



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

[www.fda.gov](http://www.fda.gov)

# Leveraging Innovation and Change Through Regulatory Science Initiatives

*ShaAvhrée Buckman-Garner, M.D., Ph.D., F.A.A.P.*

*Director*

*Office of Translational Sciences*

*Center for Drug Evaluation and Research*

*Food and Drug Administration*

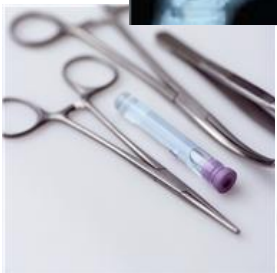
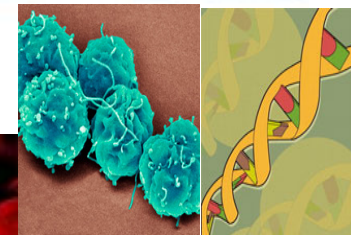




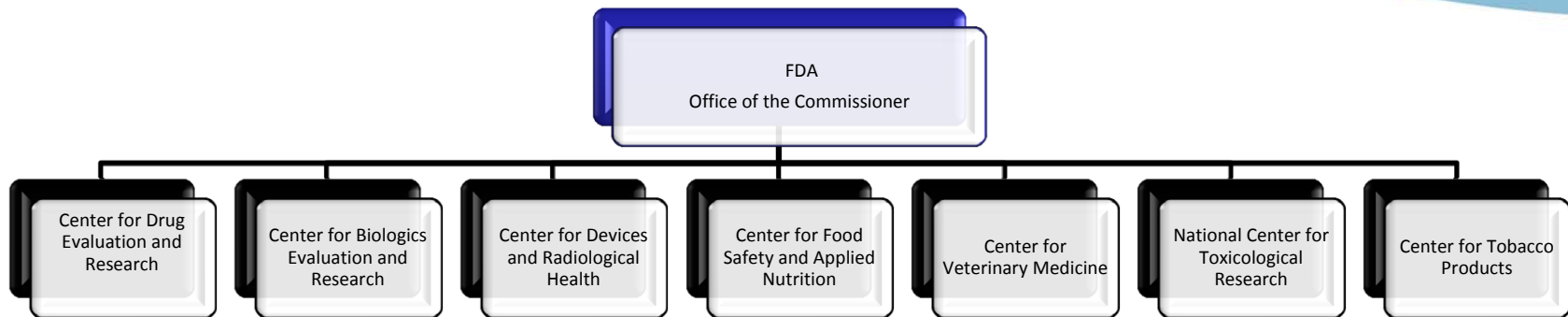
# Plan for My Talk

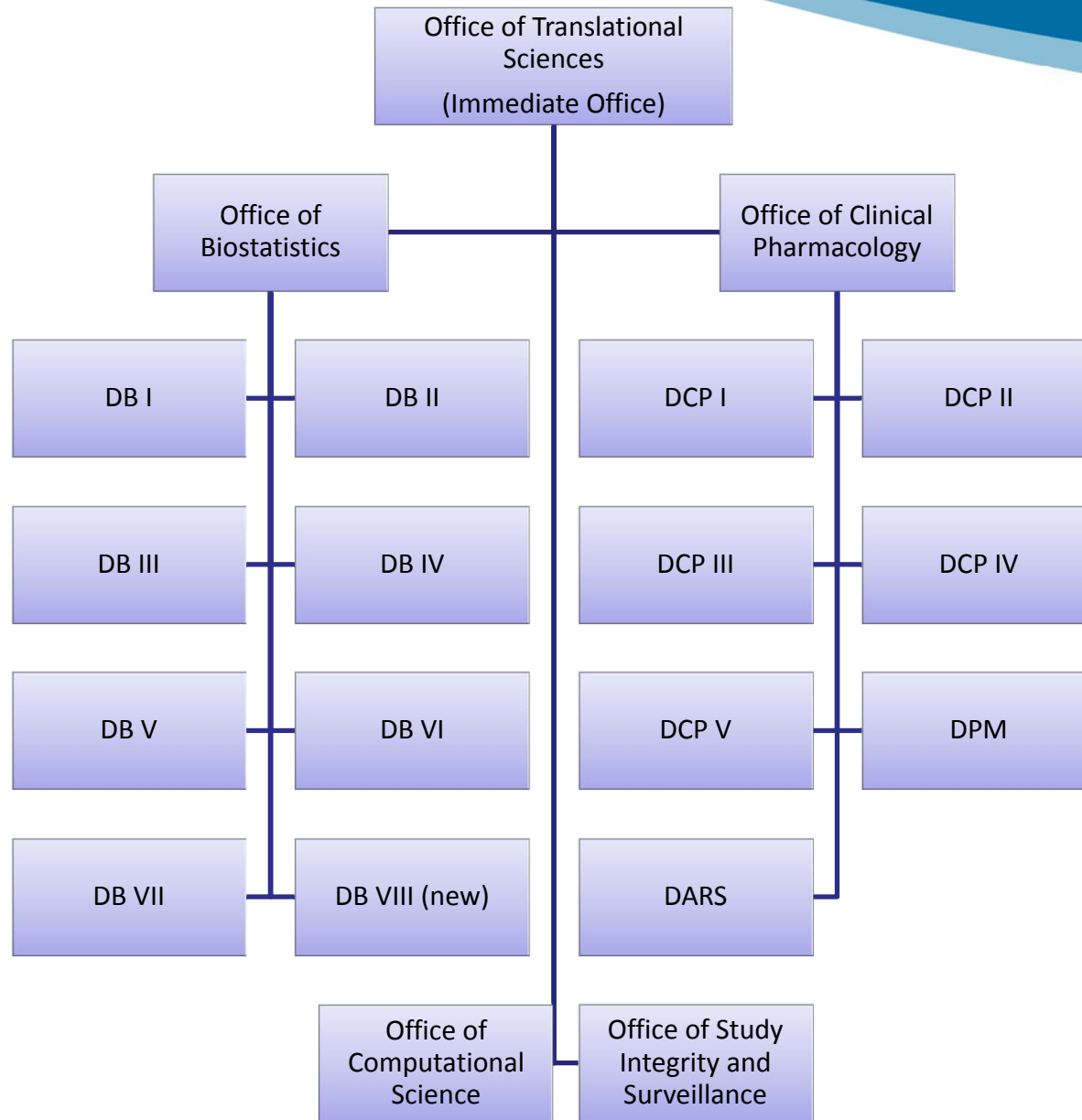
- Orientation to FDA and the CDER Office of Translational Sciences
- Regulatory Science Challenges
- Our approach:
  - Initiatives
  - Collaboration
  - Integrating New Science
  - Communication
  - Information Technology
  - Training
  - People

# FDA's Regulatory Scope: 25 cents of every GDP dollar











# What We Do:

OTS promotes and protects public health by assuring that safe and effective drugs are available to Americans by:

- Promoting innovation in drug regulatory review across CDER
- Assuring the validity of clinical trial design and analysis in regulatory decision making
- Developing and applying quantitative and statistical approaches to decision making in the regulatory review process
- Promoting scientific collaboration to advance regulatory review
- Ensuring alignment of CDER research with CDER goals



# Where we are now...

## Office of Translational Sciences

### Senior Management



ShaAvhree Buckman-Gamer  
Director



Jan Johannessen  
Deputy Director for  
Science



Susan McCune  
Deputy  
Director



Ekip Francis  
Director for Data  
Mining &  
Informatics  
Evaluation &  
Research



Rubynell Jordan  
Associate  
Director for  
Regulatory  
Affairs



Raya McCree  
Director,  
Program  
Management  
& Analysis Staff



Mara Walton  
Associate  
Director for  
Translational  
Medicine



Lisa LaVange  
Director, Office  
of Biostatistics



William Rosario  
Director, Office of  
Computational  
Science



Issam Zineh  
Director, Office of  
Clinical  
Pharmacology

## Office of Translational Sciences

### Office of Biostatistics



Lisa LaVange  
Director



Ed Nevius  
Deputy Director



Mohammad Huque  
Senior Scientific Advisor



Ram Tiwari  
Associate Director



Sue-Jane Wang  
Associate Director

### DBI DBII DBIII DBIV DBV DBVI DBVII



James  
Hung  
DBI  
Director



Tom  
Permut  
DBII  
Director



Steve  
Wilson  
DBIII  
Director



Dianne  
Price  
DBIV  
Director



Rajeshwari  
Sridhara  
DBV Director



Yi Tsong  
DBVI  
Acting  
Director



Alok  
Chakravarty  
DBVII Director



Kocooz  
Mahjoob  
DBI Deputy  
Director



Vacant  
DBII  
Deputy  
Director



Mike  
Welch  
DBII  
Deputy  
Director



Daphne  
Lin  
DBIV  
Deputy  
Director



Thomas  
Gwise  
DBV  
Deputy  
Director



Stella  
Grosser  
DBVI  
Acting  
Deputy  
Director



Mark  
Levenson  
DBVII Deputy  
Director

## Office of Translational Sciences

### Office of Clinical Pharmacology



Issam Zineh  
Director



Shiew-Mei Huang  
Deputy Director



Darrell Abernathy  
Associate Director  
Drug Safety



Gilbert Burckhardt  
Associate Director  
Pharmacokinetics



Michael Papanicolaou  
Associate Director  
Genomics & Target  
Therapy



Lei Zhang  
Senior Advisor for  
Regulatory Program  
and Policy

### DCPI DCPII DCPIII DCPIV DCPV DPM DARS



Mahul  
Mahajan  
DCPI  
Director



Chandra  
Sahajwala  
DCPII  
Director



Dennis  
Seshaw  
DCPIII  
Director



John  
Lopez  
DCPIV  
Director



Akbar  
Siddiqui  
DPM  
Director



Vikram  
Singh  
DPM  
Director



Thomas  
Colatsky  
DARS  
Director



Romona  
Vagstad  
DCPII  
Deputy  
Director



Suresh  
Dasgupta  
DCPII  
Deputy  
Director



Hae-Young  
Ahn  
DCPIII  
Deputy  
Director



Kelle  
Reynolds  
DCPIV  
Deputy  
Director



Brian  
Booth  
DCPIV  
Deputy  
Director



Yanning  
Wang  
DPM  
Deputy  
Director



Vikram  
Patel  
DARS  
Deputy  
Director

## Office of Translational Sciences

### Office of Computational Science



William Rosario  
Director



Vacant  
Deputy Director



Amanda Oiva  
Associate  
Director  
Informatics

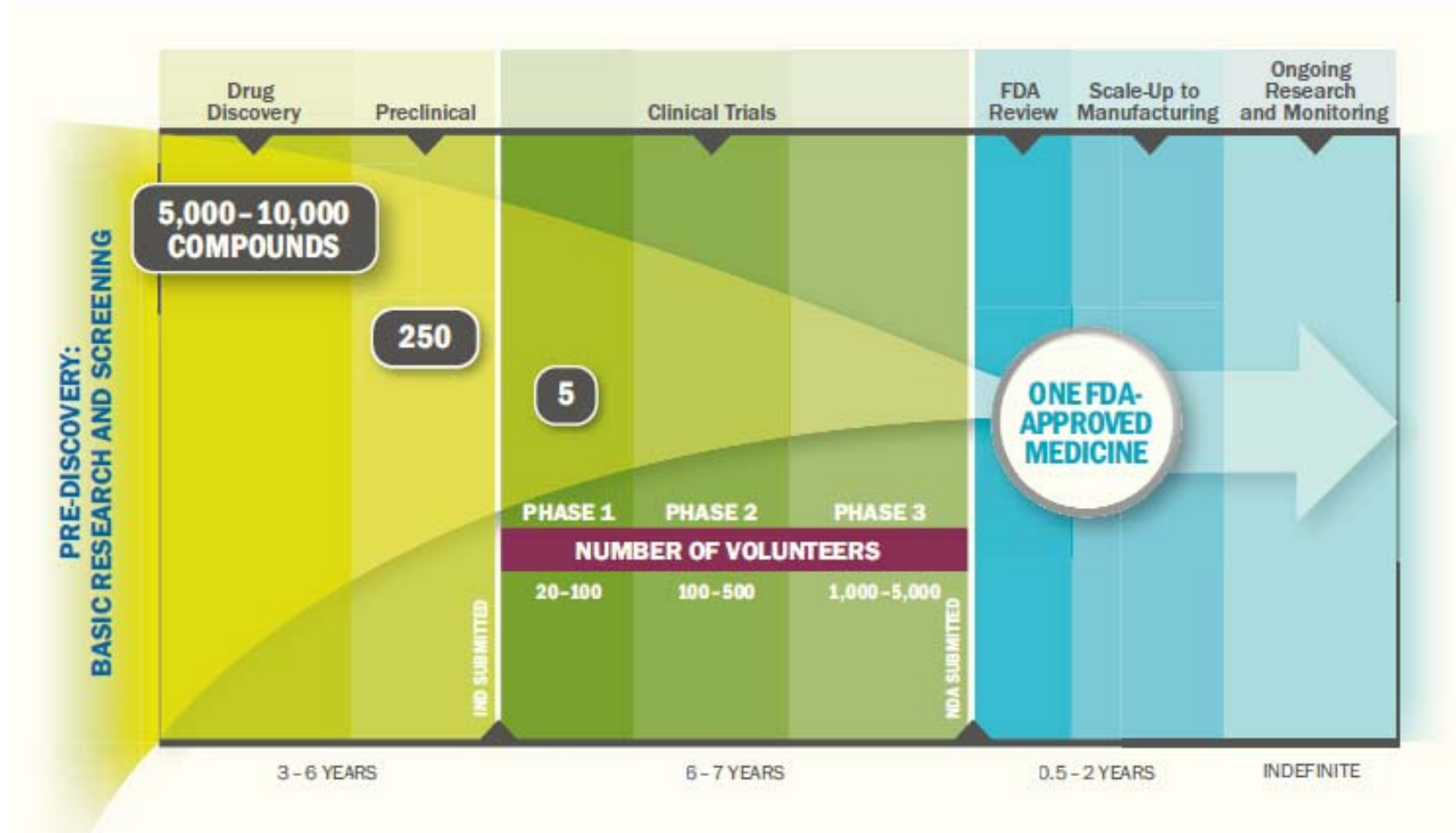
*New office—Office of Study Integrity and Surveillance*

# Realities of the 21st Century

- Over two decades ago we lacked effective treatments for many life-threatening illnesses.
- Today many more treatments are available, but patterns of drug manufacturing, use and guiding information have shifted dramatically.
- Patients and clinicians want more accurate, up-to-date and understandable information to ensure safe use and they want it earlier.
- New science promises accelerating product development but delivery has lagged.
- FDA is only one part of an extremely complex healthcare system. Influencing change is challenging and requires collaboration.



