PhRMA

Role of the FDA and PDUFA in Drug Development

Questions to be addressed

1. What is the Food and Drug Administration and why is it important?

2. Why was the Prescription Drug User Fee Act (PDUFA) created?

3. How does PDUFA work?

4. How does PDUFA help strengthen our economy, contribute to economic growth and encourage innovation?

5. PDUFA V

What is the Food and Drug Administration (FDA)?

The FDA is an agency within the U.S. Department of Health and Human Services that is responsible for protecting the public health by:

1) Ensuring the safety and efficacy of human and veterinary drugs, biological products, medical devices

2) Ensuring the safety and security of our nation's food supply, products that emit radiation

3) Regulating the manufacture, marketing, and distribution of tobacco products.

FDA also promotes the public health by striving to foster innovative approaches and solutions for some of our nation's most compelling health and medical challenges.

FDA Structure:
Product Centers & Support Divisions

Office of the Commissioner
Provides leadership and direction

Center for Drug Evaluation and Research
Prescription, OTC drugs, and therapeutic biologics

Center for Biologics Evaluation and Research
Vaccines, blood, gene therapeutics

Center for Devices and Radiological Health
Medical devices and radiation-emitting products

Office of Regulatory Affairs
Conducts inspections, enforces FDA regulation

National Center for Toxicological Research
Supports Product Centers with technology, training, and technical expertise

Center for Veterinary Medicine
Feed, drugs, devices for animals

Center for Food Safety and Applied Nutrition
Foods other than meat and poultry, infant formulas, dietary supplements, cosmetics

Center for Tobacco Products
Tobacco products

FDA's Center for Drug Evaluation and Research (CDER) oversees review of most new medicines

Health and Human Services

Secretary of HHS:
Kathleen Sebelius

Office of the Commissioner of the FDA

Commissioner of the FDA:
Margaret A Hamburg, MD

Deputy Commissioner:
Stephen P. Spielberg, MD, PhD

Center for Drug Evaluation & Research (CDER)
Director:
Janet Woodcock, MD

Office of Surveillance and Epidemiology (OSE)

Office of New Drugs (OND)

Advisory Committee (AC)

Oversees vaccines, blood products, and gene therapies

Center for Biologics Evaluation & Research (CBER)
Director:
Karen Midthun, MD

Panel convened by FDA to provide outside expertise

Note: Additional FDA offices not pictured

Source: FDA, **May 2011**

FDA: A Backbone of America's Economy

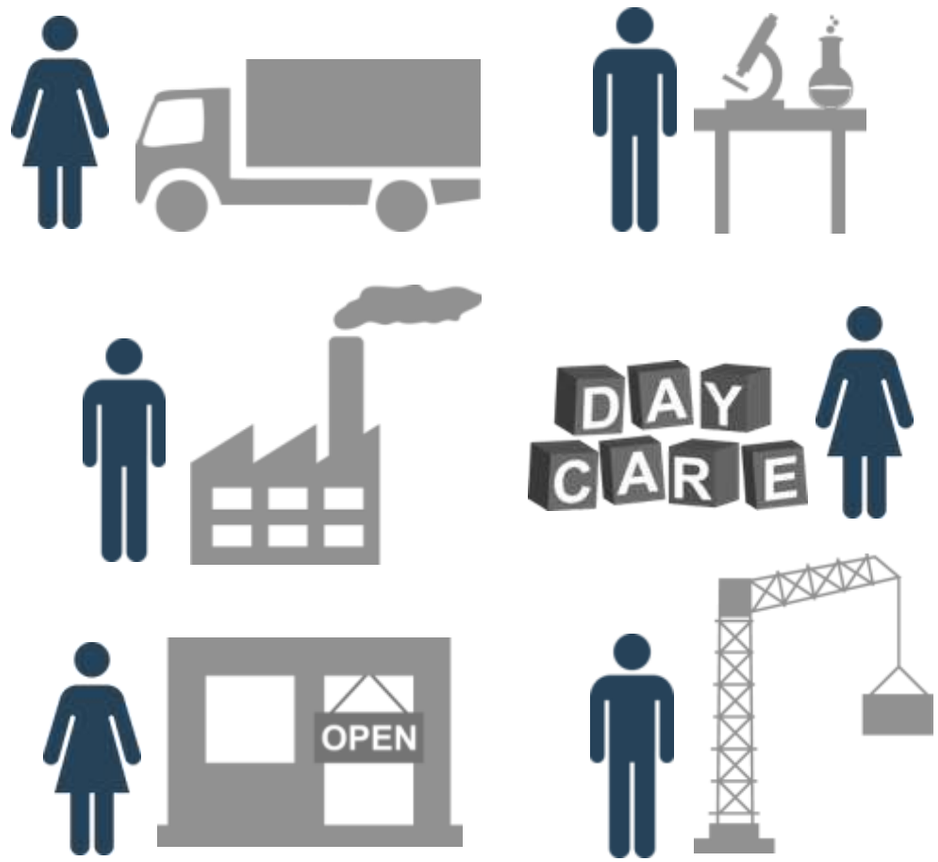
FDA-regulated industries are a vital part of the U.S. economy:

- FDA-regulated industries directly employ about 4 million Americans.
- Most FDA-regulated industries are major exporters and improve the U.S. balance of trade.
- Development of new products and more efficient means of manufacturing help assure that the FDA-regulated portion of the economy will continue to grow in economic size and number of employees
- FDA-regulated industries are innovative and can sustain innovation only with a dependable FDA

Economic Impact of Biopharmaceutical Sector

The biopharmaceutical sector supported 4 million jobs across the economy in 2009, including 3.3 million in other sectors:

Each direct biopharmaceutical job ***supports 5 additional jobs*** *in other sectors*



674,000

Jobs in the U.S. Biopharmaceutical Sector

4 Million

Total U.S. Jobs Supported by the Biopharmaceutical Sector

Source: Battelle Technology Partnership Practice, "The U.S. Biopharmaceuticals Sector: Economic Contribution to the Nation," (Washington, DC: Battelle Technology Partnership Practice, July 2011).

FDA Budget: Limited Funding, Increased Responsibility

BUDGET AND STAFFING

- FDA's responsibilities and workload increase each year– through globalization, scientific complexity of regulated products, growth of industry, and new regulatory authorities.

- Nearly two-thirds of the FDA's budget comes from appropriations ($2.5 billion) and a little more than one-third comes from user fees ($1.29 billion).

