



FDA

**U.S. FOOD & DRUG
ADMINISTRATION**

CENTER FOR DRUG EVALUATION & RESEARCH



**CAMD ANNUAL REGULATORY SCIENCE WORKSHOP
OCTOBER 19, 2016**

A CASE FOR INNOVATION, PROGRESS, AND OPTIMISM

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OVERVIEW



- **The Past**
- **The Present**
- **Opportunities and Challenges**
- **The Future**



The Past...

Where have we been?



CRITICAL PATH: WHAT WE SAID IN 2004

FDA

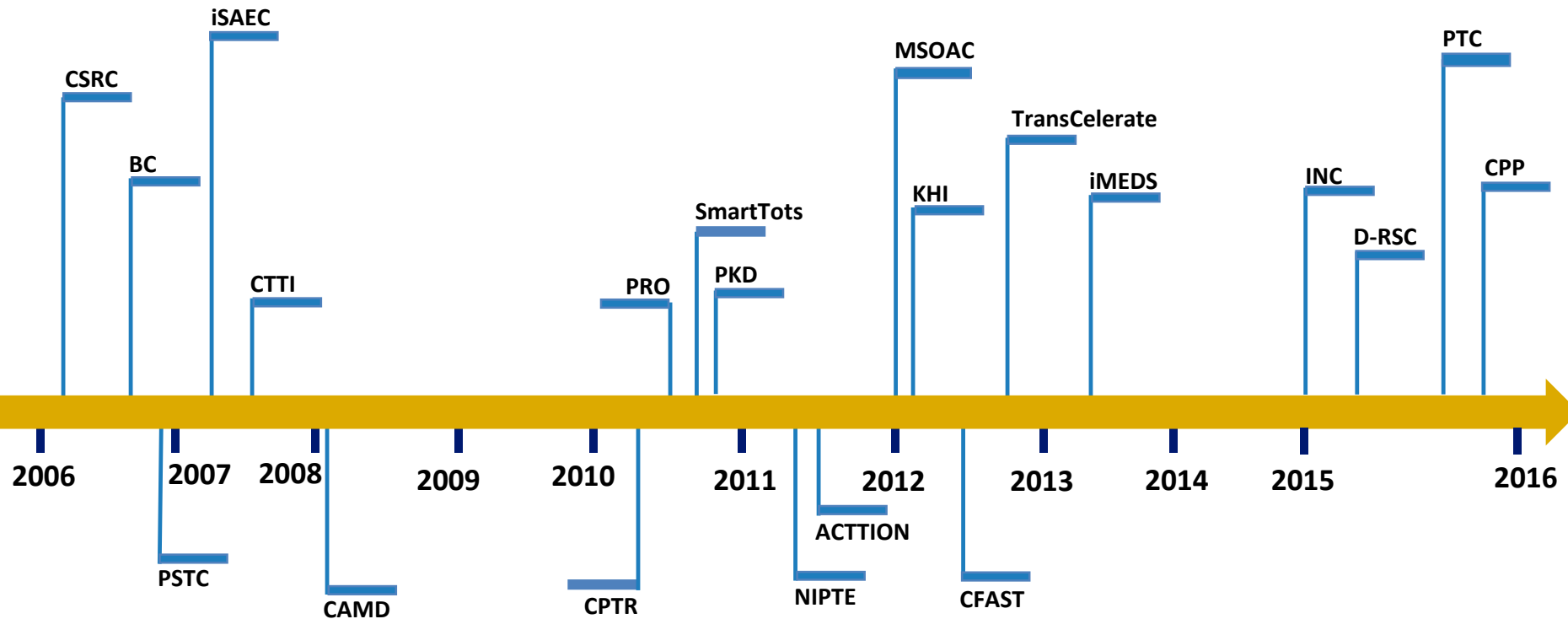
A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to **improve predictability and efficiency** along the critical path from laboratory concept to commercial product. We need **superior product-development science** to address these challenges — to ensure that basic discoveries turn into new and better medical treatments. We need to **make the effort required to create better tools for developing medical technologies**. And we need a knowledge base built not just on ideas from biomedical research, but on **reliable insights into the pathway to patients**.

Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, March 2004



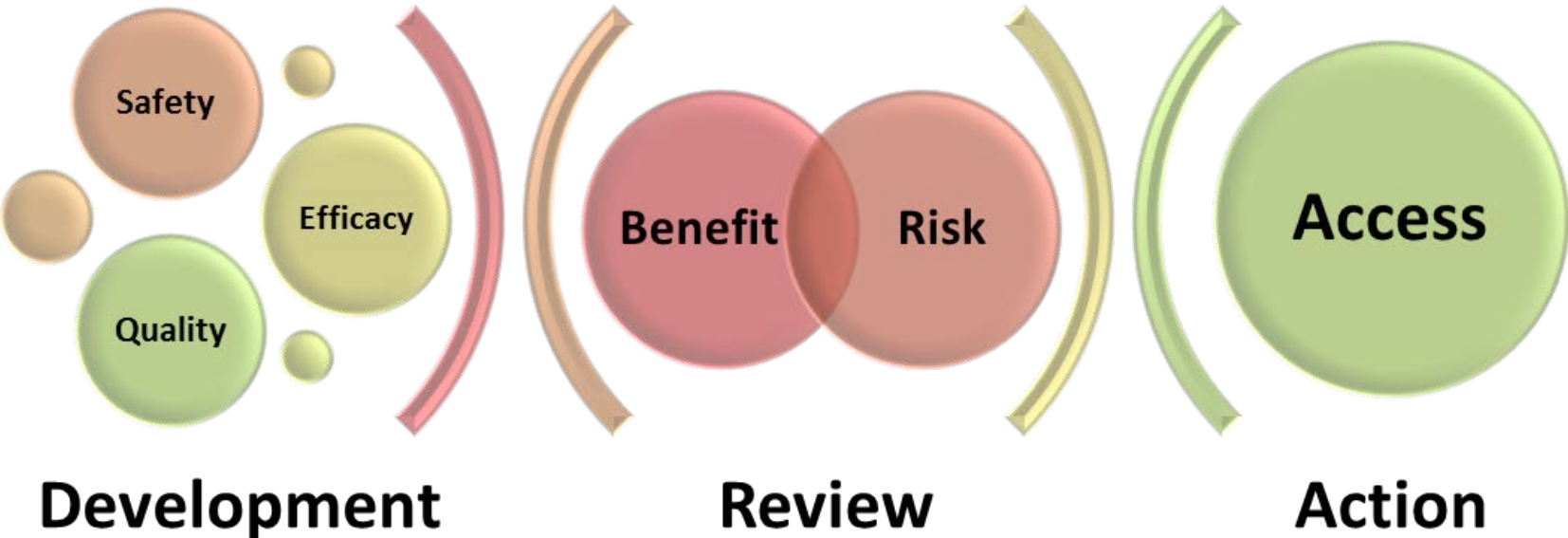


CONSORTIA RESPOND TO THE CALL



Cardiac Safety Research Consortium (**CSRC**), Biomarker Consortium (**BC**), Predictive Safety Testing Consortium (**PSTC**), international Serious Adverse Event Consortium (**iSAEC**), 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 (**ACTION**), 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, International Neonatal Consortium (**INC**), Duchenne-Regulatory Science Consortium (**D-RSC**), Pediatric Trials Consortium (**PTC**), Critical Path for Parkinson's (**CPP**) Consortium.

