U.S. FOOD & DRUG ADMINISTRATION

2019 FDA Annual Update

10th Annual PRO-Consortium Workshop

April 24, 2019

Presenters

- Peter Stein, MD, Director, Office of New Drugs
- Michelle Campbell, PhD, Sr. Clinical Analyst for Stakeholder Engagement and Clinical Outcomes, Division of Neurology Products
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Disclaimer

The views expressed in this presentation are those of the speakers, and do not necessarily represent an official FDA position.

Context is everything:

The changing drug development landscape – considerations for COA development

Peter Stein, MD

Director

Office of New Drugs / CDER / FDA

Overview

- The changing landscape
- Challenges to COA and biomarker development

The changing drug development – and drug regulatory landscape

Changing science

- Increasing **genomic/genetic** characterization of diseases – providing new targets
- Increase **molecular subtyping** of diseases - targeting disease or subtype specific targets
- Recognition of **molecular drivers** in cancer
- **New platforms** for "undruggable" targets: e.g., ASOs, siRNA , dual targeted Mabs, cell and tissue based – regenerative Tx

Changing the types & targets of drugs

- Fewer drugs targeting common diseases with more drugs targeting **rare diseases**
- Focus on **disease subtypes**: late stage disease or phenotypic or genetic subgroups; small population development
- Dramatic increase in **targeted cancer drugs**
- Rise in **biosimilar** and **complex generics**
- Focus on **drug *cost***: FDA role - Drug Competition Action Plan, Biosimilar Action Plan

Changing development and regulatory context (PDUFA VI, Cures, SUPPORT)

- Increasing role of patients and caregivers: **patient-focused drug development**
- **Focus on biomarkers/COAs**: BQP, standardizing approach to surrogate endpoints for AA
- New **approval pathways** (e.g., LPAD) and rising requests for breakthrough, fast track designations, use of AA
- **Changing nosology**: tissue agnostic drug approvals
- **Master protocols** / platform trials / basket trials
- Rising efforts on **decentralized trials**, use of **mobile technologies** for trial endpoints and monitoring
- Efforts to **integrate clinical research into practice** (EHR to eCRF) to support pragmatic trials and RWE generation and focus on use of **RWE** in a wider range of regulatory decisions
- **Novel trial designs**: Bayesian approaches, model-informed drug development
- Development of a **common protocol template**

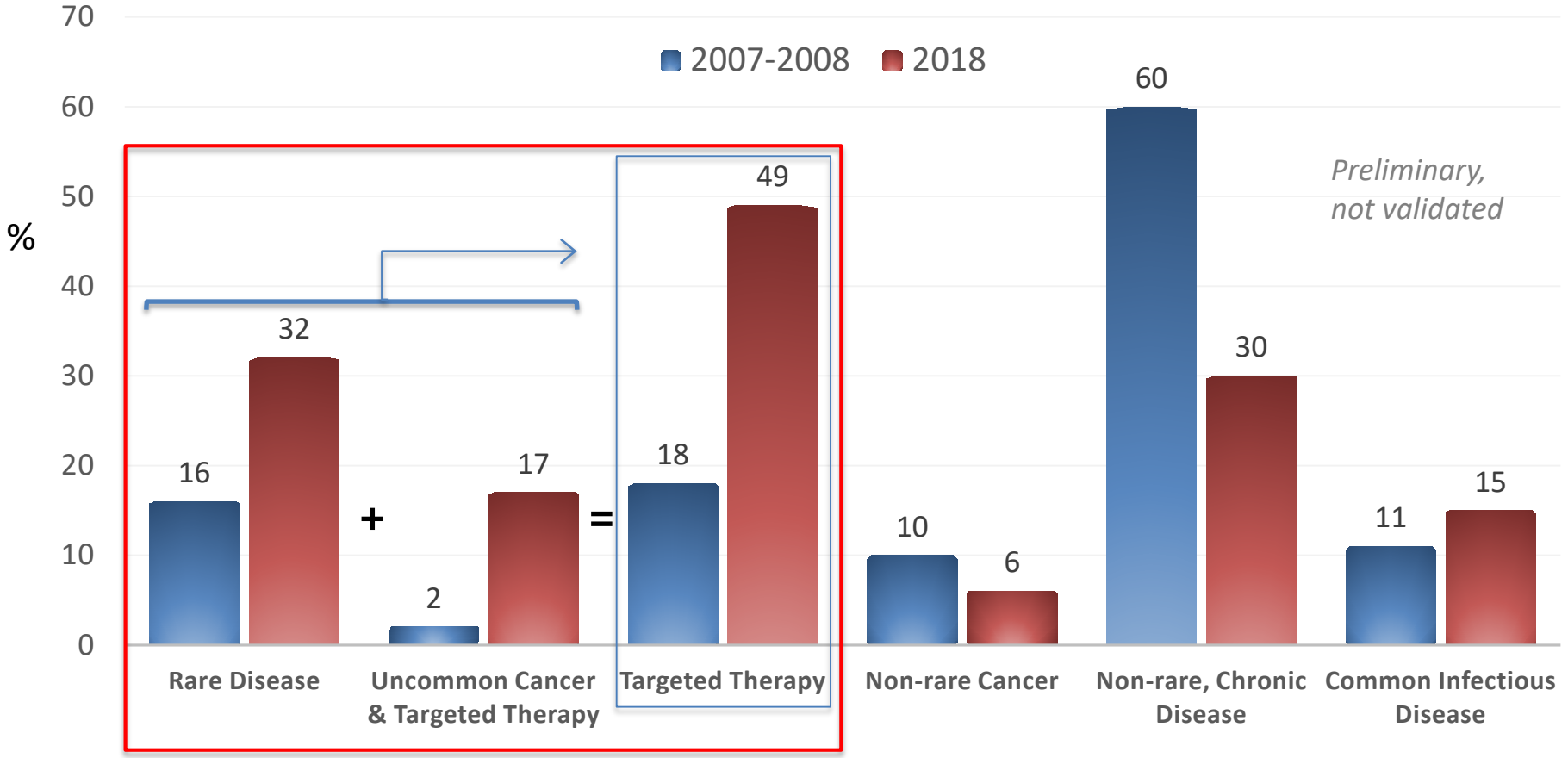
The changing landscape: implications for COA development