- The user fee component includes funds from industries regulated by FDA including drugs, devices and tobacco.

- FDA is limited in the way it spends user fee dollars based on performance goals negotiated with industry that are referenced in legislation and signed into law.

FDA has been chronically underfunded compared to other agencies

(CAGR)=Compound Annual Growth Rate

Questions to be addressed

1. What is the Food and Drug Administration and why is it important?

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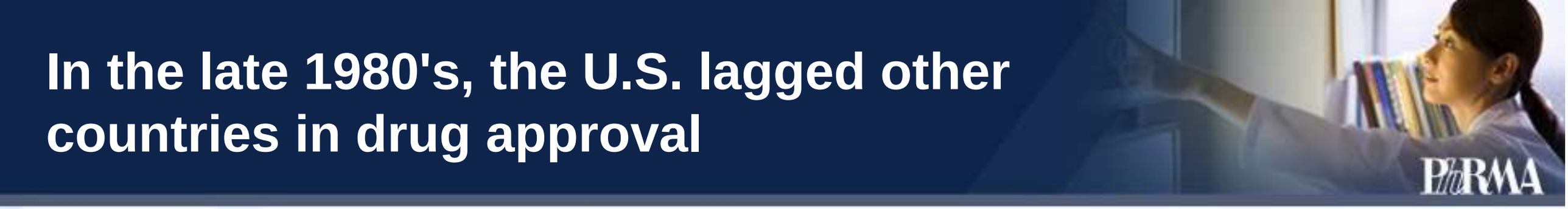
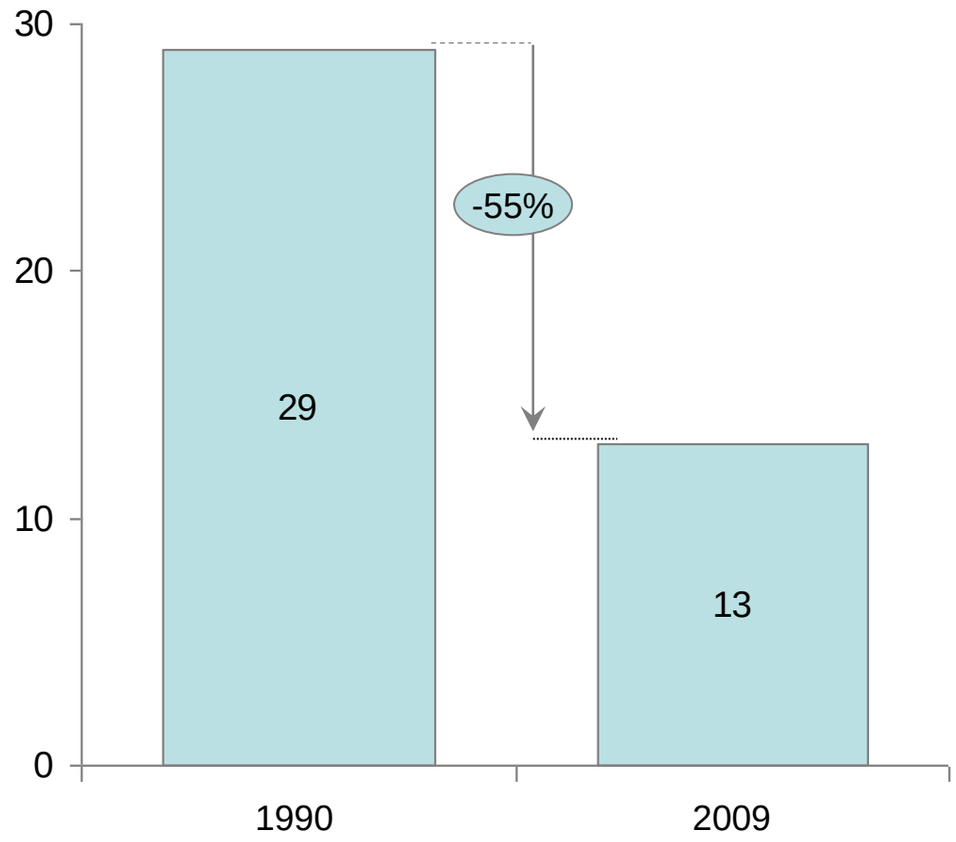
In the late 1980's, the U.S. lagged other countries in drug approval



Drug review times were twice as long as today

Review time in months 1990 vs. 2009



U.S. lagged other countries in approving new drugs

70% — **Percentage of new medicines first marketed overseas in late 80's**

60% — **Percentage new medicines on the market overseas for ≥1 year before US approval**

"Drug lag" became a significant concern for patients, Congress, and biopharmaceutical research companies

Source: FDA: Third Annual Performance Report: Prescription Drug user Fee Act of 1992, Fiscal Year 1995 Report to Congress, December 1, 1995; FDA, FY2010 Performance Report to the President and the Congress for the Prescription Drug User Fee Act,

The emerging AIDS epidemic in the 1980's sparked demand for faster review times

AIDS protesters demanded shorter review times

- AIDS activist group ACT UP! closed down the FDA to protest the slow process of drug approval
- ACT UP! argued that because there were few treatments for AIDS, new drugs should be reviewed as quickly as possible
- Their efforts helped lead the FDA, Congress and industry to work together to shorten review times

Protestors in New York City hold signs reading, "Safe Drugs Now"[1]

Patient protests helped prompt the creation of PDUFA

1. http://apps.nlm.nih.gov/ againsttheodds/exhibit/action_on_aids/fighting_discrimination.cfm

Solution to slow review times was the 1992 Prescription Drug User Fee Act (PDUFA I)

PDUFA Objective: Hire additional FDA drug reviewers to improve drug and biologics review times

PDUFA I authorized the FDA to collect user fees from the pharmaceutical industry

- User fees supplement, but do not replace, Congressional appropriations
  - Fees must be reasonable
  - Revenues must be entirely dedicated to improvement of review process