Critical Path to Informed Decision Making





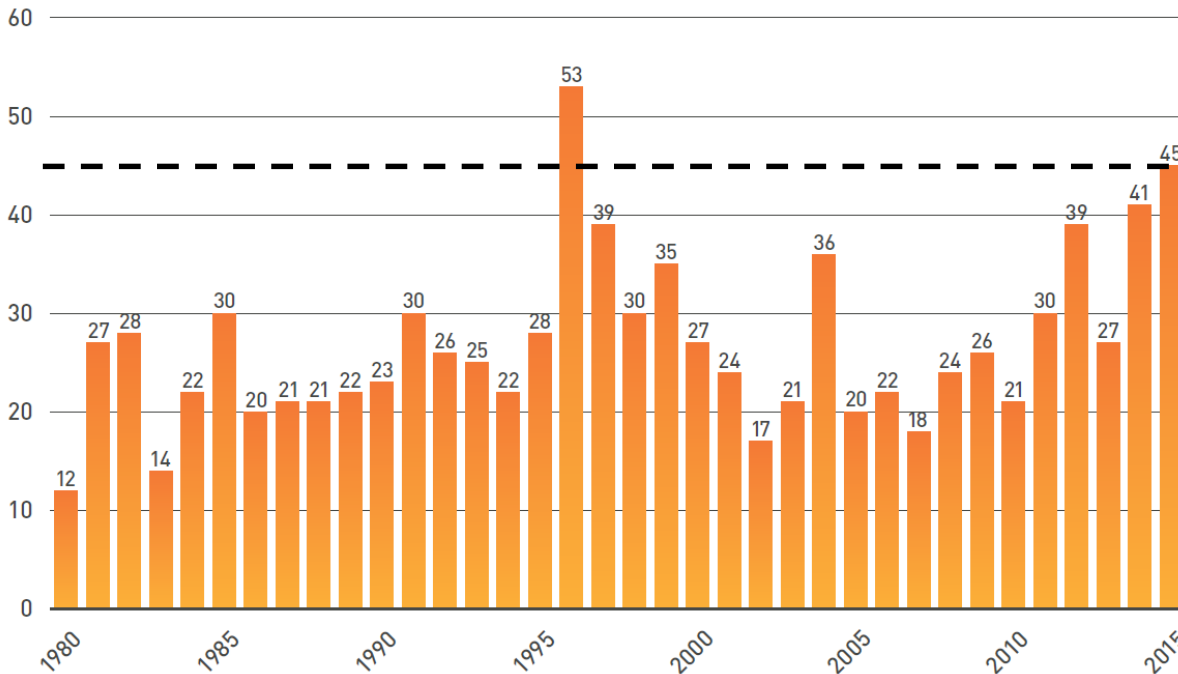
The Present:

Laying the groundwork...

A CASE FOR OPTIMISM

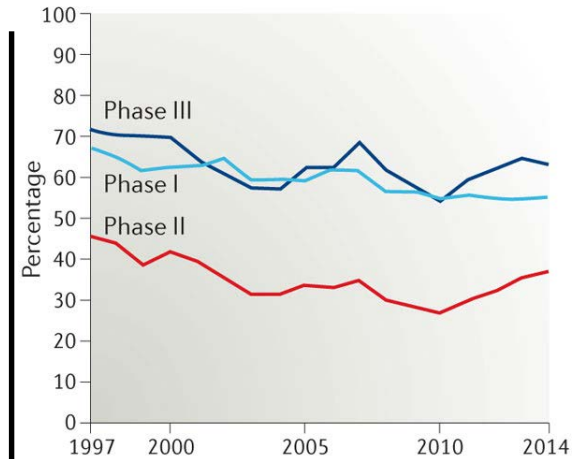


FDA-Approved Medicines (CDER)



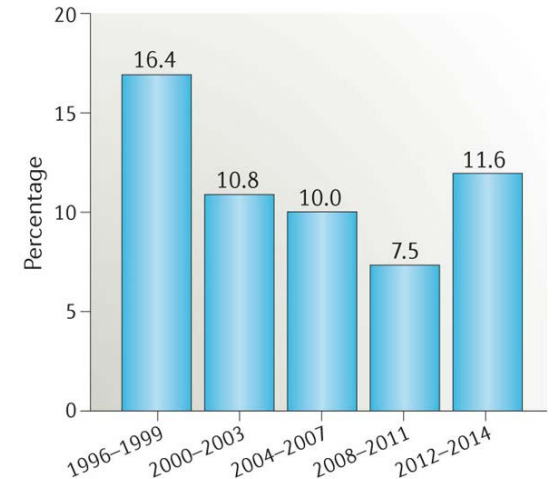
a Success rates by phase

Percentage likelihood of moving to next phase, 3-year rolling average*



b Cumulative success rate Phase I to launch

Percentage likelihood of moving from Phase I to launch



A CASE FOR OPTIMISM

MEDICINES IN DEVELOPMENT

Medicines in development globally = **7,000**¹⁴

Potential first-in-class medicines** across the pipeline = an average of **70%**¹⁵

Medicines in development to treat rare diseases = more than **450**¹⁶



CANCERS

1,919



CARDIOVASCULAR DISEASE

563



INFECTIOUS DISEASES

1,261



IMMUNOLOGICAL DISORDERS

1,123



DIABETES

401



MENTAL HEALTH DISORDERS

510



HIV/AIDS

208

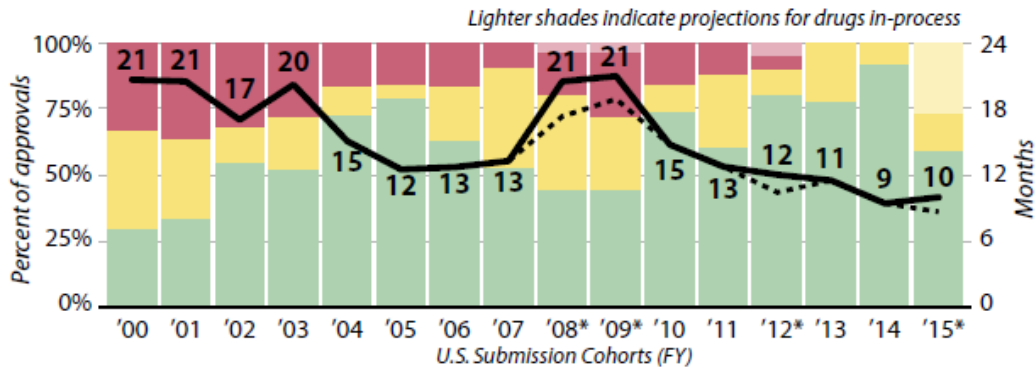
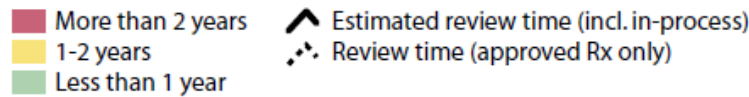


