires validated instrument
  - Define minimum important difference
- Clinical benefit, such as anti-tumor effects, lends credibility to the outcome

# Oncology Drug Approvals – PRO

Product	Year	Outcome
Porfimer		
Esophageal	1995	Dysphasia
Non-small cell lung cancer (NSCLC)	1998	3 NSCLC symptoms
Gemcitabine		
Pancreatic	1996	Pain/analgesic use
NSCLC	1998	HRQOL
Topotecan – Small cell lung cancer (SCLC)	1998	9 SCLC symptoms
Amifostine – Head & neck cancer	1999	Xerostomia
Imatinib – Chronic Myelogenous Leukemia (CML)	2003	Interferon toxicity
Palifermin – Bone marrow transplant (BMT)	2004	Mucositis

# Accelerated Approvals in Oncology

- First agent approved in 1995
  - 18 oncology agents
  - 22 indications
  - 8 have been converted to regular approval
  - 11 without a comparator arm
  - 7 with an active or placebo control arm

# Drug Approvals in Oncology

Product	Accel	Reg	Indication	Endpoints
Docetaxel	1996	1998	2 <sup>nd</sup> line breast	RR
Irinotecan	1996	1998	2 <sup>nd</sup> line colon	RR
Dexrazoxane	1995	2002	↓ Cardiomyopathy	Cardiotox
Capecitabine	1998	2001	Refractory breast	RR
Imatinib	2001	2003	CML	Cr <sub>h</sub> , Cr <sub>c</sub>
Oxaliplatin	2002	2004	2 <sup>nd</sup> line colon	RR, TTP
Bortizemib	2003	2005	Multiple myeloma	RR
Alemtuzumab	2001	2007	B-cell chronic lymphocytic leukemia (B-CLL)	RR

# Example: Imatinib (Gleevec<sup>®</sup>)

- Accelerated approval granted in 2001 on the basis of 3 single-arm studies of 1027 patients with CML
- Patients in blast crisis/accelerated or chronic phase CML
- Endpoints were:
  - Cytogenetic response rate ( $Cr_c$ ) (chronic phase)
  - Hematologic response rate ( $Cr_h$ ) (accelerated/blast phases)

# Example: Imatinib (Gleevec<sup>®</sup>)

- Chronic phase
  - $Cr_c = 53\%$
- Accelerated/blast phase
  - $Cr_h = 69\%$
- Sponsor agreed to follow safety and efficacy of the three studies
- Sponsor agreed to randomized study of imatinib vs IFN $\alpha$  plus cytarabine in newly diagnosed CML
- Converted to regular approval in 2003

# Example: Imatinib (Gleevec<sup>®</sup>)

- Chronic phase
  - All 532 patients remained in chronic phase at a median of 32 months
  - $Cr_h = 95\%$ ; major cytogenetic response = 60%
  - 2-year survival was 90.8%
- Accelerated/blast phase
  - Response rates remained stable
  - Response duration
    - Blast = 10 months
    - Accelerated = 29 months

# Criteria for Withdrawal of Approval

- Under FDAMA, a product approved under accelerated status may be withdrawn if:
  - Post-marketing study fails to verify benefit
  - Sponsor fails to perform required study with due diligence
  - Post-marketing restrictions inadequate to assure safe use
  - Failure to adhere to post-marketing restrictions
  - Promotional materials false/misleading

# Example: Gefitinib (Iressa<sup>®</sup>)

- 2003 – Approved through accelerated program
  - Approved for NSCLC in patients that had received 2 previous chemotherapy regimens
  - Approved on surrogate endpoint – response rate
  - 10% of the patients had significant decrease in tumor size
  - FDA felt that this was likely to translate into a survival advantage

# Example: Gefitinib (Iressa<sup>®</sup>)

- 2005 – FDA withdrew approval
  - Negative follow-up trial data
  - 1700 patients
  - Placebo-controlled trial
  - No survival advantage

# Accelerated Drug Approvals in Oncology

## *Need Conversion to Full Approval*

Product	Year	Indication
Liposomal doxorubicin	1995	2 <sup>nd</sup> Line Kaposi sarcoma
	1999	Ovarian cancer
Amifostine	1996	Prevent renal toxicity in lung cancer
Denileukin	1999	T-cell lymphoma
Liposomal cytarabine	1999	Lymphomatous meningitis
Gemtuzumab	2000	Acute myelogenous leukemia
Ibritumomab	2002	Non-Hodgkin's lymphoma
Anastrozole	2002	Adjuvant breast cancer
Tositumomab	2003	NHL
Cetuximab	2004	Colon cancer

# Accelerated Drug Approvals in Oncology

## *Need Conversion to Full Approval*

Product	Year	Indication
Premetrexed	2004	NSCLC
Letrozole	2004	Adjuvant breast cancer
Clofarabine	2004	Pediatric acute lymphocytic leukemia
Nelarabine	2005	T-cell lymphoblastic leukemia/lymphoma
Panitumumab	2006	Colon cancer
Sorafenib	2006	Renal cell carcinoma
Sunitinib	2006	Renal cell carcinoma
Lapatinib	2007	Breast cancer
Nilotinib	2007	CML
Temsirolimus	2007	Renal cell carcinoma

# Conclusions

- FDA and Congress have made attempts to improve and speed up drug delivery
- Accelerated approval allows for “alternative” endpoints to be used for drug approval
- Alternative endpoints require supportive data for the product to be converted to regular approval
- Patient reported outcomes and biomarkers will become more important as oncology drug development evolves