To ensure timely reviews, FDA is required to meet certain performance benchmarks

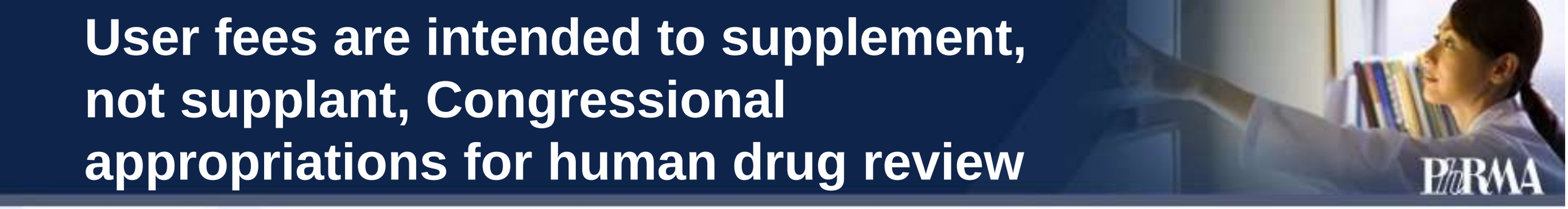
- Priority Review: 6 month goal
  - Designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists
- Standard Review: 10 month goal[1]
  - Applied to medicines that provide therapeutic options and advance medical science

PDUFA is legislation that must be reauthorized every five years

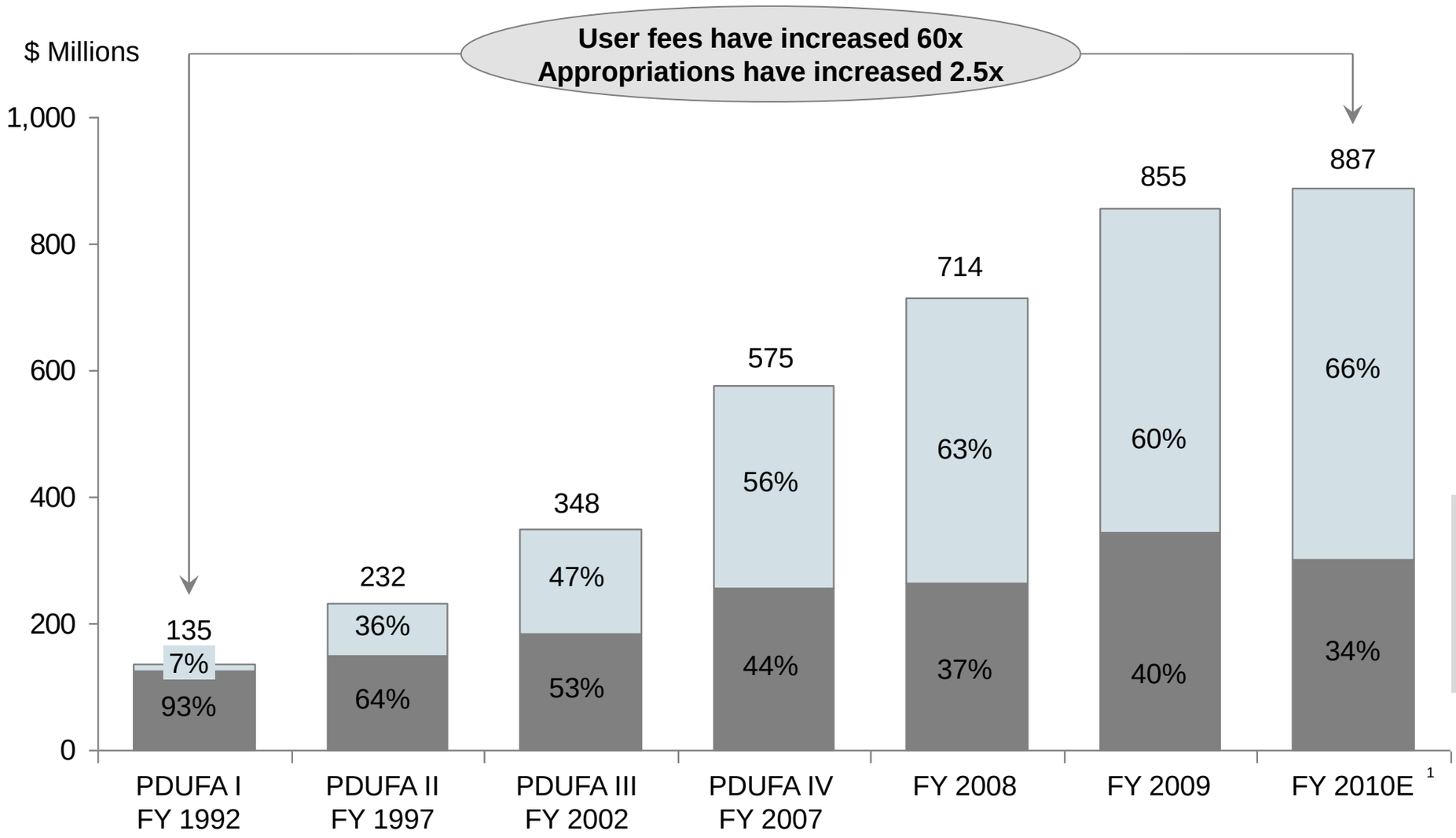
- PDUFA IV expires September 30, 2012
- If not reauthorized by July 2012, layoff notices will be sent to ~2,000 FDA employees

1. Under PDUFA I, standard review goal was set at 12 months. This was revised to 10 months under PDUFA II

User fees are intended to supplement, not supplant, Congressional appropriations for human drug review



Human drug review funding includes funds from **appropriations** and **user fees.**



User fees: Fees paid by pharmaceutical companies to the FDA

Appropriations: Tax dollars appropriated to the FDA by Congress

User fees expected to contribute 66% of the cost of human drug review in FY 2010

Note: Fiscal year in which PDUFA was authorized
1. FY 2010 appropriations estimate based on FY 2009 budget request and FY 2010 increase
Source: FDA PDUFA Webinar; 2009: http://www.hhs.gov/asl/testify/2008/02/t20080227h.html; 2010: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM153491.pdf