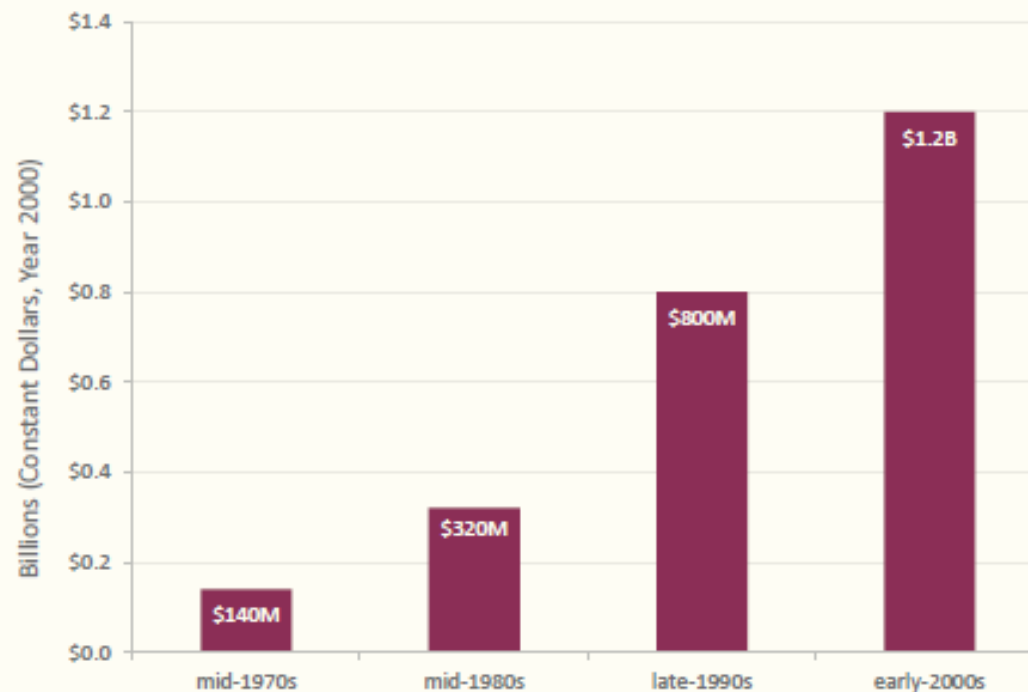
# Drug Development Process



Source: PhRMA

# Average Cost to Develop One New Medicine

*The Average Cost to Develop One New Approved Drug — Including the Cost of Failures*

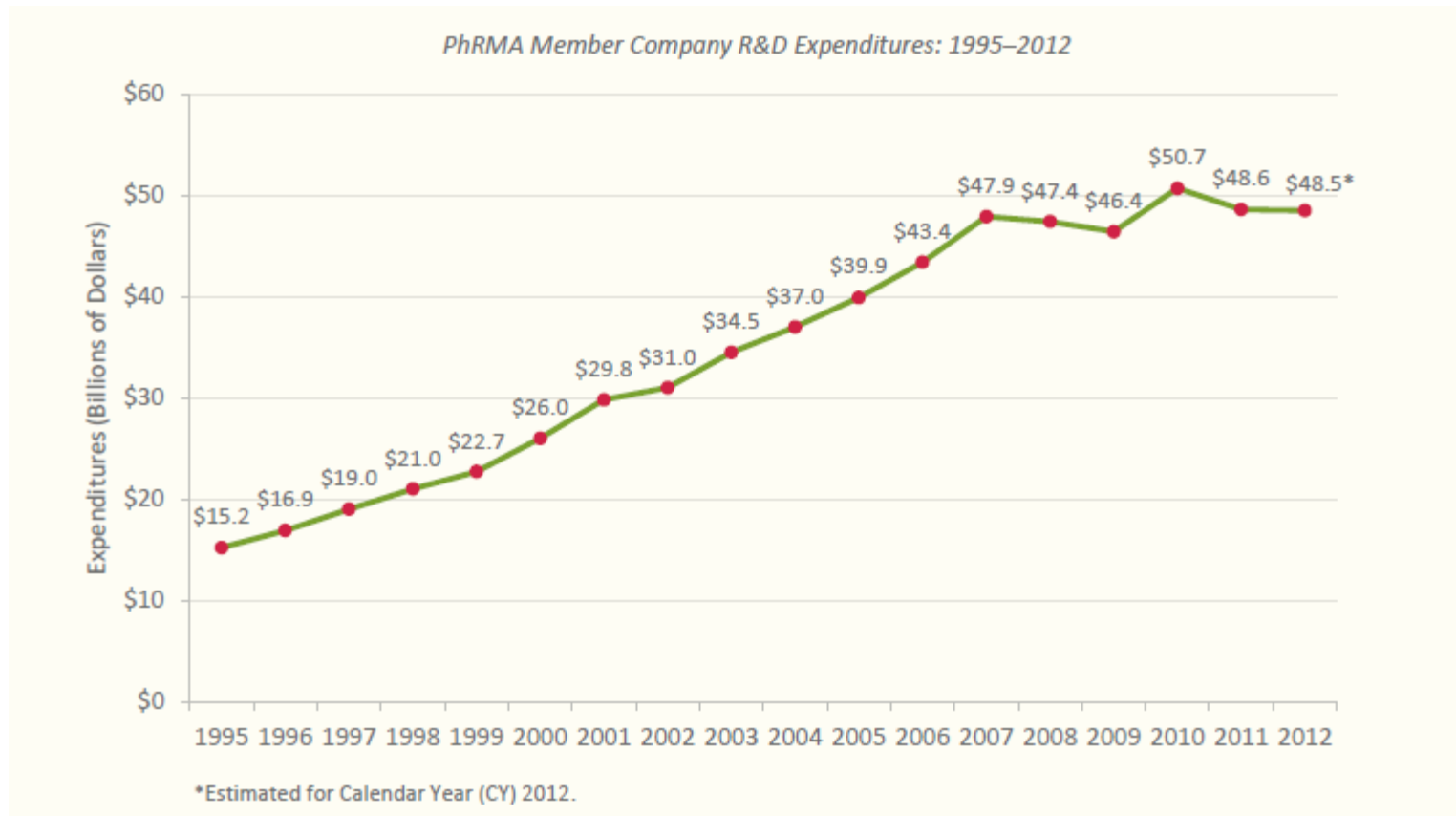


SOURCES: J.A. DiMasi, R.W. Hansen, and H.G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22(2): 151–185; J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4–5): 469–479; More recent estimates range from \$1.5 billion to more than \$1.8 billion. See for example J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.

NOTE: Data is adjusted to 2000 dollars based on correspondence with J.A. DiMasi.



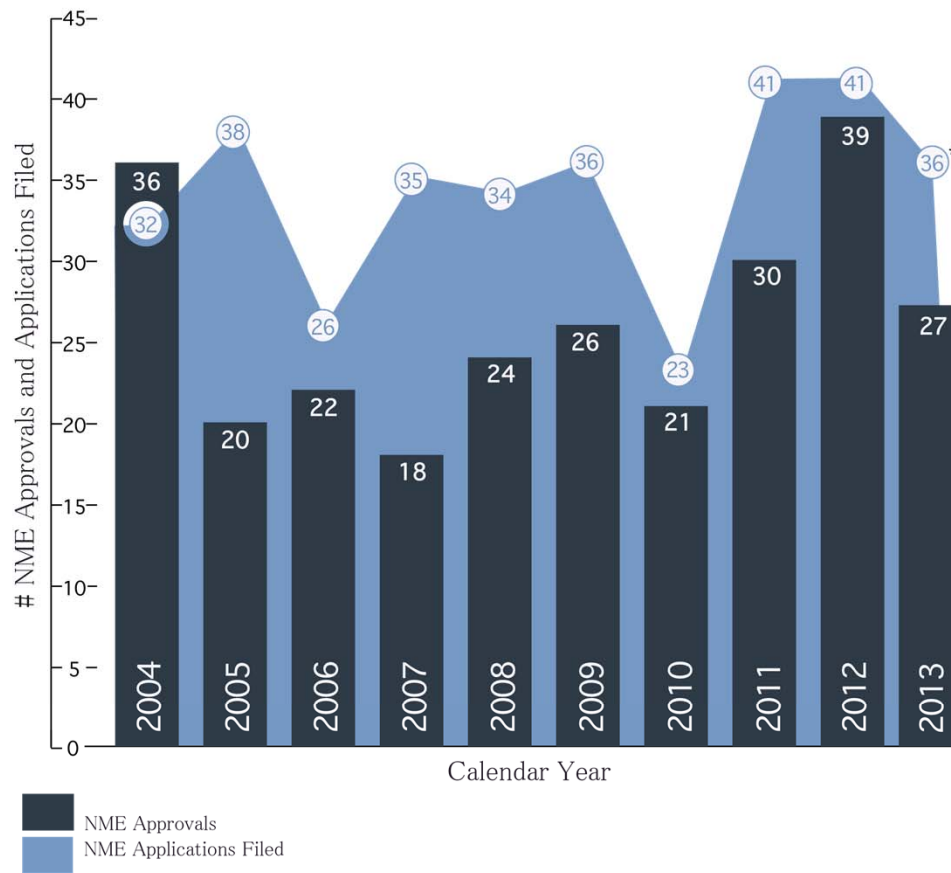
# R & D Expenditures



SOURCE: Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 1996–2013.



# New Molecular Entities

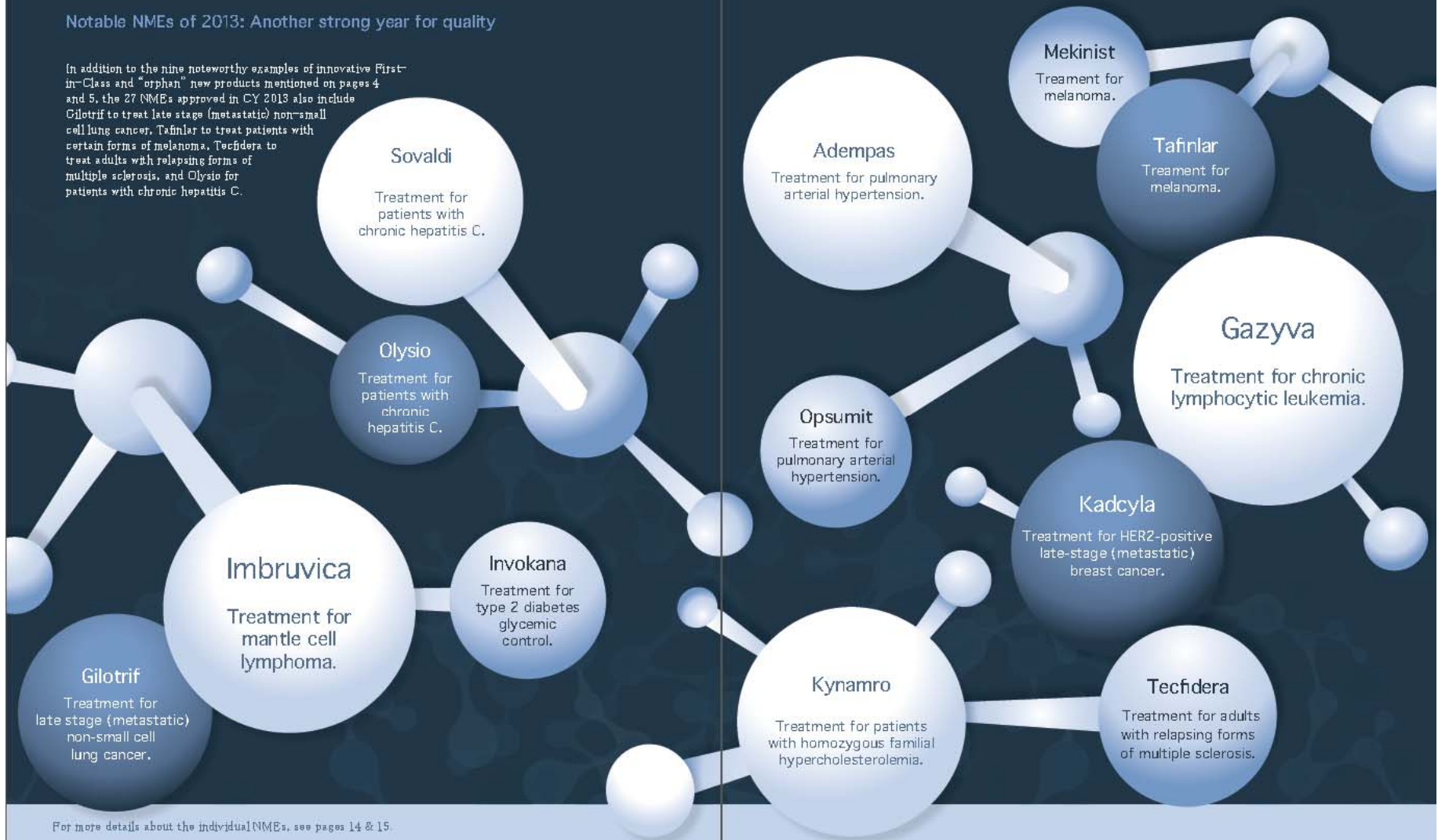


- \* - The filed numbers include those filed in CY 2013 plus those currently pending filing (i.e., within their 60 day filing period) in CY 2013.
- Receipts that received a "Refuse to File" (RTF) or "Withdrawn before filing" (WF) identifier are excluded.
- Multiple submissions (multiple or split originals) pertaining to a single new molecular/biologic entity are only counted once.
- There is a BLA included that does not currently have a review schedule but is known to contain a new active ingredient.
- The filed number is not indicative of workload in the PDUFA V Program.