NEUROLOGICAL DISORDERS

1,308

DRUG APPROVAL TIMES

Estimated review time to approval for NME/NBE submission cohorts, FY 2000-2015



*Includes estimates of approval times for drugs still in process

INCREASED FOCUS ON ADVANCING REGULATORY SCIENCE



1993-1997

PDUFA I

Add funds for pre-market review; reduce backlog and set predictable timelines (goals) for review action

1998-2002

PDUFA II

Shorten review timelines; add review goals; add process and procedure goals

2003-2007

PDUFA III

Increase interaction in first review cycle (GRMPs); allow limited support for post-market safety

2008-2012

PDUFA IV

Enhance pre-market review; modernize post-market safety system

2013-2017

PDUFA V

Review enhancement; increase communication with sponsors; strengthen regulatory science & post-market safety; electronic data standards

2018-2021

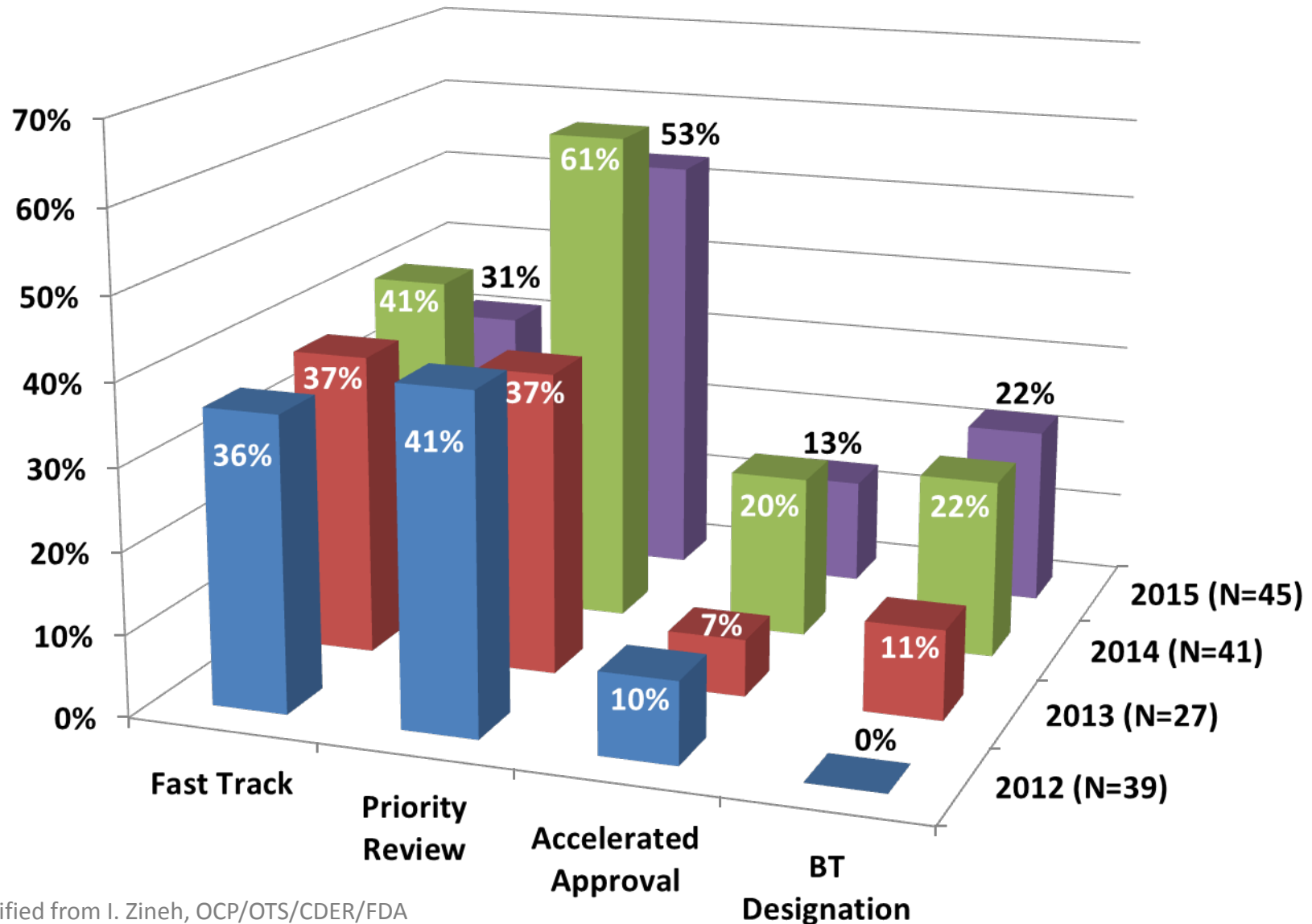
PDUFA VI

Program/process enhancement; improve staff hiring and retention; enumerate IT goals and standards; enhance regulatory science & promote innovative tools

Regulatory Innovation



Use of Expedited Pathways (2012-2015)





OPPORTUNITIES FOR ENGAGEMENT WITH CDER



Critical Path Innovation Meeting

Discussion on potential tools, methodologies, or approaches that might enhance drug development



Letter of Support Initiative

Letter issued for promising biomarkers based on research findings



DDT Qualification Programs

Guidance issued for qualified DDTs

MODEL INFORMED DRUG DEVELOPMENT

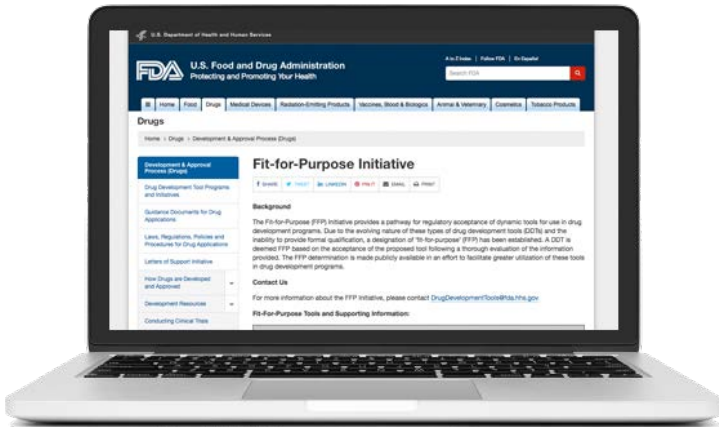
- “Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making” (Lalonde)