Questions to be addressed

1. What is the Food and Drug Administration and why is it important?

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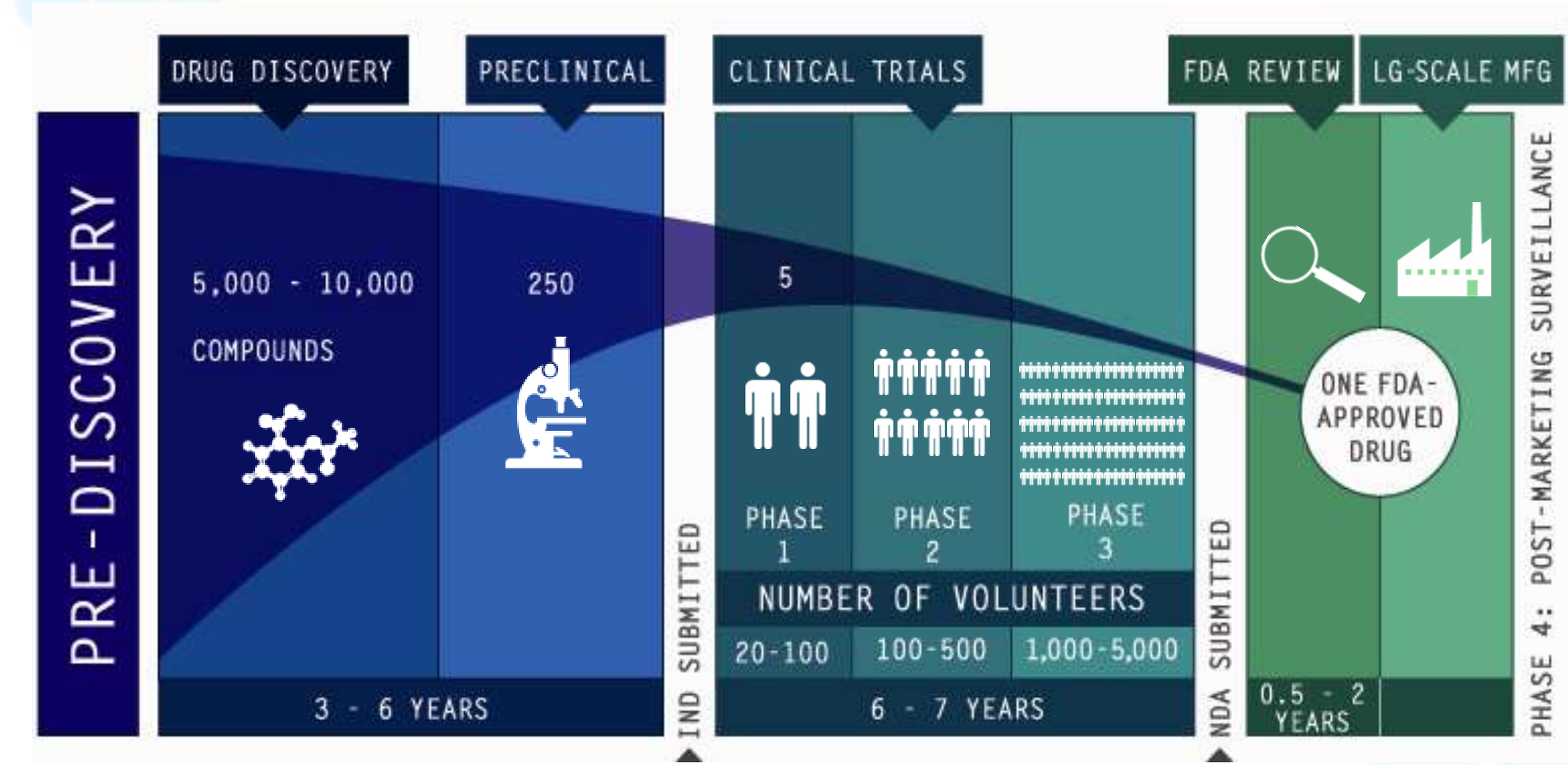
Drug Discovery & Development Overview: A Difficult Road



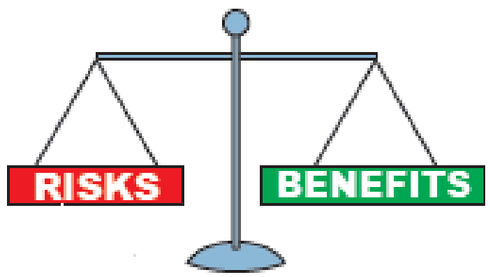
Source: Drug Discovery and Development: Understanding the R&D Process. www.innovation.org

Human drug approval process within Center for Drug Evaluation and Research (CDER) has four basic steps

Application filed

- A drug company (also called a "sponsor") submits an application to the FDA
- FDA decides if application is complete

FDA Review



- The FDA reviews the application and considers benefits and risks
- May hold an Advisory Committee meeting to gain expert advice
- FDA may require sponsor to create a risk evaluation and mitigation strategy (REMS) to ensure benefits outweigh risks
- FDA inspects the facilities the drug will be made
- FDA reviews information that will be on the drug's labeling

FDA takes action

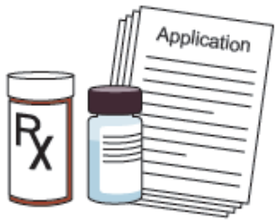
- FDA decides whether the drug's benefits outweigh the risks and can be approved, which would allow the drug to be sold in the US

FDA monitors safety post-approval

- After a drug is approved, FDA monitors the safety of that drug
- Based on new safety data, FDA can decide to take appropriate action, including adding new warnings or requiring new studies, contraindications, withdrawal, REMS etc.

Source: "FDA Drug Approval Process" http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/UCM195671.pdf

PDUFA was designed to add resources to the FDA review step

		CDER	OSE	OND	Advisory Committee
Application filed				• Determines if application is complete and can be filed	
FDA review			• Assesses if risk evaluation and mitigation strategy (REMS) or new studies are needed to ensure benefits outweigh risks	• Assesses benefits and risks • Assesses if risk evaluation and mitigation strategy is needed to ensure benefits outweigh risks • May require an Advisory Committee meeting to gain expertise • Reviews drug label information	• Generally required for drugs with active ingredient not previously approved in U.S. • Offers expert opinion to FDA on drug under review, based on expertise and experience
FDA takes action			• OSE advises OND regarding safety issues and postmarket requirements	• Determines whether or not drug should be approved for sale in US	
FDA monitors safety post-approval			• Identifies new adverse events and re-evaluates known risks • Reassesses if risk evaluation and mitigation strategy or new studies are needed to ensure benefits outweigh risks		

Source: "FDA Drug Approval Process" http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/UCM195671.pdf

PDUFA I– PDUFA IV

Activities required by PDUFA

PDUFA I 1992

- Review goals:
  - 12 months standard
  - 6 months priority

PDUFA II 1997

- Standards for scheduling meetings
- More review guidance

- Review goals:
  - 10 months standard
  - 6 months priority

PDUFA III 2002

FDAAA significantly expanded post-approval safety activities and required Advisory Committees for most new medicines