# Notable 2013 NMEs

## Notable NMEs of 2013: Another strong year for quality

In addition to the nine noteworthy examples of innovative First-in-Class and "orphan" new products mentioned on pages 4 and 5, the 27 NMEs approved in CY 2013 also include Gilotrif to treat late stage (metastatic) non-small cell lung cancer, Tafinlar to treat patients with certain forms of melanoma, Tecfidera to treat adults with relapsing forms of multiple sclerosis, and Olysio for patients with chronic hepatitis C.



For more details about the individual NMEs, see pages 14 & 15.



# Some Notable 2014 NMEs

Harvoni  
Chronic Hep C

Zontivity  
Thrombotic CV

Keytruda  
Metastatic Melanoma

Vimzim  
Morquio A Syndrome

Impavido  
Leishmaniasis

Sylvant  
MCD

Cerdelga  
Gaucher Disease

Esbriet  
Pulmonary Fibrosis

Ofev  
Pulmonary Fibrosis

Farxiga  
Diabetes

Tanzeum  
Diabetes

Jardiance  
Diabetes

Trulicity  
Diabetes

Dalvance  
ABSS

Sivextro  
ABSS

Orbactiv  
ABSS

*ABSS—Acute Bacterial Skin and Skin Structure  
MCD- Multicentric Castleman's Disease*

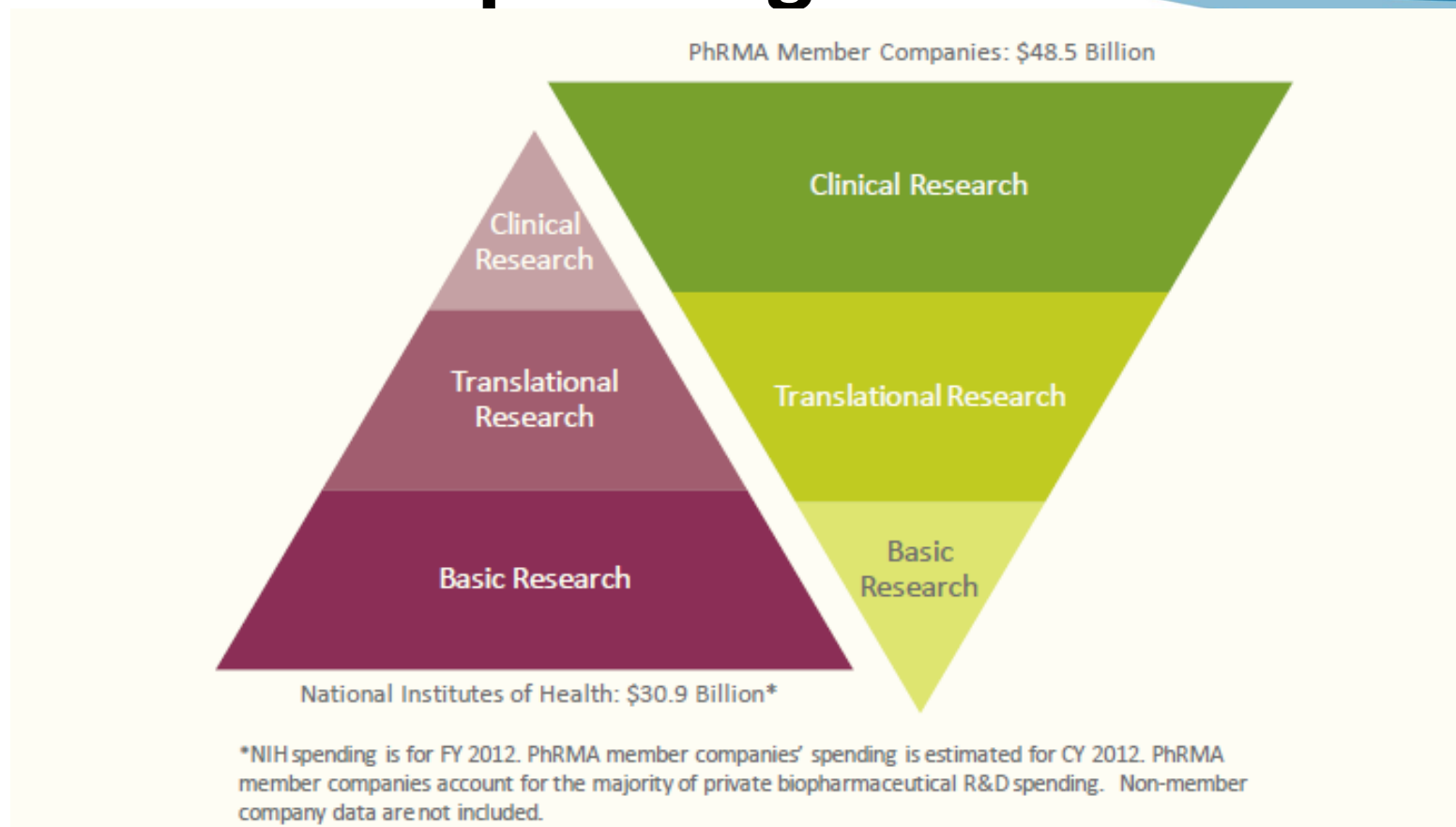
# Expedited Programs for Serious Conditions

Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
<ul style="list-style-type: none"> <li>• A drug that is intended to treat a serious condition <b>AND</b> nonclinical or clinical data demonstrate the potential to address unmet medical need <b>OR</b></li> <li>• A drug that has been designated as a qualified infectious disease product</li> </ul>	<ul style="list-style-type: none"> <li>• A drug that is intended to treat a serious condition <b>AND</b> preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</li> </ul>	<ul style="list-style-type: none"> <li>• A drug that treats a serious condition <b>AND</b> generally provides meaningful advantage over available therapies <b>AND</b> demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity of mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)</li> </ul>	<ul style="list-style-type: none"> <li>• An application (original or efficacy supplement) for a drug that treats a serious condition <b>AND</b> if approved, would provide a significant improvement in safety or effectiveness <b>OR</b></li> <li>• Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A <b>OR</b></li> <li>• An application for a drug that has been designated as a qualified infectious disease product <b>OR</b></li> <li>• Any application or supplement for a drug submitted with a priority review voucher</li> </ul>

Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics .

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

# Research Spending



SOURCES: Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2013; National Institutes of Health (NIH), Office of Budget. "History of Congressional Appropriations, Fiscal Years 2000–2012." Bethesda, MD: NIH, 2012. [http://officeofbudget.od.nih.gov/pdfs/FY12/Approp.%20History%20by%20IC\)2012.pdf](http://officeofbudget.od.nih.gov/pdfs/FY12/Approp.%20History%20by%20IC)2012.pdf) (accessed February 2013); Adapted from E. Zerhouni. "Transforming Health: NIH and the Promise of Research." Transforming Health: Fulfilling the Promise of Research. Washington, DC. November 2007. Keynote address. [www.researchamerica.org/transforming\\_health\\_transcript](http://www.researchamerica.org/transforming_health_transcript) (accessed January 2013).



# Why Regulatory Science?

# Why Regulatory Science?

- Major investments and advances in basic science are not effectively translating into products to benefit patients
  - Product development is increasingly costly, success rates remain low, and time is money
  - Development/evaluation tools and approaches have neither kept pace with nor incorporated emerging technologies
- Collaboration through partnerships can promote innovation through synergistic problem solving
- FDA's essential role recognized in the President's 2012 **National Bioeconomy Blueprint\***
  - And....it's about our nation's health and our economic well being, the health of the 25% of the economy that is fueled by the research and innovation that FDA regulates

\*[http://www.whitehouse.gov/sites/default/files/microsites/ostp/national\\_bioeconomy\\_blueprint\\_april\\_2012.pdf](http://www.whitehouse.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf)



# Regulatory Science – A Science of Evaluation and Decision Making (*FDA definition*)

- Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products. Knowledge gained from CDER science and research increases the certainty and consistency of regulatory decisions, and contributes to the development of regulatory guidance documents and best practice standards for pharmaceutical companies.



# What are we doing about this?

# FDA has a Unique Vantage Point

- Use experience to help identify targeted activities
- Serve as catalyst
- Bring stakeholders together
- Translate findings to update policies and standards

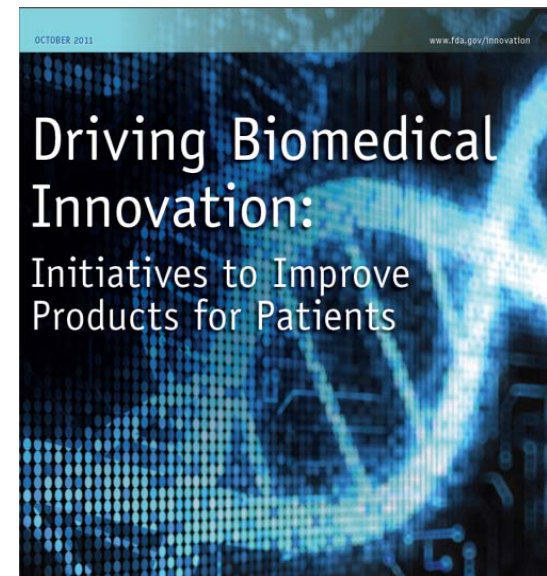
# Critical Path Initiative



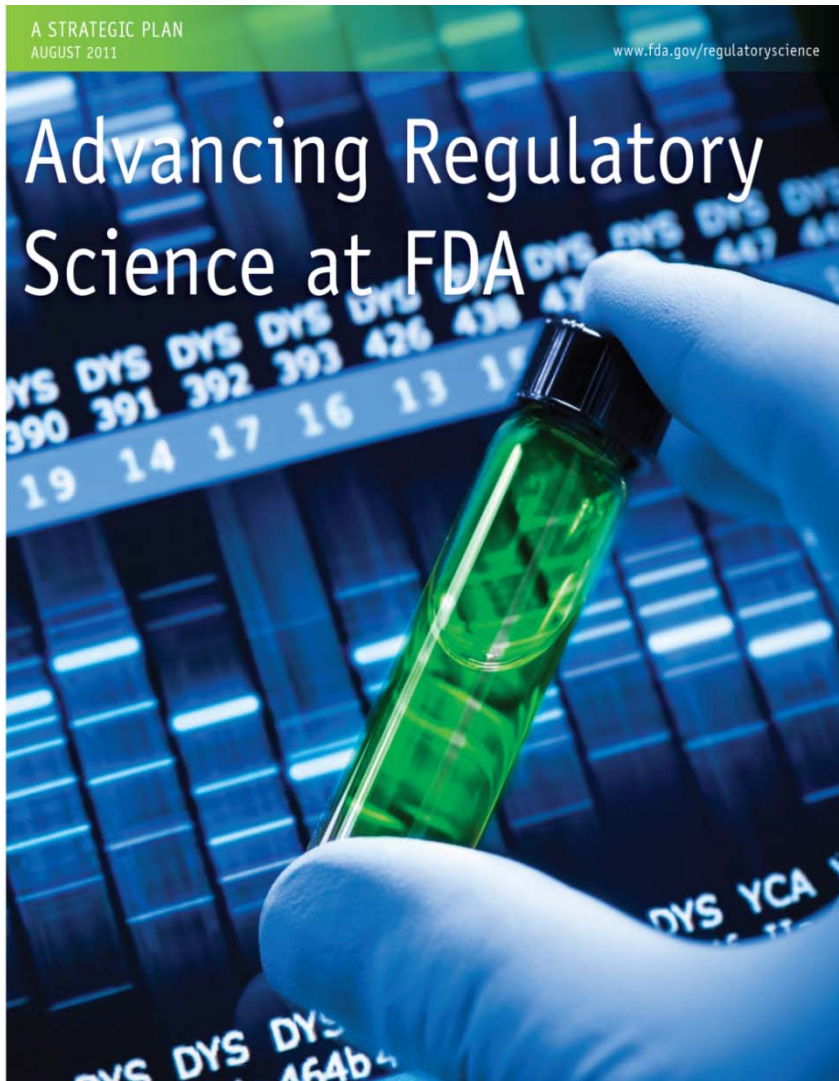
*March 2004*



*March 2006*



*October 2011*







July | 11

## Identifying CDER's Science and Research Needs Report

July 2011

The CDER Science Prioritization and  
Review Committee (SPaRC)