Indication	MBDD approach adopted	Efficiencies gained over historical designs and analysis
Thromboembolism ^a	Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design	2,750 Fewer patients, 1 year shorter study duration
Hot flashes	Model-based dose–response relationship	1,000 Fewer patients
Fibromyalgia	Prior data supplementation, model-based dose–response relationship, sequential design	760 Fewer patients, 1 year shorter study duration
Type 2 diabetes	Prior data supplementation, model-based dose–response relationship	120 Fewer patients, 1 year shorter study duration
Gastroesophageal reflux	Model-based dose–response relationship	1,025 Fewer patients
Rheumatoid arthritis	Model-based dose–response relationship	437 Fewer patients, increased probability of success
Global anxiety disorder	Omit phase IIb	260 Fewer patients, 1 year shorter study duration
Lower urinary tract symptoms	Meta-analysis	Increased probability of success
Urinary incontinence	Meta-analysis	Increased probability of success

MBDD, model-based drug development.

- FDA identified MIDD as an important pathway for lowering drug attrition and dealing with regulatory uncertainty

Fit-for-Purpose



Disease Area	Submitter	Tool	Trial Component	Issuance Date and Supporting Information
Alzheimer's disease	The Coalition Against Major Diseases (CAMD)	Disease Model: Placebo/Disease Progression	Demographics, Drop-out	<p>Issued June 12, 2013</p> <ul style="list-style-type: none"> Determination Letter <p>The tool is freely available at: https://bitbucket.org/metrumrg/alzheimers-disease-progression-model-adascog/wiki/Home</p>
Multiple	Janssen Pharmaceuticals and Novartis Pharmaceuticals	Statistical Method: MCP-Mod	Dose-Finding	<p>Issued May 26, 2016</p> <ul style="list-style-type: none"> Determination Letter Statistical Review Pharmacometric Review

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm>

CLINICAL OUTCOME ASSESSMENT COMPENDIUM



FDA's effort to foster patient-focused drug development by collating and summarizing COA information for many different diseases and conditions into a single resource intended to:

- facilitate communication
- provide clarity and transparency
- be used as a starting point for early drug development

The *COA Compendium*:

- Describes how certain *clinical outcome assessments* have been used in clinical trials to measure the patient's experience (such as disease-related symptoms) and to support labeling claims.
- Identifies clinical outcome assessments that have been qualified for potential use in multiple drug development programs
- Recognizes ongoing qualification projects to encourage community collaboration in the development of clinical outcome assessments for unmet measurement needs.

www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm459231.htm

THE CHALLENGE OF TERMINOLOGIES

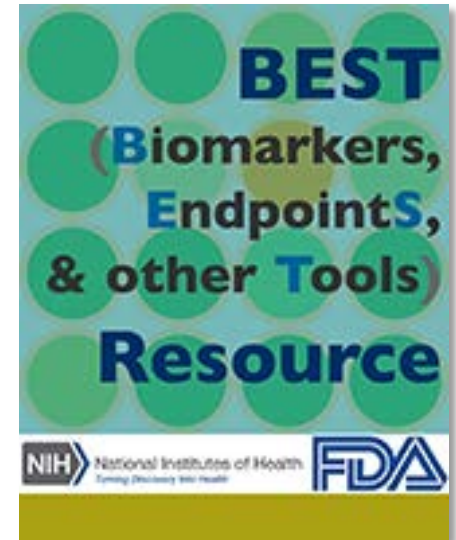
Biomarker **Fit-for-purpose** **Surrogate** **Risk**
Clinical validation **Pharmacodynamic** **Qualification** **Candidate surrogate**
Monitoring **Reasonably likely surrogate** **Biomarker** **Clinical validation**
Diagnostic **Biomarker** **Endpoint** **Monitoring** **Biomarker**
Predictive **Surrogate** **Context of use** **Diagnostic** **Predictive**
Intended use **Accelerated approval** **Prognostic** **Candidate surrogate**
Prognostic **Reasonably likely surrogate** **Fit-for-purpose** **Safety**
Analytical validation **Context of use** **Pharmacodynamic** **Intended use**
Accelerated approval **Predictive** **Diagnostic**



BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE



- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at <http://www.ncbi.nlm.nih.gov/books/NBK326791/>





CLEARING A PATH FORWARD FOR BIOMARKER DEVELOPMENT



Surveys

- Internal biomarker survey *(done)*
- External biomarker survey *(results published on the internet)*
- PhRMA survey *(done)*

Meetings and Workshops

- Meeting with University of MD and CPath on evidentiary standards *(done)*
- Biomarker Consortium evidentiary standards workshop *(done)*
- FDA-NIH Joint Biomarker Working Group *(done)*
- Analytical Validation Workshop *(planning underway)*

Tools & Other Outreach

- Inventory of biomarkers used in pivotal trials for approved drugs (2007–present) *(done)*
- Consortia-pedia website *(done)*
- Data/specimen repositories *(discussions underway)*
- Revamping regulatory science training approaches *(discussions underway)*
- Informed consent discussions *(the final frontier)*
- Improving communication tools and approaches *(underway)*