- Post-approval safety activities for 3 years
- Good Review Management Practices
- Improved performance mgmt
- Rolling applications
- Standards for scheduling meetings
- More review guidance

- Review goals:
  - 10 months standard
  - 6 months priority

PDUFA IV 2007

- Risk Evaluation and Mitigation Strategies
- Procedures to analyze drug safety data
- Post-approval safety activities for life of drug
- Mandatory advisory committees
- Good Review Management Practices
- Improved performance mgmt
- Rolling applications
- Standards for scheduling meetings
- More review guidance

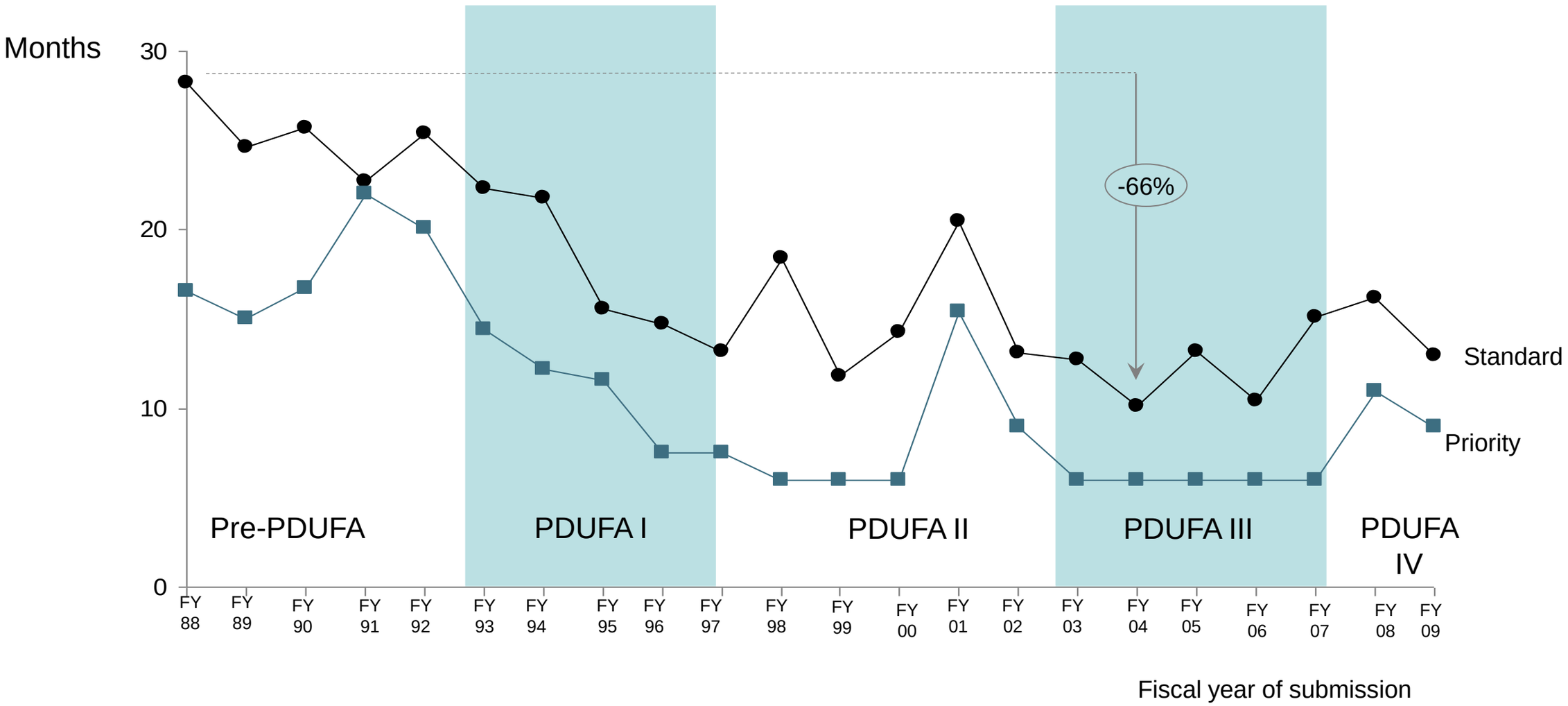
- Review goals:
  - 10 months standard
  - 6 months priority

Review process requirements

Post-approval requirements

Review times for new drugs were reduced two-thirds during PDUFA I-II, but began to increase in PDUFA III

Median approval times for Standard and Priority submissions



Review times decreased by 66% during PDUFA I & II, but began to rise under PDUFA III

Note: Standard submissions have a decision target of 10 months; Priority submissions have a decision target of 6 months. Fees are the same for both submission type
Source: PDUFA FY2009 and FY2010 Performance Reports

Questions to be addressed

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PDUFA – Helping Ensure Biopharmaceutical Innovation Continues to Thrive

PDUFA has provided faster access to over 1,500 new medicines since 1992. Today, the U.S. leads the world in the first introduction of new medicines, with **more than 3000 medicines** in development.

Medicines in Development in 2011 for Selected Conditions*

Alzheimer's and Other Dementias	98
Arthritis and Related Conditions	198
Cancer	932
Breast Cancer	129
Colorectal Cancer	84
Lung Cancer	140
Leukemia	119
Skin Cancer	82