Center for Drug Evaluation and Research



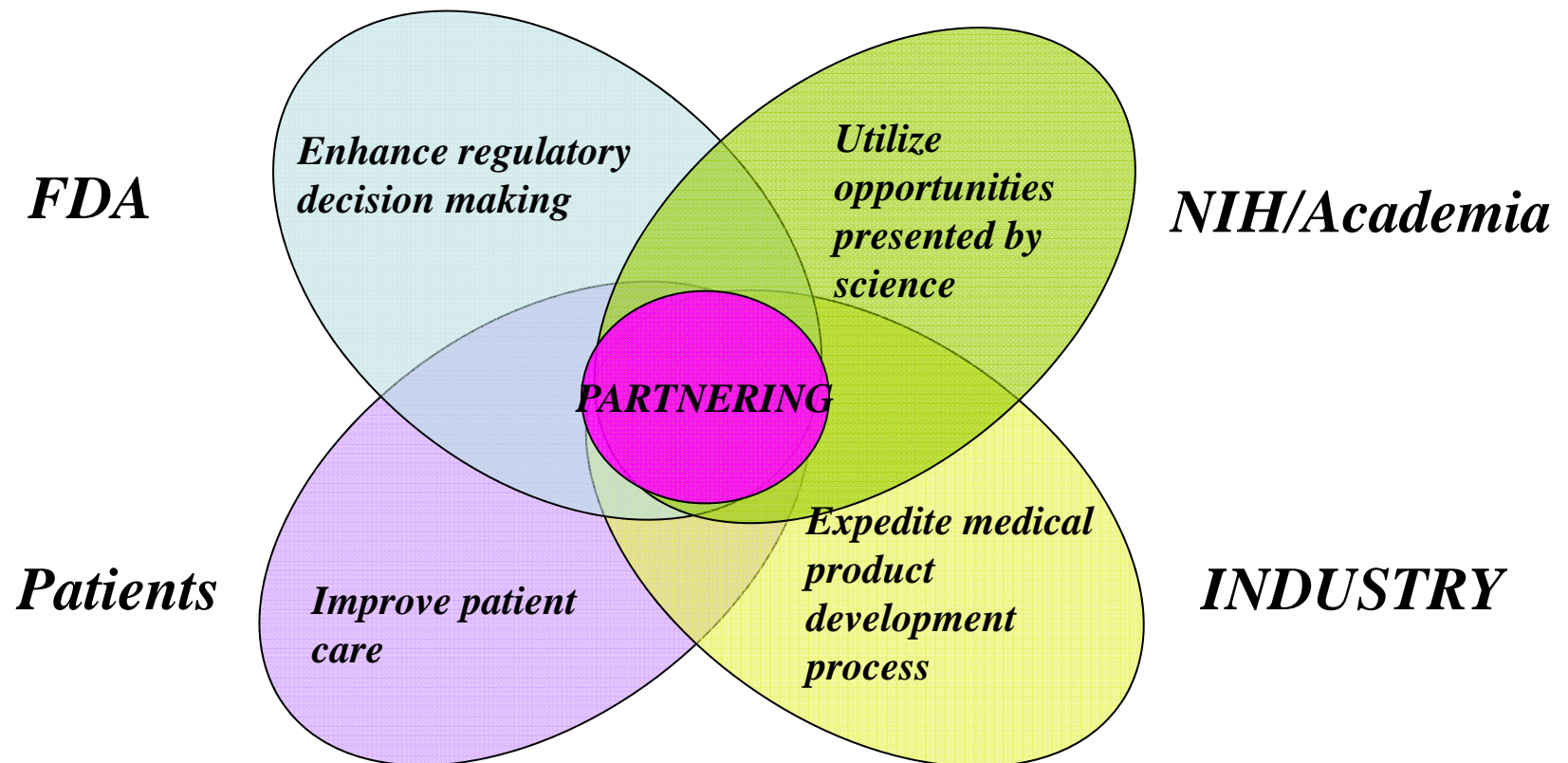
“As we work to accelerate innovation and strengthen regulatory science, it is increasingly clear that our most effective strategies are grounded in partnership.”