- **Increase in rare disease development programs**
  - Small and distributed patient populations
  - Genotypic, phenotypic diversity; patients at different stages of natural history
  - Often limited natural history information
  - Often highly engaged patient and stakeholder groups supporting development activities (COA development, natural history studies, recruitment into trials)
  - Need for regulatory flexibility: considering what is “fit-for-purpose” when limited patient population
- **Increased patient engagement – and focus on patient experience as central to development**
  - Greater input on selection of appropriate therapeutic targets, identification of unmet needs, input on burdens and issues with current therapies: rising need for COA development informed by PFDD
  - Providing framework for risk / benefit considerations
- **New drug platforms, molecular targeted therapies**
  - E.g., siRNA and ASOs – ability to target very small populations studies
  - Need for COA instruments common across subtypes

The changing landscape: implications for COA development

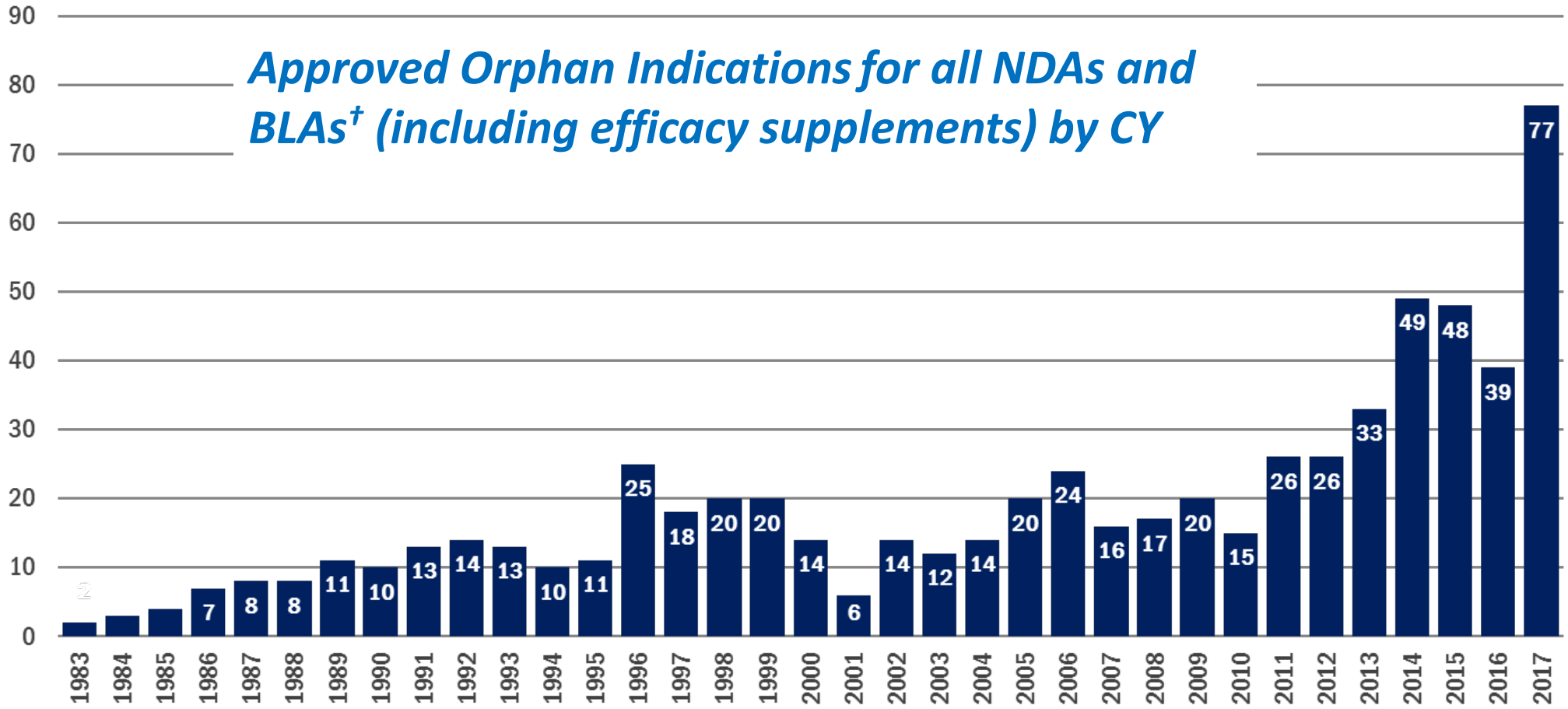
- **Increasing opportunities for mobile, digital technologies**
  - Marked rise in sources of information (active or passive) on daily patient status and functioning through mobile technologies to measure activity, ambulation, vital signs, locations
  - *Challenge* of converting wide array of mobile-technology sourced patient data into meaningful, interpretable endpoints
- **Increased interest / efforts to enable decentralized trials**
  - Enabled by rise in use and capabilities of mobile technologies
  - *Challenge* the traditional trial framework – changing the sites of trials, changing the information assembled into endpoints
  - Need to address diverse issues from validation of endpoints collected via mobile technology (vs at investigational site), obtaining informed consent, tracking drug supplies, safety monitoring
- **Increasing focus on "Real World Evidence"** (21st Century Cures)
  - Data collected from health care interactions, and other patient derived data including use of mobile technologies
  - Challenge of using RWE in the regulatory framework – e.g., meeting effectiveness standards