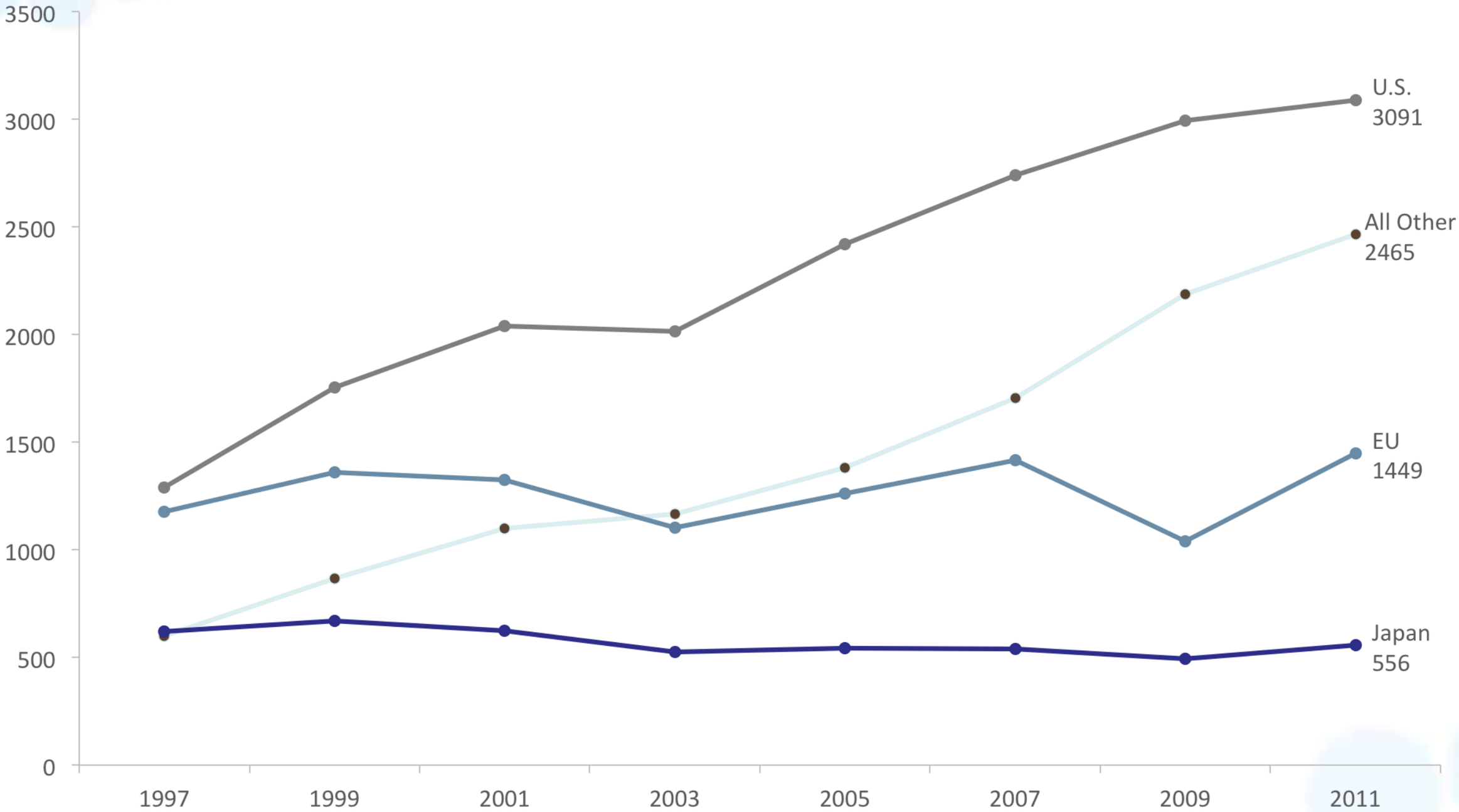
Cardiovascular Disorders	245
Diabetes Mellitus	200
HIV/AIDS and Related Conditions	88
Mental and Behavioral Disorders	250
Parkinson's and Related Conditions	36
Respiratory Disorders	383
Rare Diseases[1]	460

*Reflects number of compounds in clinical trials or under review by the FDA for approval through New Drug Application (NDA) or Biologic License Application (BLA) pathways. Medicines with multiple indications may appear in more than one category but are counted only once for total (3,091).

Source: PhRMA[2]

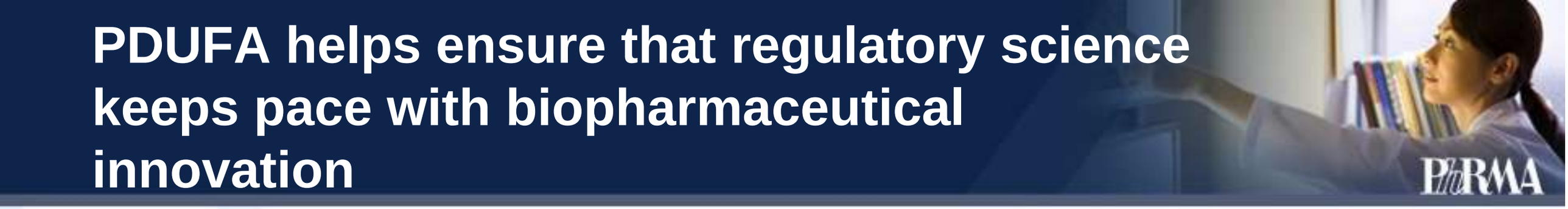
U.S. market drives global development of medicines

Number of Compounds in Development, by Geographic Region[4], 1997–2011



Source: Adis R&D Insight Database[5]