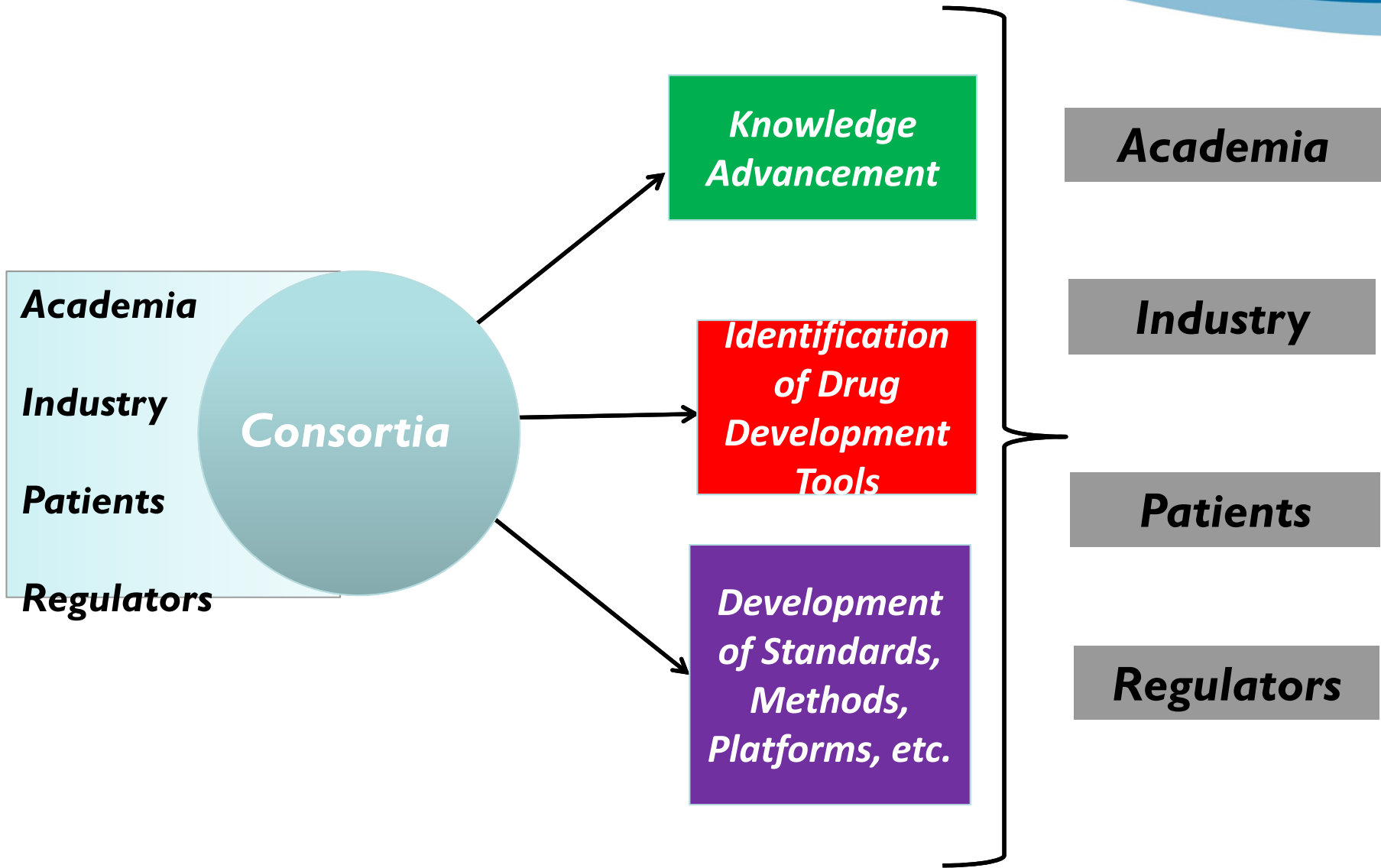
Margaret Hamburg, FDA  
Commissioner

November 10, 2011

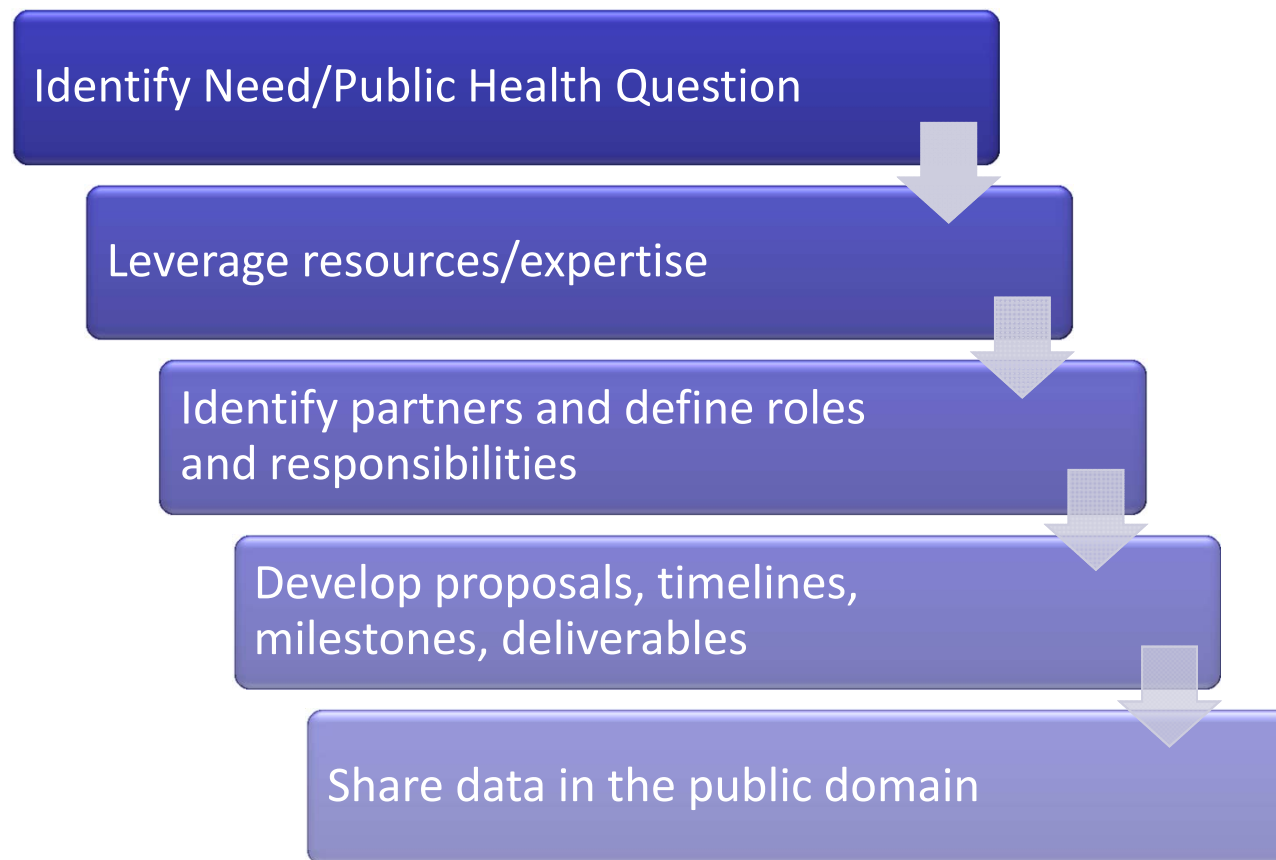


# The Power of Public Private Partnerships



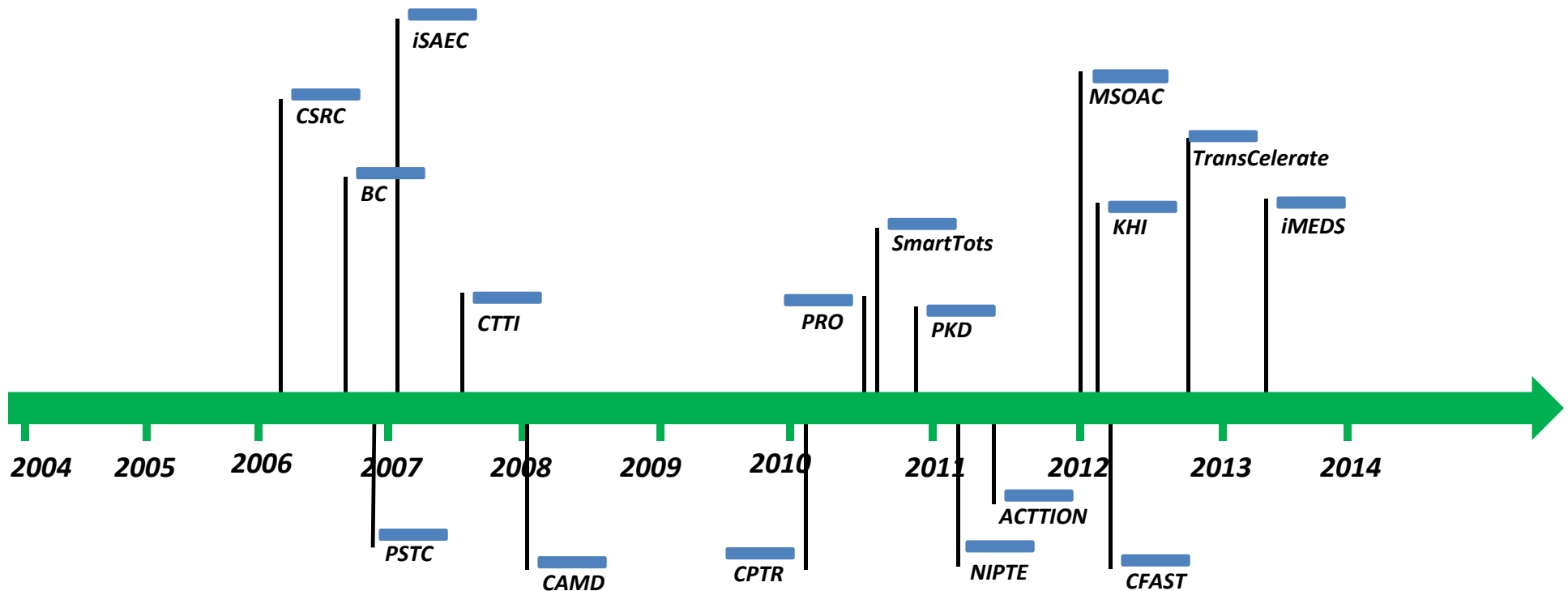


# Development of Consortia





# Examples of Consortia



*Cardiac Safety Research Consortium (CSRC), Biomarker Consortium (BC), Predictive Safety Testing Consortium (PSTC), Clinical Trials Transformation Initiative (CTTI), Coalition Against Major Disease Consortium (CAMD), Critical Path to TB Drug Regimens (CPTR) Consortium, Patient Reported Outcomes (PRO) Consortium, Polycystic Kidney Disease Outcomes (PKD) Consortium, National Institute for Pharmaceutical Technology and Education (NIPTE), Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (ACTTION), Multiple Sclerosis Outcome Assessments Consortium (MSOAC); Kidney Health Initiative (KHI), Coalition For Accelerating Standards and Therapies (CFAST), Innovation in Medical Evidence Development and Surveillance (iMEDS) Program*

# Examples of Current Efforts

**Cardiac Safety Research Consortium (CSRC)**

**CTTI  
Clinical Trials  
Transformation  
Initiative**

**Biomarker  
Consortium (BC)**

**Analgesic, Anesthetic, and Addiction  
Clinical Trial Translations, Innovations,  
Opportunities, and Networks (ACTION)  
Initiative**

**International Serious  
Adverse Events  
Consortium (iSAEC)**

**SmartTots**

**Critical Path Institute (CPath)**

**Coalition Against Major Diseases  
Consortium (CAMD)**

**Patient Reported  
Outcomes  
Consortium (PRO,  
ePRO)**

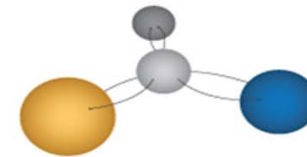
**Predictive Safety  
Testing  
Consortium  
(PSTC)**

**Coalition for Accelerating  
Standards and Therapies  
(CAFAST)**

**Multiple Sclerosis Outcome Assessment  
Consortium (MSOAC)**

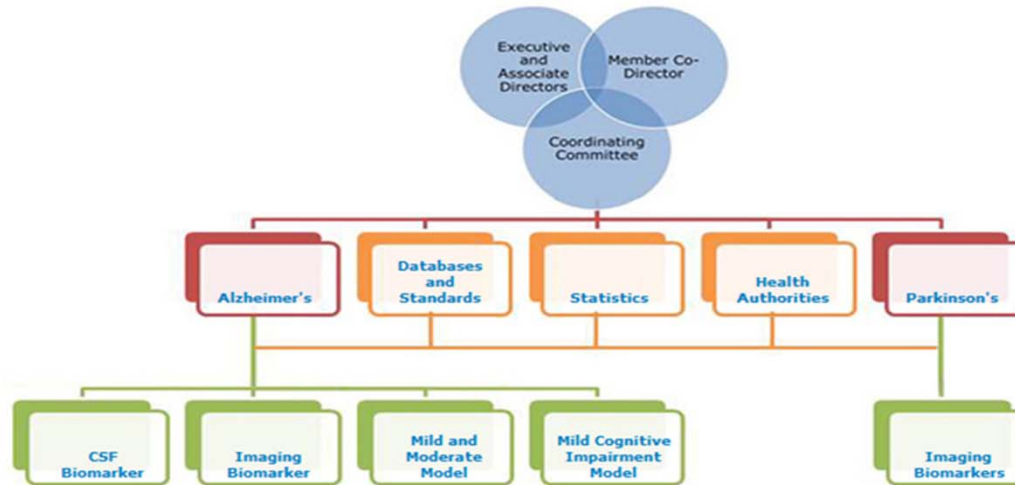
**Polycystic Kidney Disease  
Consortium (PKD)**

**Critical Path to TB Drug Regimens  
Consortium (CPTR)**



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### Consortia Structure

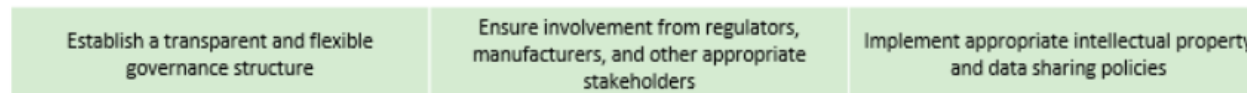


# Medical Device Innovation Consortium (MDIC)

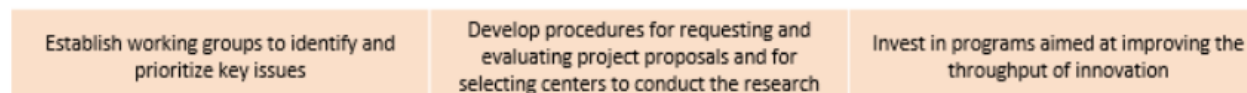
MDIC IS THE FIRST-EVER PUBLIC-PRIVATE PARTNERSHIP (PPP) CREATED WITH THE SOLE OBJECTIVE OF ADVANCING MEDICAL DEVICE REGULATORY SCIENCE.

- We are a nonprofit 501(c)(3) organization that operates in partnership with the FDA to improve the medical technology environment.
- Participation in MDIC is open to representatives of organizations that are substantially involved in medical and/or medical device research, development, treatment, or education; that are involved in the promotion of public health; or that have expertise in regulatory science.

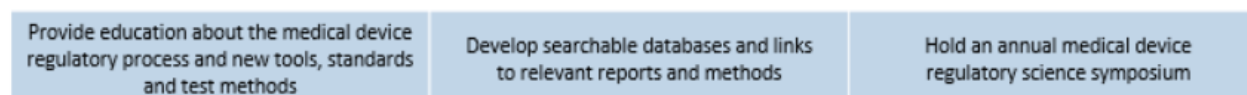
## Create A Forum For Collaboration & Dialogue



## Make Strategic Investments In Regulatory Science



## Provide Tools To Drive Innovation



# TOOL KIT DEVELOPMENT

## Reducing uncertainty...





# The need for better predictivity

“Given the high societal and economic cost of late stage drug failures because of efficacy or safety concerns, it is important to thoroughly assess the added value of predictive modeling to regulatory decision making during drug development ...”

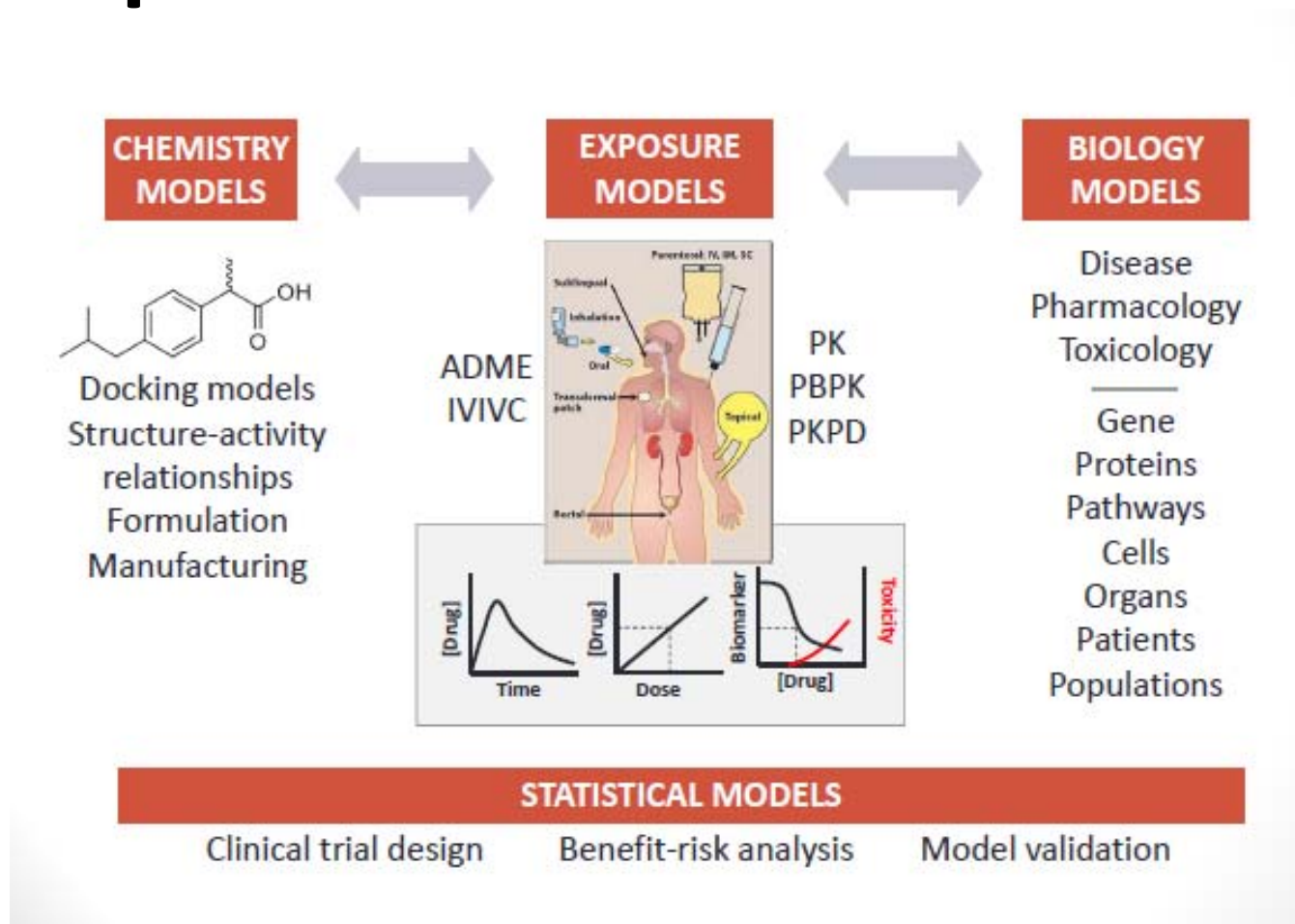
- *Identifying CDER's Science and Research Needs Report*, The CDER Science Prioritization and Review Committee, July 2011

“No branch of science can be called truly mature until it has developed some form of predictive capability.”