Opportunities and Challenges

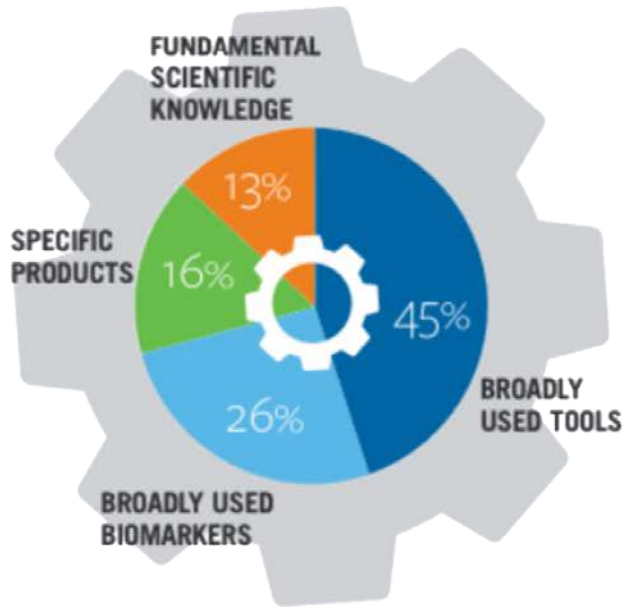


PRODUCTS CREATED BY CONSORTIA

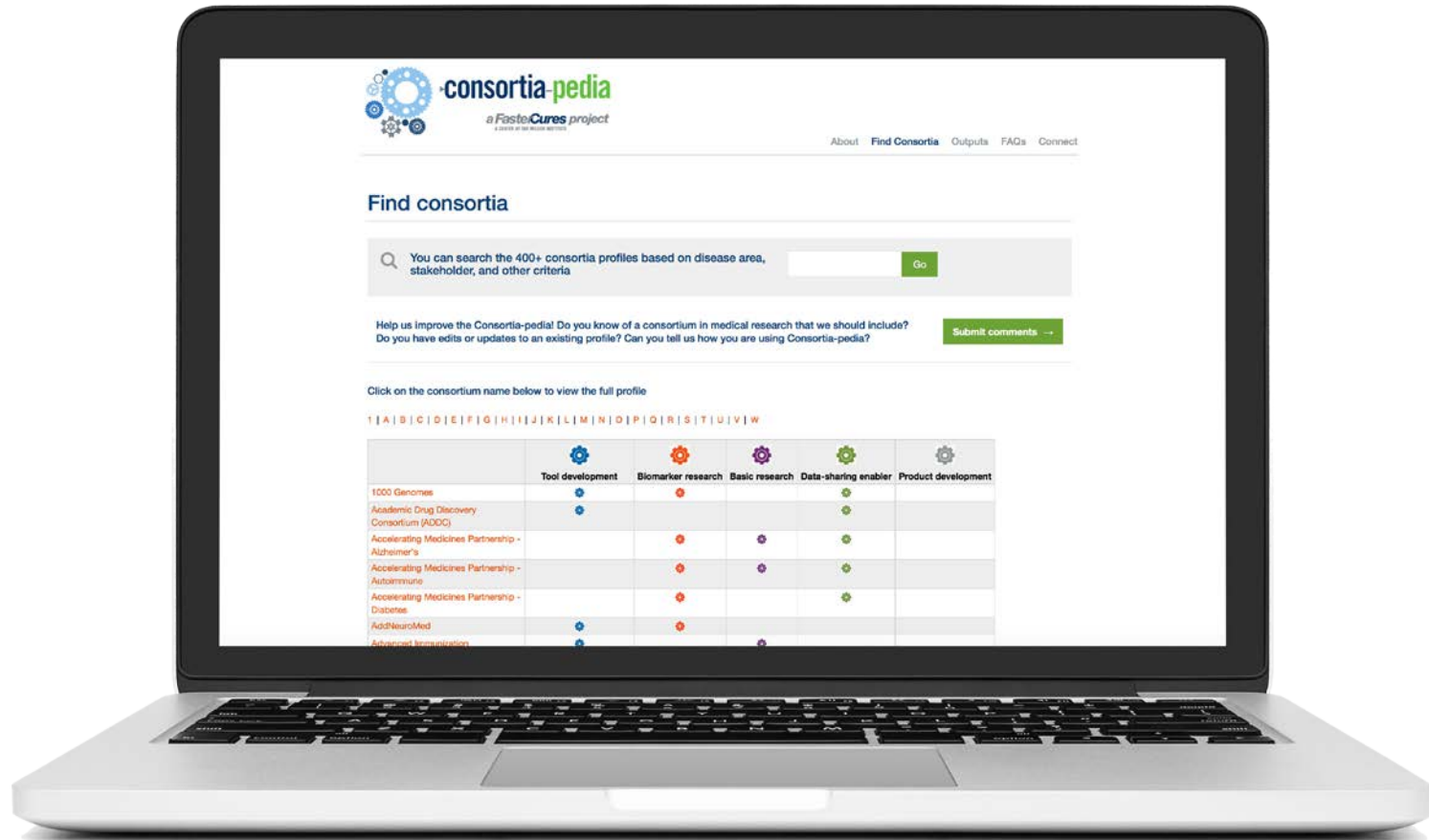




PRODUCTS CREATED BY CONSORTIA



<http://consortiapedia.fastercures.org/>



<http://consortiapedia.fastercures.org/consortia/>



DATA SHARING: KEY SUCCESS FACTORS



Collaboration

- Buy-in to value proposition and project objectives
- Structure
- Governance



Expertise

- Scientific and medical subject matter experts
- Full spectrum of supporting disciplines
 - Data privacy preservation
 - Data management and analysis
 - Information technology
 - Project management



Data

- Data acquisition process
- Data use/data sharing agreements
- Consistent data structure
- Scientific validation of integration approach
- Defined approach to optimize signal to noise ratio



CURRENT CHALLENGES



- Inadequate **scientific information** on the causes, biochemical pathways, and natural histories of many diseases
- Inadequate **sharing, coordination, and prioritization** of the limited public and private resources available to identify and develop tools in areas of greatest unmet need
- Lack of **standardized methods** for evaluation and a lack of **reliable evidence** about the performance of drug development tools (DDTs)
- Lack of generally accepted **evidentiary criteria** for qualifying new drug development tools for particular contexts of use
- Lack of **public access** to existing research and information to support development



The Future:

Where are we going?

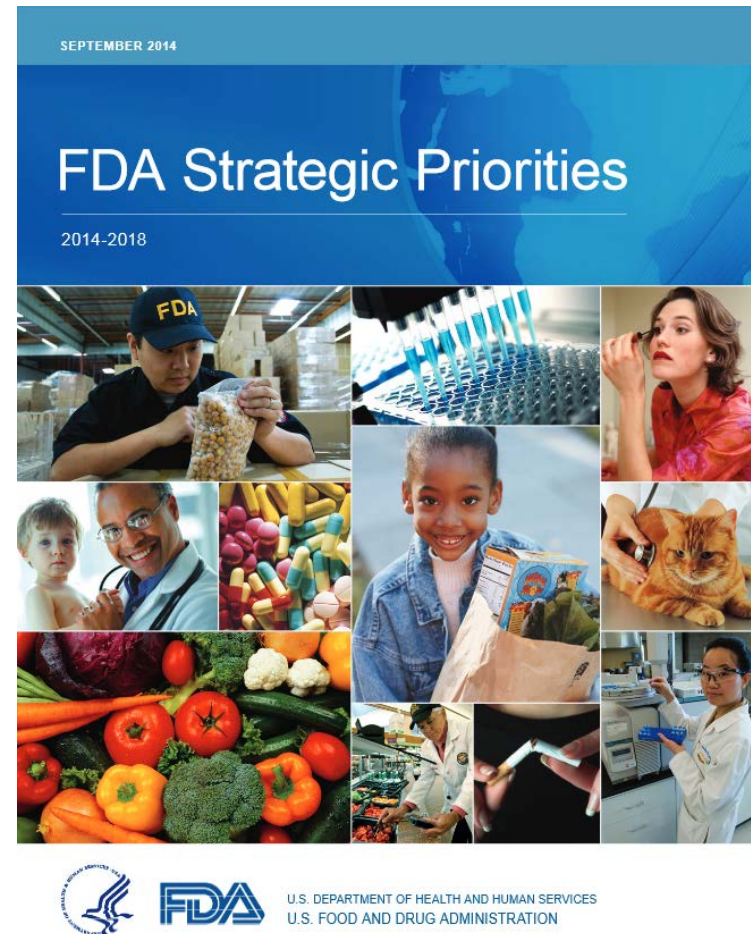
How do we get there?