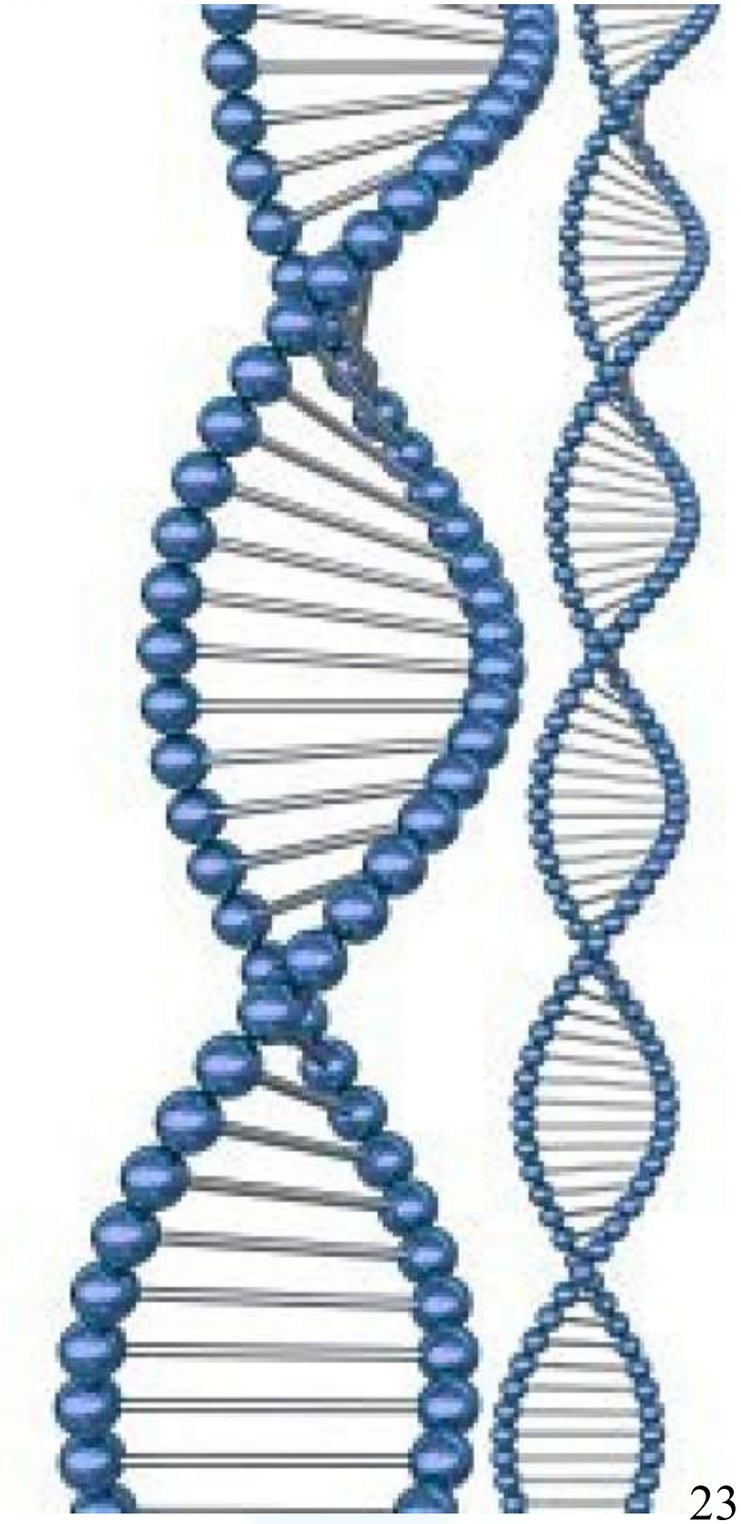
PDUFA helps ensure that regulatory science keeps pace with biopharmaceutical innovation



As science advances, so must the methods used by regulatory agencies, such as the FDA, to review products proposed by biopharmaceutical companies.

Since the inception of PDUFA, FDA has included in its review process **new approaches and new requirements** that can be traced directly to scientific advances in drug development and discovery.

For example, the PDUFA V performance goals will provide the FDA with **additional resources to augment its clinical, clinical pharmacology and statistical capacity** to better address submissions that propose to use biomarkers or pharmacogenomics.



PDUFA Provides an Opportunity to Foster Innovation

Accelerating medical advances is good for patients and for our society. As countries around the world are recognizing the opportunities and value of pursuing medical advances, it is becoming **more pressing for the U.S. to bolster its scientific research capabilities** and enhance its regulatory environment.

U.S. innovation and ingenuity represent **our comparative advantage** in the global trading arena, and will continue to be essential to American prosperity and growth.

By supporting an efficient, consistent and predictable regulatory environment, as PDUFA has provided, the U.S. could create a **more favorable environment for innovation** and retain its global leadership position in biopharmaceutical R&D.

PDUFA is Key to U.S. Job Growth and Job Creation

PDUFA has provided greater certainty, predictability and efficiency to the drug review process, which are keys to economic growth.

In order for companies to thrive and grow, they need to have a business environment that provides a level of consistency and predictability. PDUFA has provided the FDA with greater resources to enable a more efficient drug review process.

At the same time, the scientific rigor of new drug application reviews has increased since PDUFA's inception.

This **certainty and predictability** helps ensure venture capitalists and other investors will continue investing to fund new research.

Biopharmaceutical Jobs are Vital to America's Growth; Reauthorizing PDUFA Will Help Ensure that Growth Continues

A report by Battelle found that the U.S. biopharmaceutical sector is "well recognized as a dynamic and innovative business sector **generating high quality jobs and powering economic output** and exports for the U.S. economy."

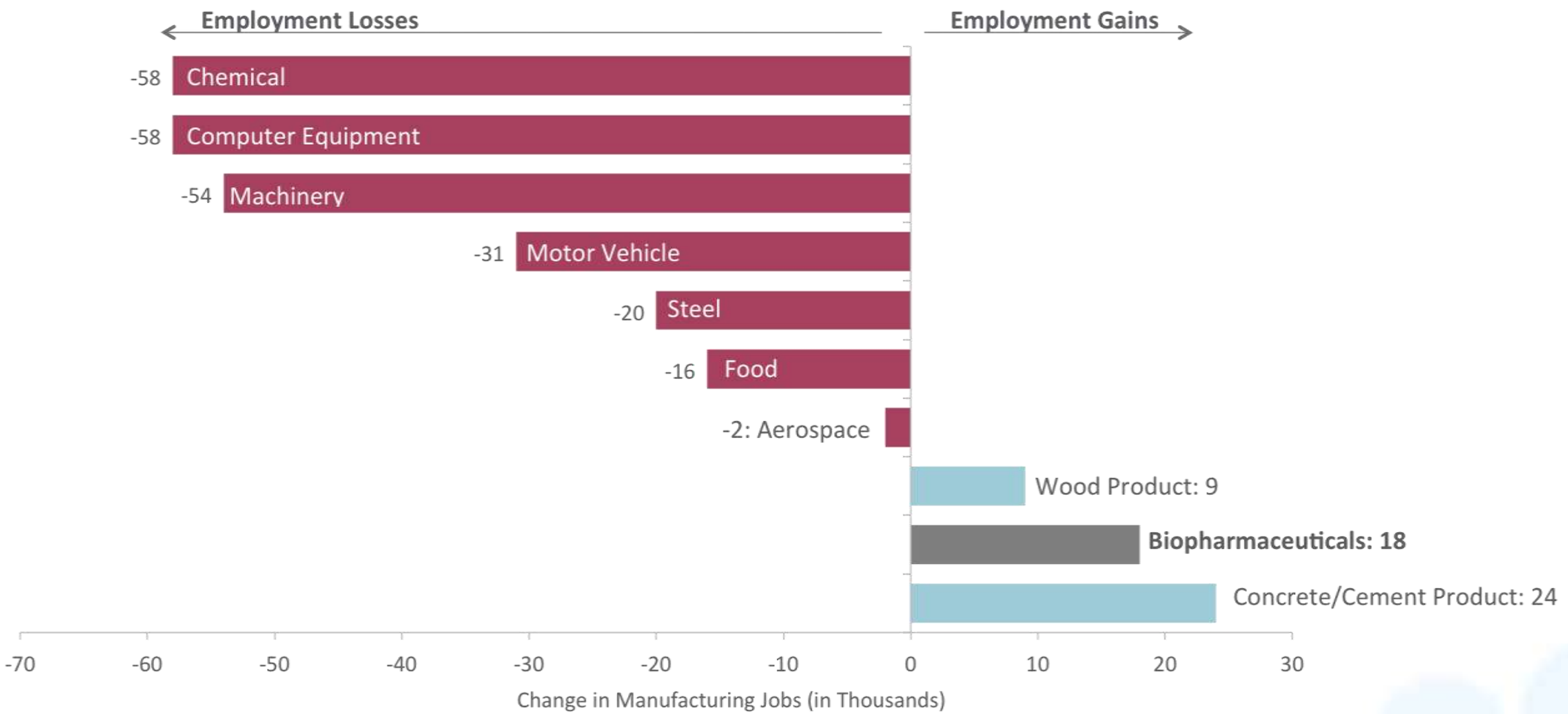
According to the report, nationwide the total economic output from the sector's direct, indirect and induced impacts was **$918 billion.** In total, the sector supported a total of **4 million jobs** in 2009, including **674,192 direct jobs**.