- Sir Peter Medawar (1915-1987)

**Knowledge management and mechanistic modeling are necessary and complementary approaches that may integrate available data and provide an analytical context in which regulatory decisions can be made.**

# In silico models in drug development

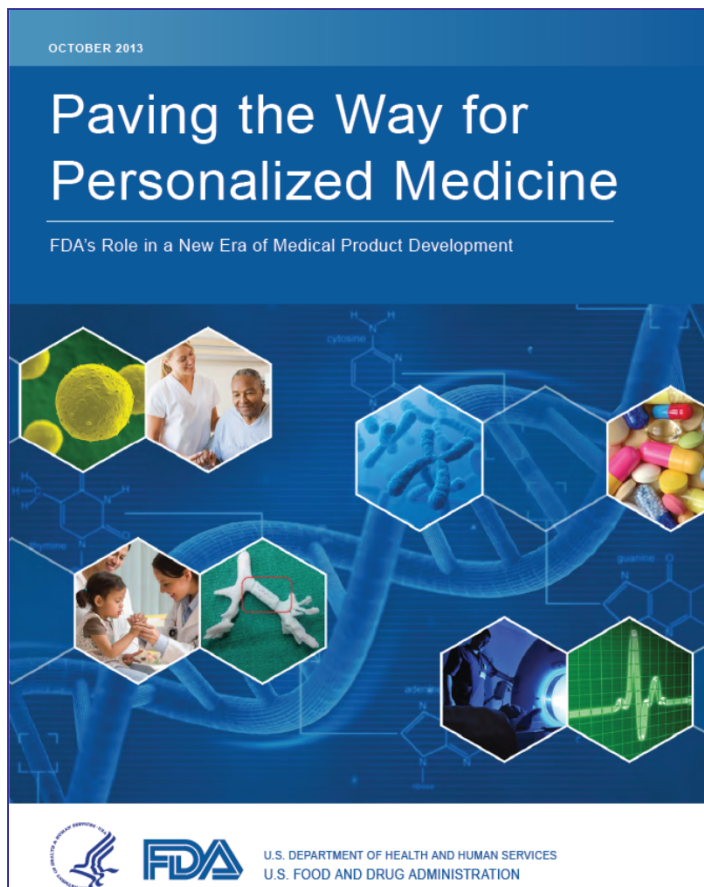


“In the computer model the only side effect was a dry mouth”



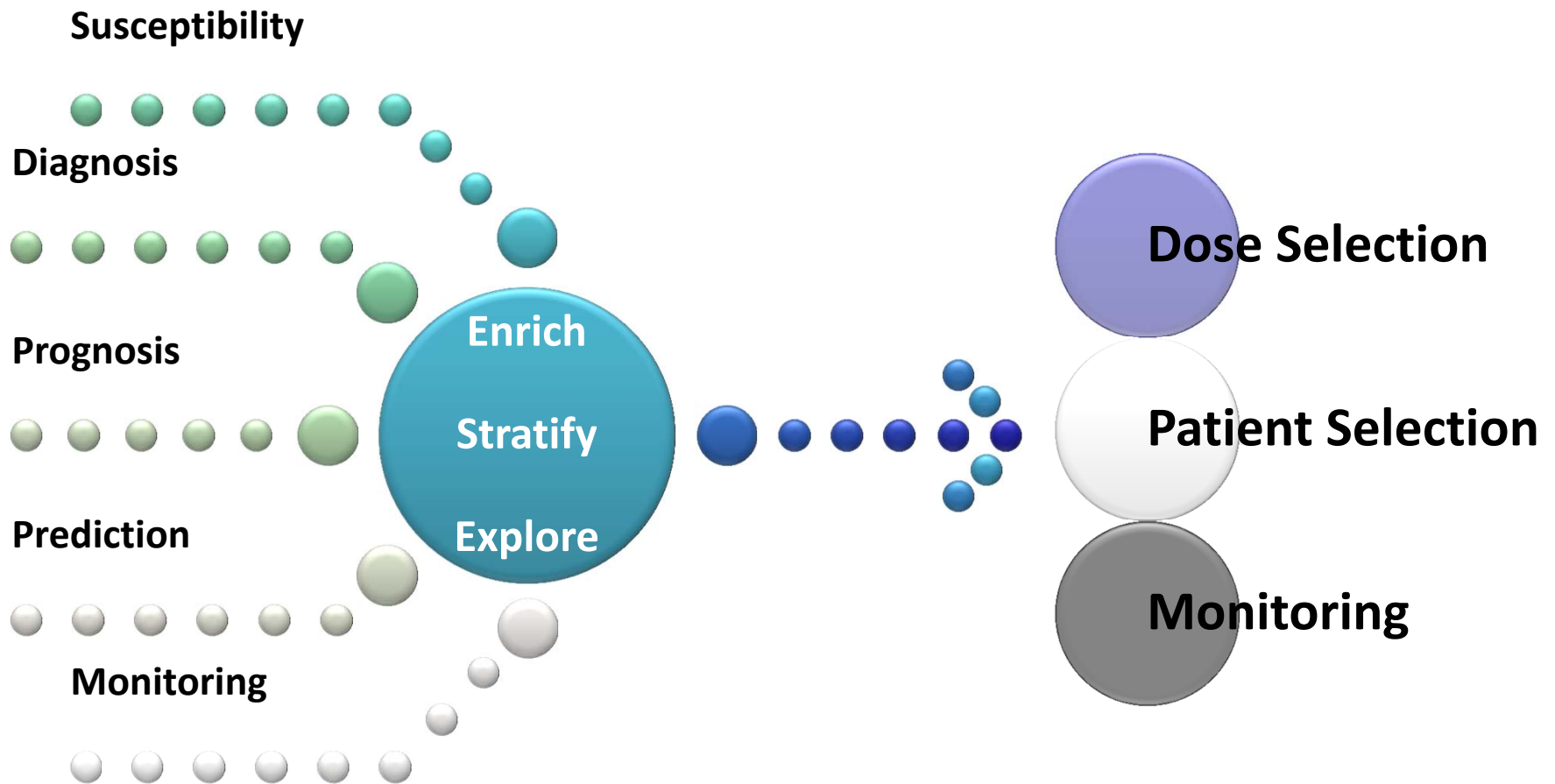


FDA has worked to respond to, anticipate and help drive scientific developments in personalized therapeutics and diagnostics



The concept of personalized medicine is not new...What is new is that advances in a wide range of fields from genomics to medical imaging...are allowing patients to be treated and monitored more precisely and effectively...

# The Role of Biomarkers in Clinical Trial Design





# Drug Development Tool Qualification Program

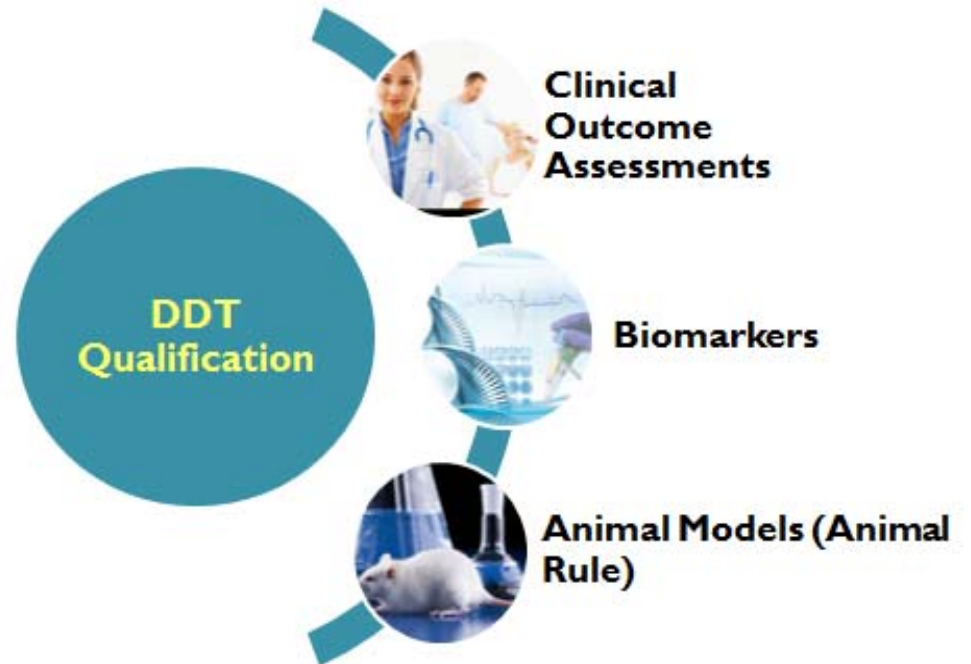
**Guidance for Industry  
and  
FDA Staff**

**Qualification Process for  
Drug Development Tools**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

January 2014  
Final





# FDA-Qualified DDTs

DDT Type	Name	Submitter	Qualification Date
Biomarker	Seven Biomarkers of Drug Induced Nephrotoxicity in Rats	Predictive Safety and Testing Consortium (PSTC)	4/14/2008
Biomarker	Nonclinical Qualification of Urinary Biomarkers of Nephrotoxicity	International Life Sciences Institute(ILSI)/Health and Environmental Sciences Institute (HESI)	9/22/2010
Biomarker	Nonclinical Qualification of Circulating Cardiac Troponins T and I as Biomarkers of Cardiac Morphologic Damage	P J O'Brien, WJ Reagan, MJ York and MC Jacobsen	2/23/2012
COA/PRO	Exacerbations of Chronic Pulmonary Disease Tool (EXACT)	Evidera	1/09/2014
Biomarker	Galactomannan for Invasive Aspergillosis	Mycoses Study Group	10/24/2014



# How we communicate...

# How We Routinely Communicate....

- **Formal Meetings with FDA:** Formal PDUFA meetings fall into one of three types – Type A, Type B, or Type C
- **Guidance**
- **Workshops/Seminars/Advisory Committee Meetings**
- **Open Public Hearings**

**But we also have become more creative....**

The more we know about rare diseases, the more likely we are to find safe and effective treatments

Posted on October 23, 2014 by FDA Voice

By: Janet Woodcock, M.D.



You may be inclined to think that rare diseases affect only a tiny fraction of the more than 320 million people in our country. That's true about a single rare disease. But there are about 7,000 rare diseases. If you add them all together, there are about 30 million – or almost one in ten – people in the U.S. with some form of rare disease. Sadly, although great progress has been made in some areas, many of these people have no FDA approved drug to cure their condition, help them feel better, or even slow the disease's progress.

That's why I am pleased about FDA's support for an exciting new tool researchers are using to study rare diseases. It's a new database with information about

the diseases' "natural history."

"Natural history" is the scientific term to describe how a disease would progress with no treatment. Since a disease can affect different people differently, scientists must study many cases of a disease to acquire a thorough understanding of its natural history. Well-conducted studies of natural history can yield vital information about:

- Biomarkers, demographic, genetic, and environmental variables that correlate with the course and stages of the disease;
- Identification of patient subpopulations with different characteristics and effects of the disease;
- Patient perspectives on what aspects of disease are most important to treat; and,
- How to quantify those aspects so that they can serve as useful outcome measures for clinical trials.

But when it comes to rare diseases, their natural histories frequently are not fully understood because there are simply not enough cases that have been observed and studied. This lack of knowledge limits researchers' ability to study rare diseases and develop new treatments. Knowledge of natural history is essential for developing more efficient clinical trial designs. It also could help reduce the length and cost of drug development and, possibly, contribute toward greater predictability of clinical development programs.

Recently The National Organization for Rare Diseases (NORD), has teamed up with the patient advocacy group that represents people with the rare disease known as Von Hippel

## twitter.com/US\_FDA





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## For Industry

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- Prescription Drug User Fee Act (PDUFA)



### User Fees

Prescription Drug User Fee Act (PDUFA)
PDUFA Legislation and Background
PDUFA Annual Reports and Plans
PDUFA Performance Evaluation Reports
PDUFA Meetings
PDUFA User Fee Cover Sheet
Additional Information (PDUFA)
Guidance Documents and MaPPs (PDUFA)
Letters (PDUFA)
Regulations and Federal Register Documents (PDUFA)

## Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2015

Note: Unless otherwise noted, this schedule is subject to change. Meeting information for each disease area will be posted as it becomes available. More information on the selection of disease areas for Patient-Focused Drug Development can be found in the Federal Register Notice (PDF - 111KB) published on April 11, 2013.

### Meetings Planned for FY 2014 and FY 2015

- **Sickle cell disease:** February 7, 2014
  - [Meeting Information](#)
- **Fibromyalgia:** March 28, 2014
  - [Meeting Information](#)
- **Pulmonary Arterial Hypertension:** May 13, 2014
  - [Meeting Information](#)
- **Neurological manifestations of inborn errors of metabolism:** June 10, 2014
  - [Meeting Information](#)
- **Hemophilia A, Hemophilia B, von Willebrand disease, and other heritable bleeding disorders:** September 22, 2014
  - [Meeting Information](#)
- **Idiopathic Pulmonary Fibrosis Patient-Focused Drug Development:** September 26, 2014
  - [Meeting Information](#)
- **Patient-Focused Drug Development Public Meeting and Scientific workshop on Female Sexual Dysfunction:** October 27-28, 2014
  - [Meeting information](#)
- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Irritable bowel syndrome, gastroparesis, and gastroesophageal reflux disease with persistent regurgitation symptoms on proton-pump inhibitors
- Parkinson's disease and Huntington's disease

# Critical Path Innovation Meetings

- New CDER program
- Promotes understanding challenges in drug development and innovative strategies to address them
- Potential biomarkers not ready for DDT Qualification Program
- Natural history study design and implementation
- Emerging technologies or new uses of existing technologies
- Novel clinical trial designs and methods
- Nonbinding on FDA and other participants
- No advice on specific approval pathways





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# Critical Path Innovation Meetings

## Guidance for Industry

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Alicia B. Stuart 301-796-3852.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

October 2014  
Procedural

---



# Guidance for Industry

## Adaptive Design Clinical Trials for Drugs and Biologics

### *DRAFT GUIDANCE*

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For questions regarding this draft document contact Robert O'Neill at 301-796-1700, Marc Walton at 301-796-2600 (CDER), or the Office of Communication, Outreach and Development (CDER) at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Center for Biologics Evaluation and Research

February 2010  
Clinical/Medical

# Guidance for Industry

## Non-Inferiority Clinical Trials

### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Robert Temple at 301-796-2270, O'Neill at 301-796-1700 (CDER), or the Office of Communication, Outreach and Development (CDER) at 301-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

March 2010  
Clinical/Medical

# Guidance for Industry

## Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301-827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)  
December 2012  
Clinical/Medical



# INFORMATICS



***A standards based end-to-end fully electronic receipt, review, and dissemination environment***



# Challenges of the current state of data submissions...



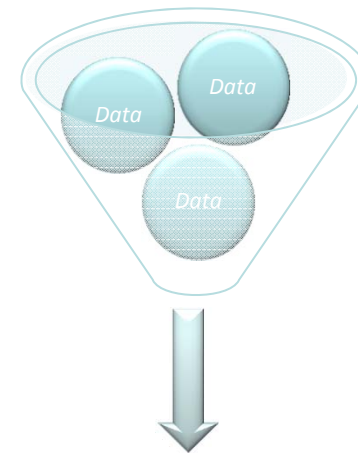
***Massive amounts of clinical research data in extremely disparate formats***

*Using a variety of proprietary standards*

***Extremely difficult to do cross-study and application reviews***

# Standardized Data

- Data standards are the foundational prerequisite to success
  - Develop re-useable tools and analytic capabilities that automate common assessments and support data exploration
  - Allow us to integrate data automatically with the Clinical Trial Repository (Janus)
  - Facilitate data integration



# Guidance for Industry

## Providing Regulatory Submissions in Electronic Format — Standardized Study Data

### DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Ron Fitzmartin at 301-796-5333, (CBER) Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

February 2014  
Electronic Submissions  
Revision 1

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FDA encourages the sponsor or applicant to discuss the waiver request prior to or at the pre-IND meeting with the appropriate review division in CDER or CBER and submit the request in writing prior to submitting the IND.<sup>11</sup> FDA will notify the sponsor or applicant in writing as to whether the waiver request is denied or granted.