How do we know if we
made it?

FDA Strategic Priority

Improve the **predictability**, **consistency**, **transparency**, and **efficiency** of the review process by:

- Improving the exchange, review, and management of information, and
- Making strategic investments in automated, standards-based IT.



KEY AREAS IN FDA-INDUSTRY DISCUSSIONS IN PDUFA VI



- Pre-market review
- Regulatory decision tools
- Post-market
- Electronic submissions and data standards activities
- Hiring capacity
- Financial management

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ENHANCING THE INCORPORATION OF PATIENT'S VOICE IN DRUG DEVELOPMENT AND DECISION-MAKING

Opportunity:

Develop systematic approaches to bridge from patient-focused drug development meetings to fit-for-purpose tools to collect meaningful patient input that can be incorporated into regulatory review.

ENHANCING BENEFIT-RISK ASSESSMENT IN REGULATORY DECISION-MAKING

Opportunity:

Strengthen sponsors' and the public's understanding of FDA's approach to B-R assessment throughout the drug lifecycle



ENHANCING CAPACITY TO REVIEW COMPLEX INNOVATIVE DESIGNS

Opportunity:

Advance simulation approaches that can support innovation and regulatory evaluation of novel complex clinical trial designs and clarify for sponsors FDA expectations for simulations needed to adequately characterize the performance of these complex trials.

ENHANCING CAPACITY TO SUPPORT ANALYSIS OF STANDARDIZED DATA FOR PRODUCT DEVELOPMENT AND REVIEW

Opportunity:

As NDAs/BLAs are increasingly submitted in fully-standardized electronic form, ensuring that sponsor analysis data sets included in the application can be readily opened and analyzed for timely review.



ADVANCING MODEL-INFORMED DRUG DEVELOPMENT

Opportunity:

Advance the development, application and benefits of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, referred to as “model-informed drug development” (MIDD) approaches

ENHANCING DRUG DEVELOPMENT TOOLS (DDT) QUALIFICATION PATHWAY FOR BIOMARKERS

Opportunity:

To handle growing number of qualification programs, improve capacity to review and the predictability of the biomarker qualification process by clarifying evidentiary criteria for biomarkers and refining processes related to review of qualification submissions and communication among FDA and other stakeholders.

FUTURE DIRECTIONS

- Model-informed drug development
- Complex adaptive, Bayesian, other innovative designs
- New endpoints and biomarkers
- Voice of the patient
- Enhanced pharmacovigilance
- “Real-world” evidence

B. Emerging Assessment Tools

- **Computational Modeling**

The use of computer modeling has the potential to streamline the design, assessment and evaluation of medical devices. These models could also make clinical trials more efficient by focusing on the most critical parameters in determining safety and effectiveness. CDRH will develop a framework for validating computer models for regulatory assessment, and will facilitate the development of computer models that are based on population characteristics and closed-loop systems.

- **Next Generation of Personalized Medicine — The Virtual Physiological Patient**

Computer modeling and simulation will be essential in creating truly personalized medicine. Personalized medicine requires more than a personalized genome, it requires personalized functional anatomy. Although developing computer models of healthy human physiology is of fundamental importance, designing interoperable computer models and simulations of diseased human states is needed as well and within reach. CDRH will continue efforts to move personalized medicine forward. This will include the development of a Library of Models to house publically available, FDA validated computer models of the human body in different disease states. We plan to make this Virtual Physiological Patient accessible to researchers and medical device developers for testing new device designs and applying for device clearance and approval.

- **Wireless Device Systems**

With the burgeoning use of wireless products that emit electromagnetic radiation, there is increasing concern

about electromagnetic interference with medical devices, and about the reliability of data that is transmitted data wirelessly through connected device networks. These are important issues in hospital settings, where conditions of use can vary widely between a private patient room, intensive care unit, operating suite, or emergency department. They are especially significant where a high number of medical and non-medical devices (such as cell phones) may be simultaneously in use. Special situations such as emergency transport and mass casualty events pose additional challenges. CDRH engineers will expand our research efforts to mitigate these problems.

- **Interoperability of Computerized Medical Devices**

Medical device or medical system interoperability usually implies that systems can exchange data with each other and control each other's functions. Although these integrated systems can provide a safety buffer in preventing medical errors, it is possible for them to pose safety problems of their own. CDRH will work to improve interoperability among diagnostic and therapeutic medical devices and ensure that interoperability does not pose a hazard to patients.

- **Genomics**

Technologies for accessing a patient's full genomic sequence are now under intensive development, along with new genomic tests for disease detection, prevention and personalized therapies. This will necessitate the development and validation of reliable tools to characterize these products and assure that they are accurate and appropriate. CDRH will play a significant role in this effort, helping to open the way for major advances in patient care.





ELECTRONIC SUBMISSIONS & DATA STANDARDS:

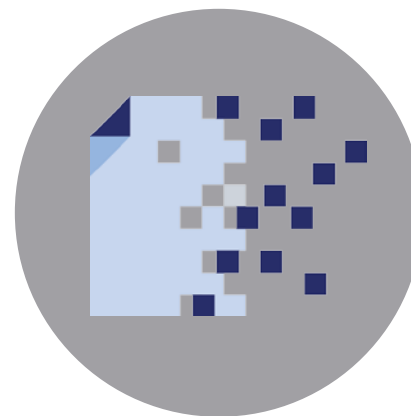
WHAT DO THEY MEAN?