Because PDUFA has injected greater consistency, certainty and predictability into the drug review process, **its reauthorization is an important factor** in ensuring that biopharmaceutical companies maintain this level of job creation and economic growth.

PDUFA Reauthorization: Important for Continued Job Creation in the Biopharmaceutical Industry

Biopharmaceuticals are a Rare Source of Projected Growth in U.S. Manufacturing Jobs

*Projected Change in Employment from 2006 to 2018**



* Selected illustrative sectors. The government projects increases in manufacturing employment in only one fifth of the sectors or subsectors it defines.

Source: PhRMA, adapted from Bureau of Labor Statistics[3]

PDUFA Has Helped to Improve America's Competitiveness

PDUFA has helped to improve America's competitiveness around the world. Since its passage, the U.S. has been the **world leader in getting new medicines to market first** and is the **world leader in biotechnology**.

Ensuring that the U.S. maintains a regulatory and policy environment that encourages an efficient, consistent and predictable drug review process is **key to keeping America competitive** in today's global economy.

Reauthorization of PDUFA helps ensure **that a timely and predictable process** exists for the review of new medicines.

U.S. biotechnology firms account for 80% of the world's research & development in biotechnology.

2008 Biotechnology Statistics*					
	USA	Europe	Asia/Pacific	Canada	**Total**
Annual R&D	**$24B**	$5B	$0.6B	$0.9B	**$30B**
Total Companies	**1,450**	1,600	760	400	**4,210**
Total Employees	**140,000**	65,000	15,000	6,000	**226,000**
Publicly Held Corporations	**336**	150	160	67	**693**

* Biotechnology companies are defined as those whose primary activity is to use biological processes to develop health care products, and other companies whose primary activity is to supply health biotechnology companies with technology-based research products.

Source: Burrill and Company[6]

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Overview of PDUFA V Performance Goals Letter

The legislative authority for PDUFA expires in September 2012. At that time, new legislation is required for FDA to collect prescription drug user fees for future fiscal years (FYs). The reauthorization of PDUFA will authorize FDA to collect user fees and use them for the process of the review of human drug applications for FYs 2013 through 2017.

- The PDUFA-V performance goals letter is the result of extensive, technical negotiations between the US Food and Drug Administration (FDA) and the innovative biopharmaceutical industry.

- FDA's process included unprecedented transparency and input from other stakeholders, including patient advocates, healthcare professionals, consumers and academia.

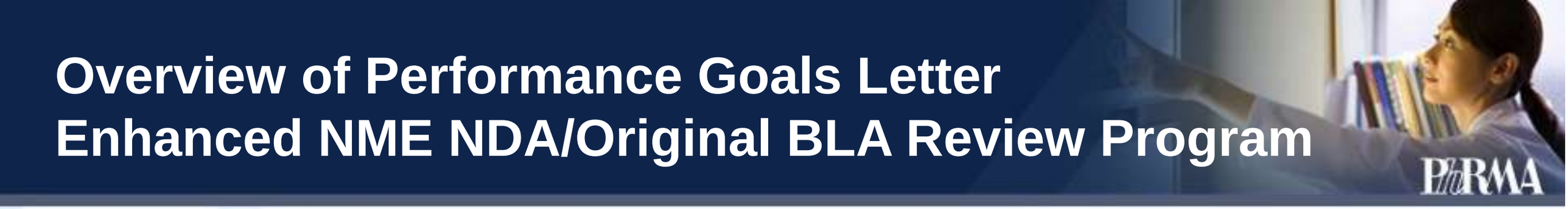
- *Basic structure* of the human drug review program, including FDA's high review standards for safety and efficacy, remains unchanged

- *New provisions* provide FDA with tools to make safe and effective new medicines available to patients in a more efficient, consistent, and timely manner

Overview of Performance Goals Letter: Enhancing Regulatory Science & Patient Safety

Overview of Regulatory Science and Patient Safety Goals
✓ Enhanced FDA/sponsor communications during drug development
✓ Advance development of drugs for rare diseases
✓ Advance biomarker qualification & pharmacogenomics
✓ Ensure quality of patient-reported outcomes
✓ Ensure quality in meta-analysis
✓ Implement Benefit/Risk framework, including patient-focused drug development
✓ REMS standardization & Sentinel
✓ Electronic regulatory submissions (eCTD) and data standards

Overview of Performance Goals Letter
Enhanced NME NDA/Original BLA Review Program



PDUFA-IV

9 months median time to approval (Priority NDA/BLA; FY 2010)

NDA/BLA Submission

PDUFA Goal

FDA Approval

PDUFA-V

8 months planned FDA review time (Priority NDA/BLA)

NDA/BLA Submission

FDA Feedback

PDUFA Goal

PDUFA Reauthorization Timeline

January 15, 2012	Presentation of final FDA recommendations to Congress
Early Q3 2012	If PDUFA not reauthorized, FDA must send notice of termination letters to ~2,000 employees
September 30, 2012	PDUFA IV expires