### E. When will electronic submission of standardized study data be required?

For additional information on how FDA intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, including timetable for implementation, please see the 745A Implementation Guidance.

#### 1. Initial Timetable for the Implementation of Electronic Submission Requirements

After we publish a notice of availability of the final guidance in the *Federal Register*, all studies with a start date<sup>12</sup> twenty-four months after the *Federal Register* notice must use the appropriate FDA-supported standards, formats, and terminologies specified in the Data Standards Catalog (see section II.C) for NDA, ANDA, and certain BLA submissions. Study data contained in certain IND submissions must use the specified formats for electronic submission in studies with a start date thirty-six months after the *Federal Register* notice of availability.

The following is an example of how a new electronic submission requirement would be implemented:

*On November 15, 2016, FDA publishes a Federal Register notice announcing the availability of the final eStudy Data Guidance. For studies with a start date after November 15, 2018, sponsors or applicants must use the appropriate FDA-supported standards, formats and terminologies specified in the Data Standards Catalog for NDA,*

<sup>11</sup> If no pre-IND meeting is held, sponsors or applicants are encouraged to contact the review division prior to the pre-BLA meeting to discuss a waiver request.

<sup>12</sup> For purposes of this guidance, the study start date is the earliest date of informed consent among any subject that enrolled in the study. For example, see Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTTC), <http://www.cdisc.org>.

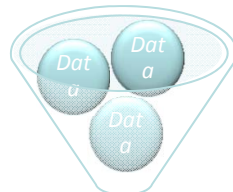
# Facilitating Modernization of the Regulatory Review Process

## CDER Computational Science Center



# Intersection of data, tools and technology

*Standardized Data*

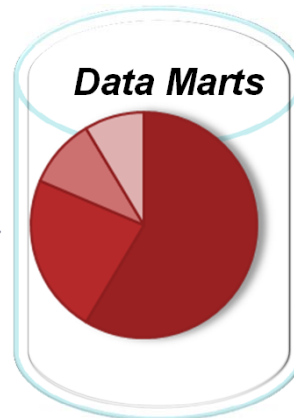


*Repositories for Electronic Data*

*Data Validation*



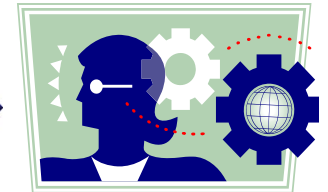
*Data Warehouse*



*Analytic Tools*



*Reviewer Decisions*





# Objective – Improve Review Effectiveness

- Provide various analytic tools and views to improve the effectiveness and efficiency of regulatory review:
  - Support the ability to answer regulatory related questions involving large amounts of data
  - Improve reviewer efficiency by providing automated analysis
  - Identify coding problems that may impact the interpretation of results







# **BUILDING HUMAN CAPITAL**

## **Training and Attracting the Best and Brightest....**

# Opportunities at FDA

- Fellowships
  - Commissioner's Fellows
  - ORISE
  - Alzheimer's Fellowship
- Sabbaticals
- Special Government Employees
- Advisory Committee Members
- Employment





- Home
- Food
- Drugs
- Medical Devices
- Radiation-Emitting Products
- Vaccines, Blood & Biologics
- Animal & Veterinary
- Cosmetics
- Tobacco Products

## About FDA



Home > About FDA > Working at FDA > Student, Fellowship, and Senior Scientist Programs

### Working at FDA

▶ Student, Fellowship, and Senior Scientist Programs

Undergraduate and Graduate Student Programs A-Z

Fellowships for Post-Graduates A-Z

Faculty and Senior Scientist Programs A-Z

Federal Information Privacy Internship Program

Graduate Certificate in Regulatory Science (NCTR)

Student Intern Program (CDRH-OSEL)

Summer Student Research Program (NCTR)

# Student, Fellowship, and Senior Scientist Programs



Whether you're an undergraduate looking to pursue a career in science, a graduate science student seeking experience in regulatory science, a postgraduate looking for fellowship opportunities, or a senior scientist pursuing research experience in your field of expertise, FDA offers you many paths to learning about the exciting field of regulatory science.

Programs FDA offers through our different product centers and offices.

- Undergraduate and Graduate Student Programs
- Fellowships for Post-Graduates
- Faculty and Senior Scientist Programs
- Student, Fellowship, and Senior Scientist Programs A - Z

<http://www.fda.gov/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/default.htm>

U.S. Department of Health & Human Services
A A A

U.S. Food and Drug Administration  
Protecting and Promoting *Your* Health

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## About FDA

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Working at FDA

- Fellowship, Internship, Graduate, & Faculty Programs
- Commissioner's Fellowship Program
- Application
- Project and Course Details
- Frequently Asked Questions
- Class of 2013 Preceptors by FDA Regulatory Science Priority Areas
- Class of 2013 Preceptors by Center/Office/Initiative
- Class of 2014 Preceptors by FDA Regulatory Science Priority Areas and by FDA Product Center and Office
- Program Participant Testimonials
- Publication and Presentation Citations

Resources for You

### Commissioner's Fellowship Program



FDA invites outstanding healthcare professionals, scientists, and engineers to apply to its two-year Fellowship Program, where they will receive regulatory science training and the chance to conduct cutting-edge research on targeted scientific, policy, or regulatory issues under the mentorship of an FDA senior scientist.

*Please note: The application period for the Class of 2013 is over. Applications were accepted from April 16, 2013 through May 25, 2013 5 p.m. EST. Letters of recommendation were due June 4th by 5 p.m. EST.*

#### Class of 2014 Application Process Key Dates

Application period for the CFP Class of 2014:

- Applications will be accepted from **April 16, 2014 through May 26, 2014 5 p.m. EST**. Letters of recommendation will be due **June 4th by 5 p.m. EST**. [Application website](#).
- Late June/July – Interviews

### Spotlight

- [Office of Scientific Professional Development](#)
- [Chief Scientist Discusses Fostering Scientific Talent at the FDA](#)
- [Interested in a Science Career at FDA? Our Web Portal Opens the Door](#)

### Class Overviews

- [The Class of 2008 Overview \(PDF - 1.3MB\)](#)
- [The Class of 2009 Overview \(PDF - 4.6MB\)](#)
- [The Class of 2010 Overview \(PDF - 3MB\)](#)
- [The Class of 2011 Overview \(PDF - 2.1MB\)](#)
- [The Class of 2012 Overview \(PDF - 1.7MB\)](#)



## Building Scientific Capacity

### Alzheimer's Disease Regulatory Science Fellowship

The Reagan-Udall Foundation for the FDA (RUF), in partnership with the Alzheimer's Association and the U.S. FDA, Division of Neurology Products (DNP), is offering a two-year Regulatory Science Fellowship focused in the area of Alzheimer's Disease. The fellow will have an unparalleled opportunity to receive training in regulatory science at the FDA, gaining valuable experience and knowledge working with the DNP.

#### Background and Goals:

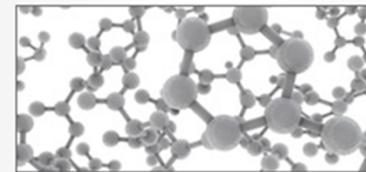
There are currently no drugs available to prevent Alzheimer's Disease (AD) or even slow its course. A recent series of high-profile late stage drug failures have led those in Alzheimer's research to begin to rethink many of the underlying hypotheses related to drug development including therapeutic targets, trial design, appropriate patient populations, biomarkers, and clinical outcome measures. Patient groups, academic researchers, pharmaceutical manufacturers, and other stakeholders have formed a wide array of consortia and initiatives to examine many of these issues. A primary goal of this fellowship is to facilitate communication and collaboration between DNP and the various AD stakeholders and to help identify opportunities for DNP participation in relevant partnerships and activities to address critical issues in AD research and product development.

#### Fellowship Activities:

The fellow will work with DNP to identify opportunities advance the development of treatments for Alzheimer's and related diseases. Activities will include:

- Develop a comprehensive understanding of the regulatory review process.
- Learn current challenges facing Alzheimer's drug development and regulation.

### Building Scientific Capacity



#### Learn More About Our Work

The Reagan-Udall Foundation leads and collaborates on programs, projects and other initiatives that advance its mission in support of the FDA. [Find Out More »](#)



#### Learn About Our Commitment to Regulatory Science

Separate of the FDA, the Foundation identifies and supports research and collaborations that can help achieve a more efficient development and approval process while ensuring product safety. [Find Out More »](#)

Stay Updated on the Latest FDA Regulatory Science Initiatives.



# Research Participation Programs at the U.S. Food and Drug Administration (FDA)

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## Welcome to the ORISE Research Participation Programs at the U.S. Food and Drug Administration (FDA).

On this site you will find information about these educational and training programs, designed to engage students and recent graduates in the research performed at FDA. Whether you are interested in joining the programs, are a current participant, or are an FDA employee sponsoring or mentoring participants, our site has valuable information for you. We welcome you to learn more about our programs by selecting the category that best describes you.





# Institute of Medicine Report Reinforces Need for Regulatory Science Curricula

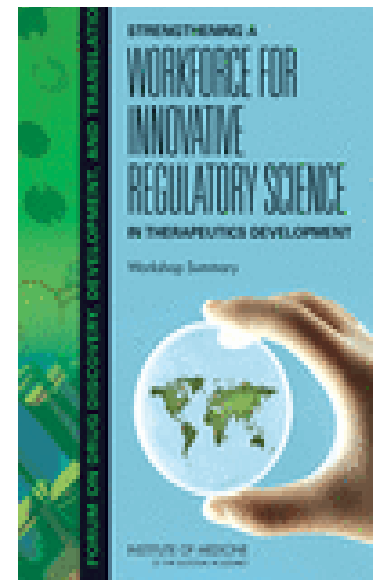
In 2010, the IOM's Forum on Drug Discovery, Development, and Translation held a workshop that examined the state of regulatory science and considered approaches to enhance it. As a follow-up to that workshop, the Forum held a workshop on September 20-21, 2011, to provide a format for establishing a specific agenda to implement the vision and principles relating to a regulatory science workforce and infrastructure as discussed in the 2010 workshop. At the workshop, speakers considered opportunities and needs for advancing innovation in the discipline of regulatory science for therapeutics development through an interdisciplinary regulatory science workforce and examined specific strategies for developing a discipline of innovative regulatory science through the development of a robust workforce within academia and industry and at FDA. This document summarizes the workshop.

## Report



### Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development – Workshop Summary

Released: December 21, 2011  
 Type: Workshop Summary  
 Topic: Biomedical and Health Research  
 Activity: Forum on Drug Discovery, Development, and Translation  
 Board: Board on Health Sciences Policy



## No institution currently has ownership of a regulatory science initiative

- Possible to create modules of course content to be made available to university programs
- University systems might be networked either by centers of excellence or modeled after CTSA's
- Blended learning, distance learning possible
- National and international impacts, especially for new regulators and new scientists entering the field
- Our academic centers currently do not support the research studies outside the NIH model

# ***FDA Centers of Excellence in Regulatory Science and Innovation (CERSI)***

***Collaborative Research, Scientific Exchanges, and Professional Development***

*Developing network of regulatory science centers to enhance FDA research and science infrastructure and resources, including robust staff training and education system nationwide.*

<http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm301667.htm>



## First Two CERSIs established in 2011



[www.cersi.umd.edu](http://www.cersi.umd.edu)

**University of Maryland: CBER,  
CDER, & CDRH**



**Georgetown University:  
CBER & CDER**

## Two New CERSIs established in 2014



**Stanford University**

**UCSF and Stanford University:  
CBER, CDER, CDRH**



**Johns Hopkins University:  
CBER, CDER, CDRH, & CFSAN**

PERSPECTIVES

have to learn to use disparate collections of apps, each serving a different purpose.