Predictability



Traceability



Data Quality

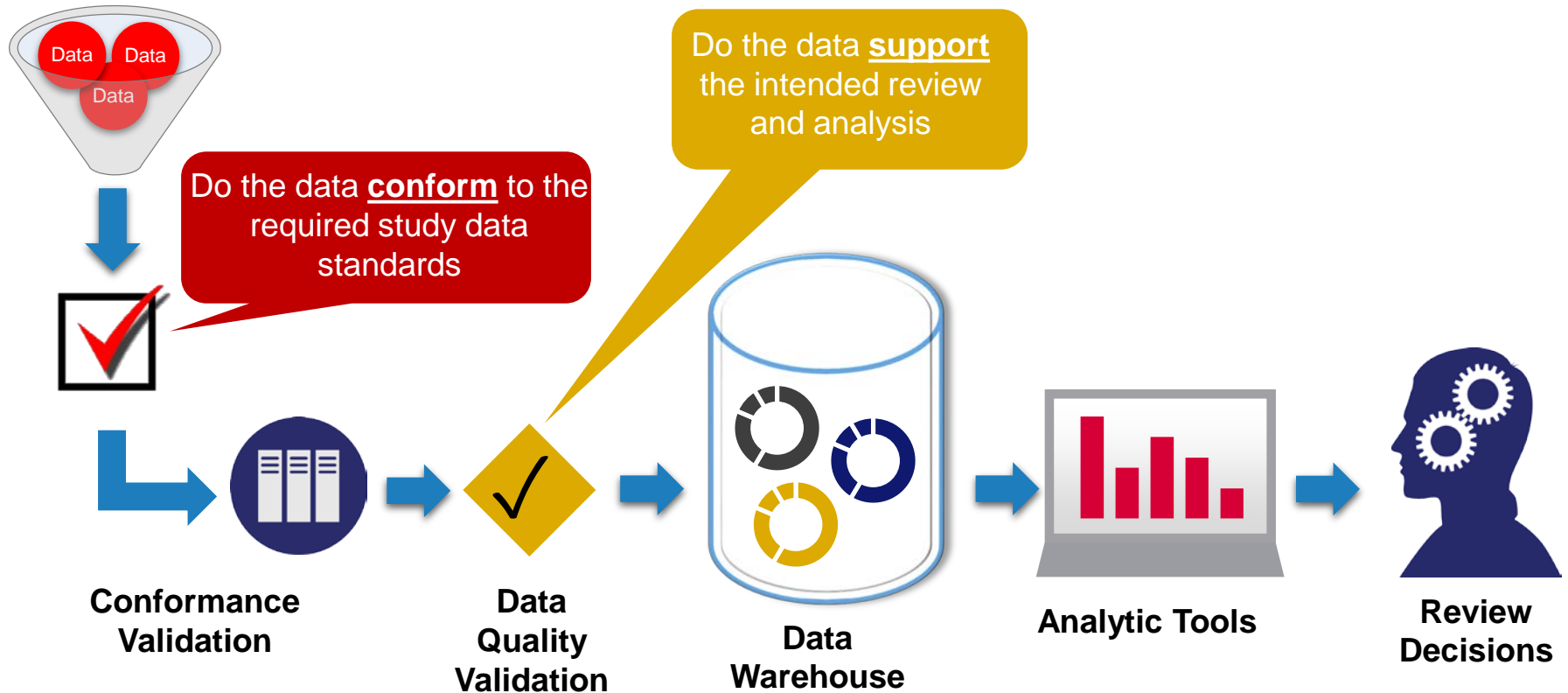
= More efficient review process



VISION: INTERSECTION OF DATA, TOOLS, AND TECHNOLOGY



Standardized Data Submission



STANDARDIZED ELECTRONIC DATA:



HOW IS IT LOOKING TODAY...FY2016?*



75%

of **study data** submitted within all NDA submissions are in standardized SDTM format**



88%

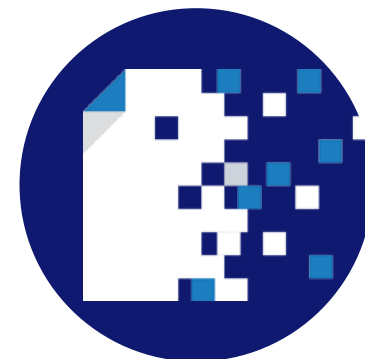
of **study data** submitted in support of NEW NDAs are in standardized SDTM format**

*FY2016 (Q1-Q2)

**Source: Office of Business Informatics, CDER - One or more explicitly stated SDTM studies (or study data structure that resembled SDTM).



STUDY DATA STANDARDS REQUIREMENTS



**NDAs, BLAs,
ANDAs, and
DMFs**

**Required
December 17, 2016**

**Commercial
INDs**

**Required
December 17, 2017**



REAL WORLD DATA AND REAL WORLD EVIDENCE

REAL WORLD DATA AND REAL WORLD EVIDENCE

“Although ‘data’, ‘information’, and ‘evidence’ are often used as if they were interchangeable terms, they are not. Data are best understood as raw measurements of some thing or process. By themselves they are meaningless; only when we add critical context about what is being measured and how do they become information. That information can then be analyzed and combined to yield evidence, which in turn, can be used to guide decision-making. In other words, it’s not enough merely to have data, even very large amounts of it. What we need, ultimately, is evidence that can be applied to answering scientific and clinical questions.”

- Drs. Rob Califf and Rachel Sherman, US FDA

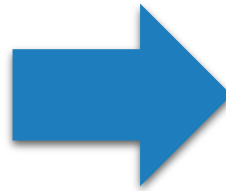
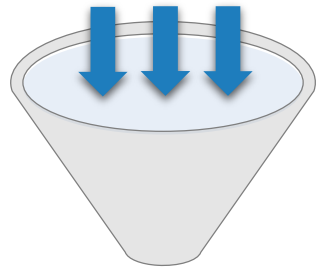
<http://blogs.fda.gov/fdavoices/index.php/tag/real-world-evidence/#>