The evolution of drug targets over 10 years



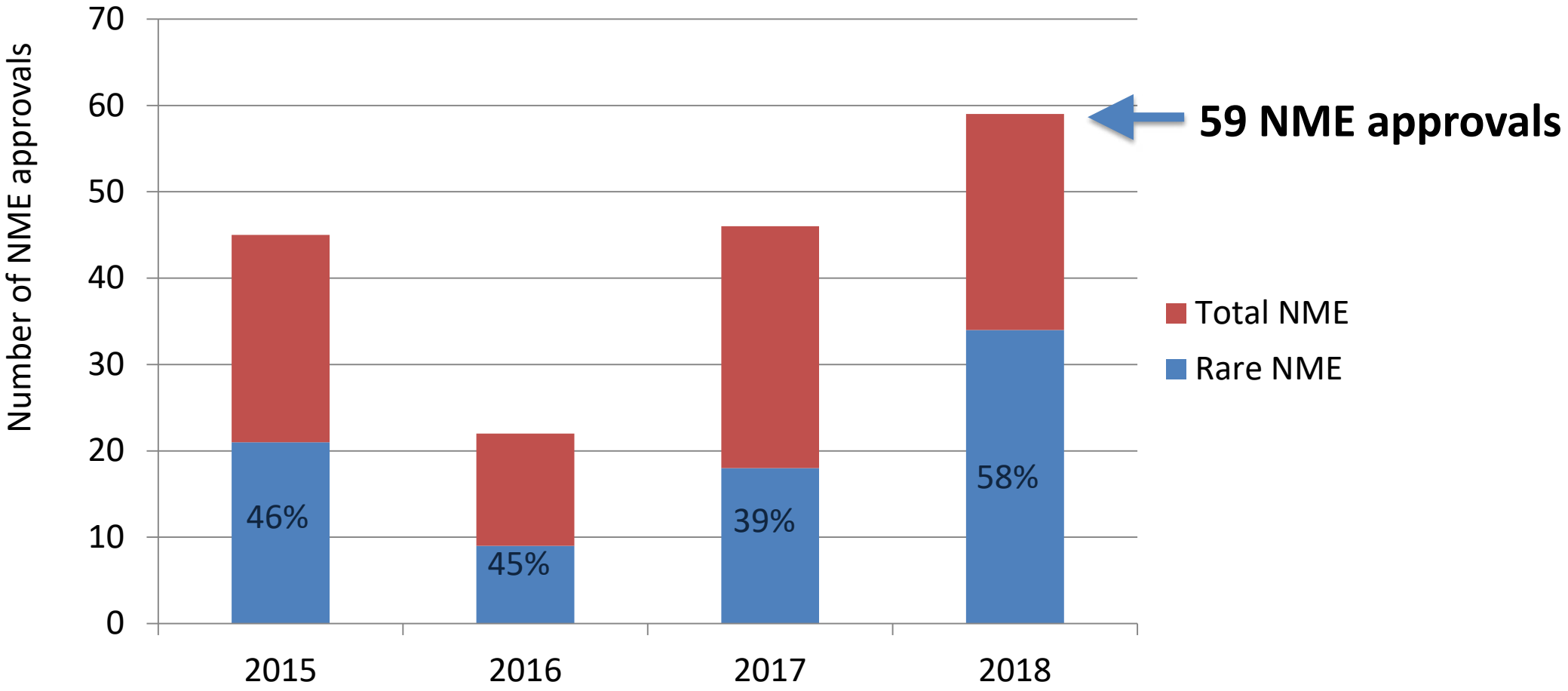
- *Increased proportion of targeted therapies*
- *Increased proportion are drugs for rare diseases*
- *Among drugs for common, chronic diseases – most targeting late stage / failing other therapies, subgroups or subtypes of disease*

The rise in drugs for orphan indications



A **rare disease** is defined (in the Orphan Drug Act) as a disease or condition that affects < 200,000 people in the US

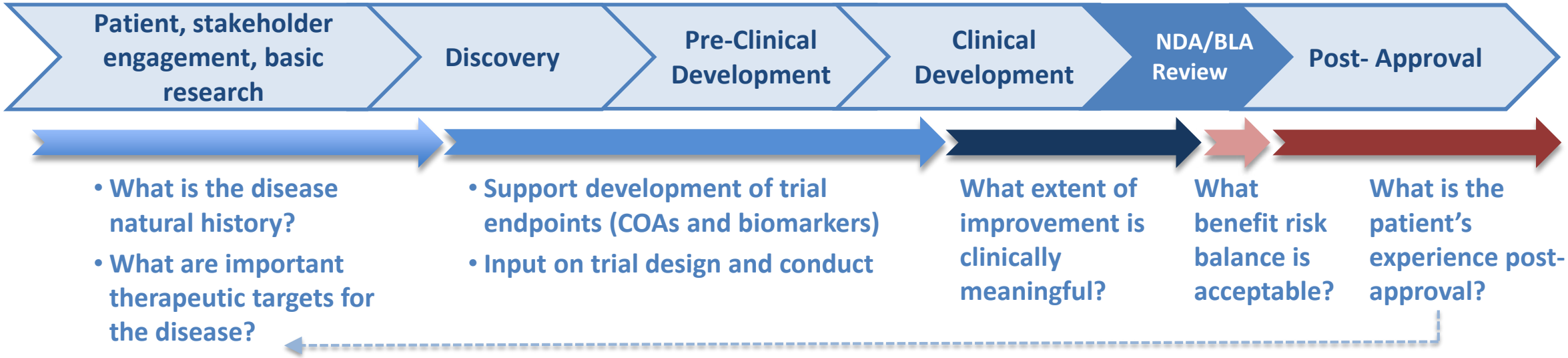
Proportion of rare disease-targeted NMEs of total NMEs



Challenges for rare disease drug development

- Rare diseases **natural history** is often poorly understood and characterized
- Diseases tend to be progressive, **serious**, **life-limiting and life-threatening** and lack **approved therapy**
- **Small populations** often restrict study design and replication
- **Phenotypic** diversity within a disorder adds to complexity, as do **genetic subsets**
- **Drug development tools** such as well defined and validated **endpoints**, **outcome measures**/tools, and **biomarkers** are often lacking
- Lack of **precedent** for drug development
- **Ethical** considerations for children in clinical trials