Despite the challenges, we have found in our own organization that optimism exists, that the regulatory environment is navigable, that the technical and quality systems controls are achievable, and that digital means provide an immense opportunity to reach patients and to improve their health care.

**CONFLICT OF INTEREST**

The authors declared no conflict of interest.

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1. Kamenew, D. Regulating medical apps: which ones and how much? *BMJ* 347:f6009. <http://www.bmj.com/content/347/bmj.f6009> (8 October 2013).
2. Dwyer, L., Heldenbrand, S., Anderson, F., Guldem, P.D., & Martin, B.C. Smartphone medication adherence apps: potential benefits to patients and providers. *J. Am. Pharm. Assoc.* 53, 172–181 (2013).
3. US Food and Drug Administration, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research. Mobile medical applications: guidance for industry and Food and Drug Administration staff. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf> (25 September 2013).

## The Role of Academic Medical Centers in Advancing Regulatory Science

RJ Meyer<sup>1</sup>

**The US Food and Drug Administration (FDA) has oversight of an increasingly complex array of therapeutic and scientific advances, as well as an expanded mission that now includes enabling innovation. This complex mission necessitates access to and understanding of relevant scientific expertise in what is commonly called “regulatory science.” Academic medical centers have much of this relevant expertise, and there is an increasing need and opportunity for the FDA to engage with them to shape the regulatory science agenda.**

*“A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty.”*

—Winston Churchill

Several important trends are foundational to a discussion of the role of academic medical centers in regulatory science. First, the pharmaceutical industry continues to struggle with a changing business model that stems, at least in part, from a continuing decline in their returns from research and development (R&D).<sup>1</sup>

One consequence of this trend is that many large companies have dramatically reduced internal R&D efforts, replacing them with external partnerships and/or therapeutic candidate acquisitions, which often involve academia.<sup>2</sup> This external R&D model has elevated academic institutions into an even more critical role in translational medical research. As pharma has struggled with a failing business model, the FDA has broadened its mission statement to include “advancing the public health by helping to speed

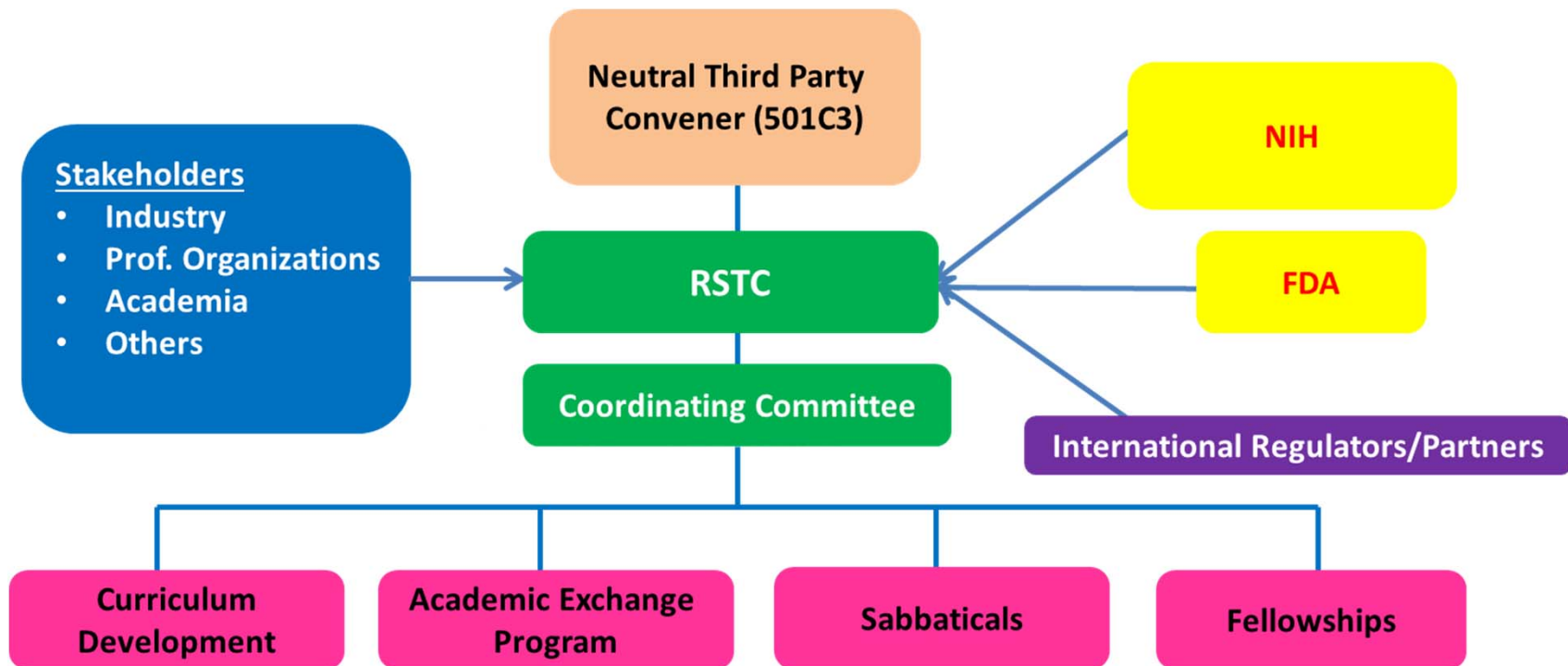
innovations that make medicines more effective, safer, and more affordable.”<sup>3</sup> This expanded mission has increased the need for the FDA to bring to bear the best science available to inform its regulatory decisions and oversight. That in turn has led the agency to focus on promoting excellence in regulatory science.

Although regulatory science is defined variably, the FDA’s definition characterizes it as “the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.”<sup>4</sup> This definition encompasses the need for the FDA to fully understand the science it is regulating, as well as the timely incorporation of scientific advances in evaluative methods, as it strives to regulate evolutionary and revolutionary advances in therapeutics.

Given the enormous number of scientific advances in all aspects of medical therapeutics, it is critical that the FDA have access to the best expertise from a broad array of scientific disciplines. Although it might be considered ideal for the agency to have that expertise internally, this is neither practical nor feasible given the broad array of applicable science and the pace at which it is changing. Additionally, cultivating substantive regulatory knowledge in its scientific staff is itself in tension with their scientific currency, as FDA employees have only limited time for professional education beyond their daily workload. For these reasons, the FDA must effectively leverage outside expertise to complement its scientific and educational capabilities. Academic medical centers, seeking to educate researchers in the interplay between regulation and medical sciences, are developing advanced-degree programs in regulatory sciences. These programs represent an important opportunity for the FDA to forge more effective academic relationships. However, some universities are also evolving to provide a broader array of therapeutic development capabilities (through efforts such as the Academic Drug Discovery Consortium, <http://www.addconsortium.org>), making them more subject to regulatory oversight from the FDA and thereby raising conflict-of-interest issues should the agency also view them as academic partners. Nonethe-

<sup>1</sup>Virginia Center for Translational and Regulatory Sciences, University of Virginia School of Medicine, Charlottesville, Virginia, USA. Correspondence: RJ Meyer (rjm7cd@eservices.virginia.edu) doi:10.1038/clpt.2014.33

# New Proposal—Regulatory Science Training Consortium

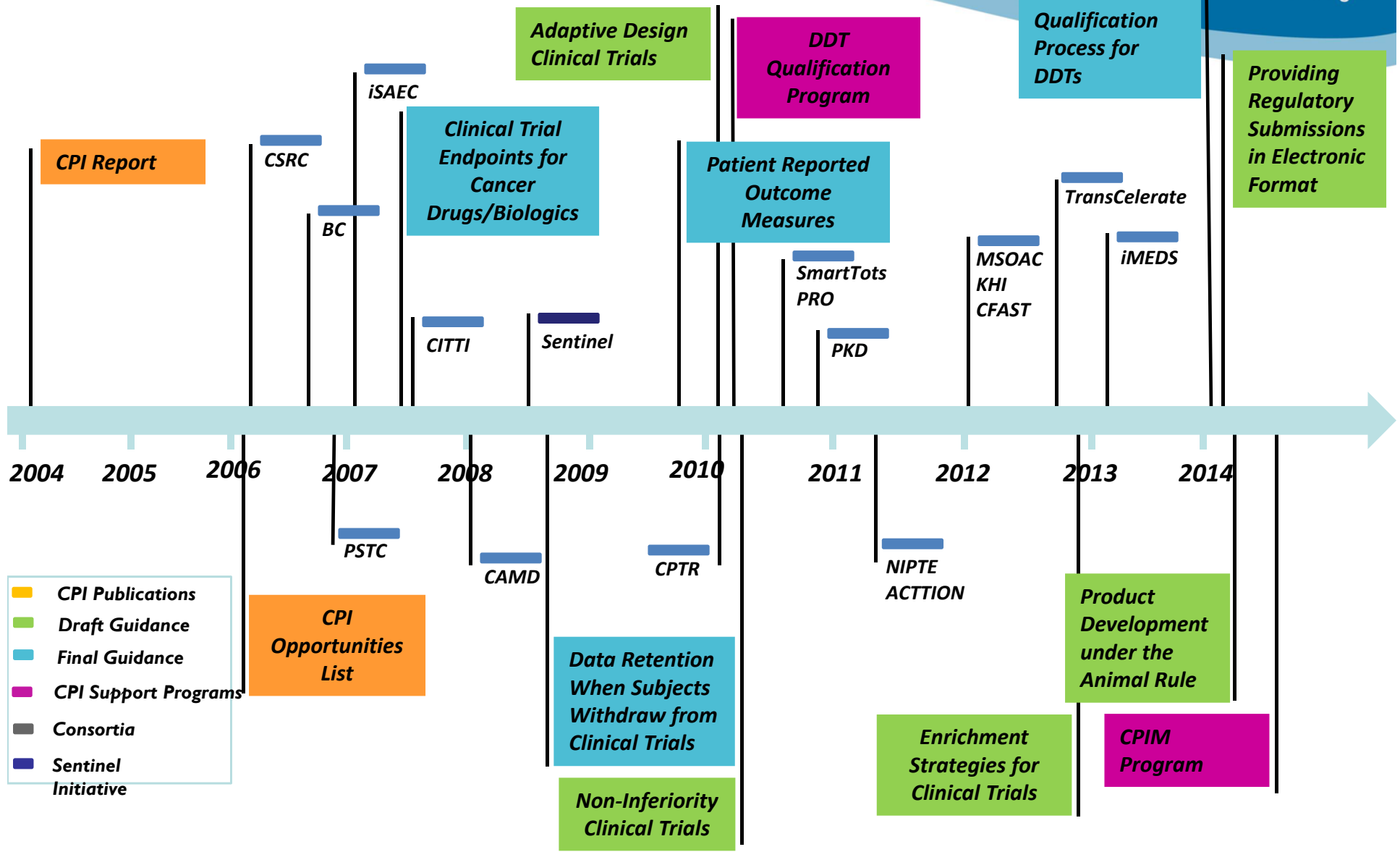




# (Some) Training Areas of Focus

Develop training modules to support regulatory science education in key areas including:

- Statistics, CMC, pharmtox, clinical pharmacology, clinical trial design and analysis methods to support the development of biologics, drugs and medical devices
- PRO development, endpoints to support the development of biologics, drugs and medical devices
- subtopics of rare diseases
- pediatrics, elderly, and other vulnerable populations
- drug-device interactions
- investigator responsibilities (regulatory, legal, ethical)
- microbiological, chemical and analytical methods to support food safety



# Moving Forward...



# Summary

- Regulatory Science is an emerging field of value for medical professionals
- We need to partner with our academic colleagues to enhance the development of new approaches to enhance medical product development
- Early communication and education is key to efficient development
- There are many opportunities to work with FDA



## To Contact Us:

*Office of Translational Sciences/CDER/FDA*  
*301-796-2600*

*[shaavhree.buckman-garner@fda.hhs.gov](mailto:shaavhree.buckman-garner@fda.hhs.gov)*



OFFICE *of* TRANSLATIONAL SCIENCES  
Where Innovation Meets Implementation



# Back Up Slides



# Early communication: A key to drug development and approval times

- *For all new drug approved between 2010-2012, the average clinical development time was 3 years faster when a pre-IND meeting was held than it was for drugs approved without a pre-IND meeting.*
- *For orphan drugs used to treat rare diseases, the development time for products with a pre-IND meeting was 6 years shorter on average (~ half) than for orphan drugs without a pre-IND meeting.*

*Posted on February 6, 2013 by FDA Voice (Anne Pariser, M.D.)*



# The Sentinel Initiative

National Strategy for Monitoring Medical Product Safety

May 2008



Department of Health and Human Services  
U.S. Food and Drug Administration  
Office of Critical Path Programs  
[www.fda.gov/oc/initiatives/criticalpath/](http://www.fda.gov/oc/initiatives/criticalpath/)

<http://www.fda.gov/oc/initiatives/advance/reports/report0508.html>

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Cover photos: top left Centers for Disease Control and Prevention (CDC); subsequent photos Getty Images