VISION: ENTER ONCE, USE REPEATEDLY



Data from clinical care



Uses

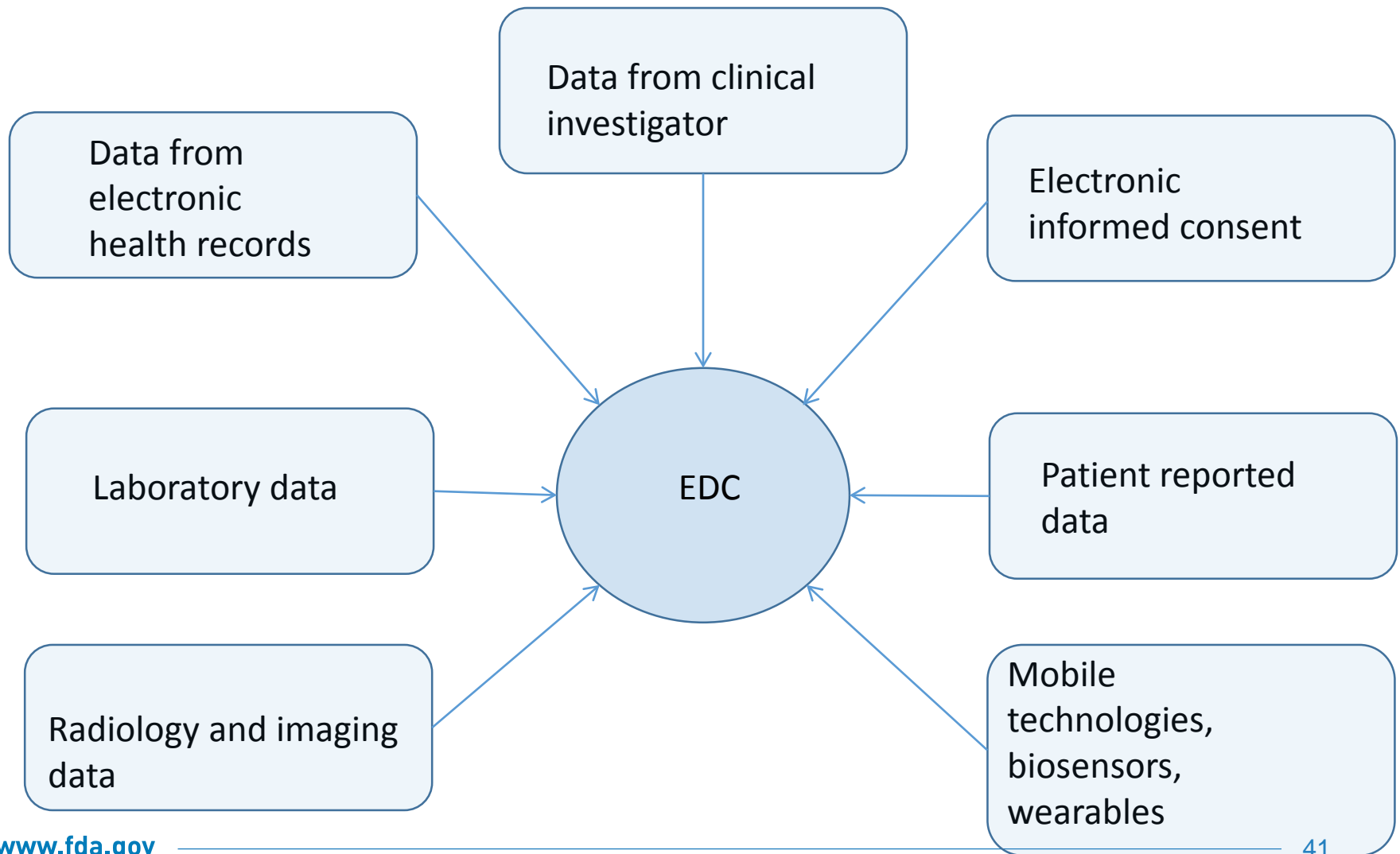
Coordination of Patient Care

Checklists for consistency, correctness, quality, and safety

Facilitate compilation of medical records

Review of patient history with only relevant data

MODEL FOR ELECTRONIC DATA CAPTURE





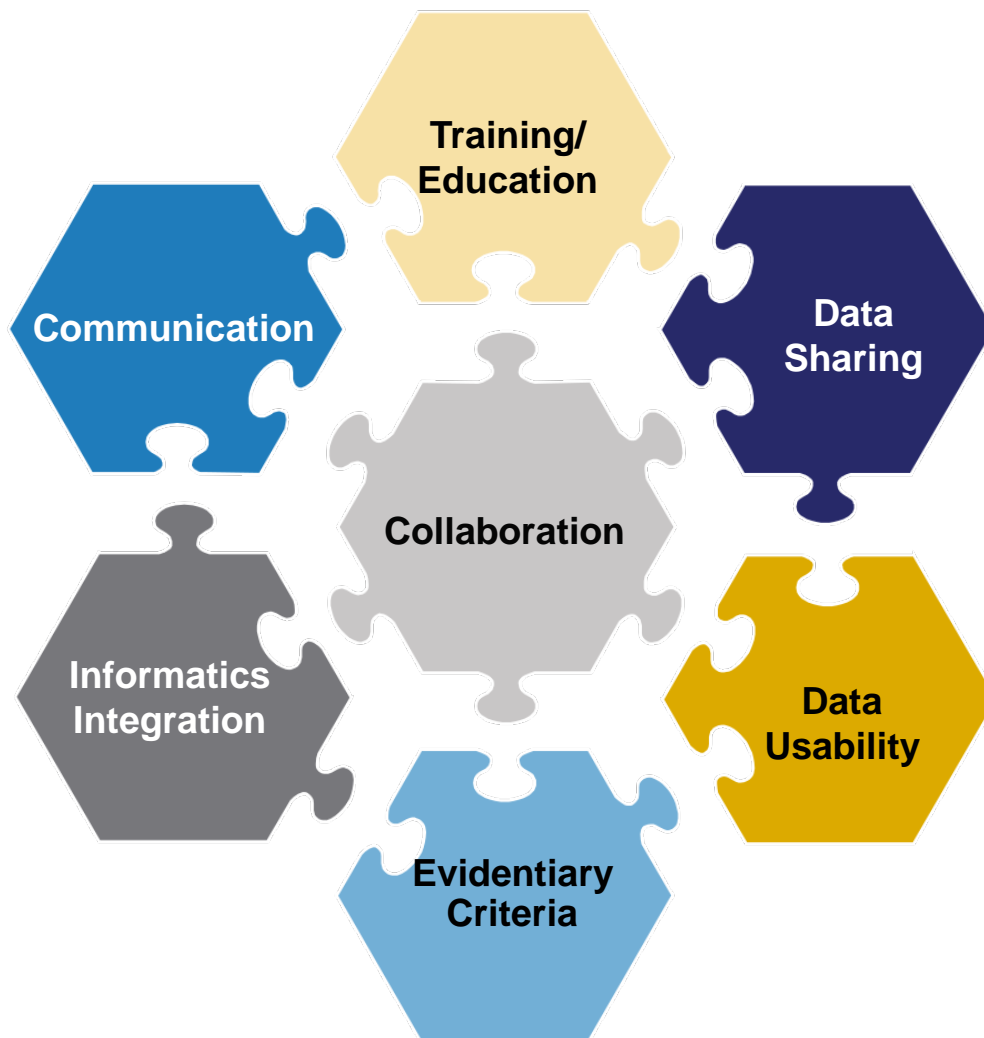
NEXT STEPS...WHAT IS NEEDED



- Enhanced data sharing and collaborative efforts among consortia
- Coordination of existing partnerships and consortia (internationally) so that they effectively and collaboratively direct their efforts toward progress of priority initiatives
- More communication about the value and progress made by consortia
- Greater clarity around levels of evidence for regulatory utility of drug development tools, this takes the entire scientific community, not just FDA
- Train and expose investigators to regulatory considerations for DDT development
- Although significant progress has been made... we are still learning as we go



KEY COMPONENTS





“The bottom line is that I’m an optimist. These challenges don’t discourage me, I get excited about them and I always look on the bright side—we’ll solve this problem and move on to the next.”

Janet Woodcock
U.S. Food and Drug Administration