Increasing the role of the patient in regulatory decision making: patient-focused drug development



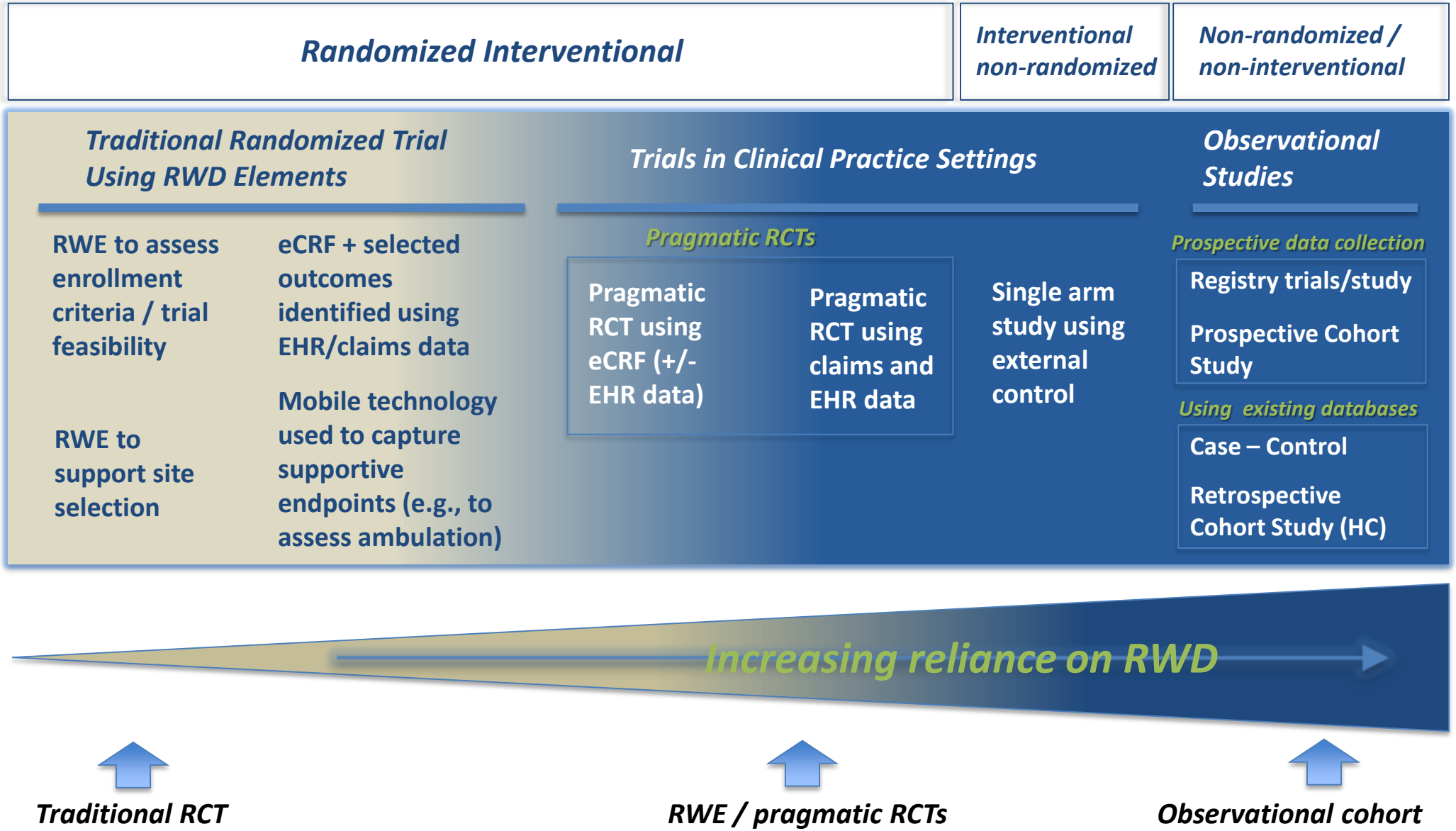
Key areas of input from patients can include:

- Impact of disease on patient: important goals and targets for therapy
- Developing appropriate "tools" (e.g., patient-reported outcome endpoints)
- Progression of disease over time: understanding "natural history"
- Impact and burden of treatments and unmet needs
- How clinical trials can be improved, facilitating participation
- What benefits do patients seek and what risks are they willing to accept?

RWD/RWE: The potential and value of expanding regulatory use

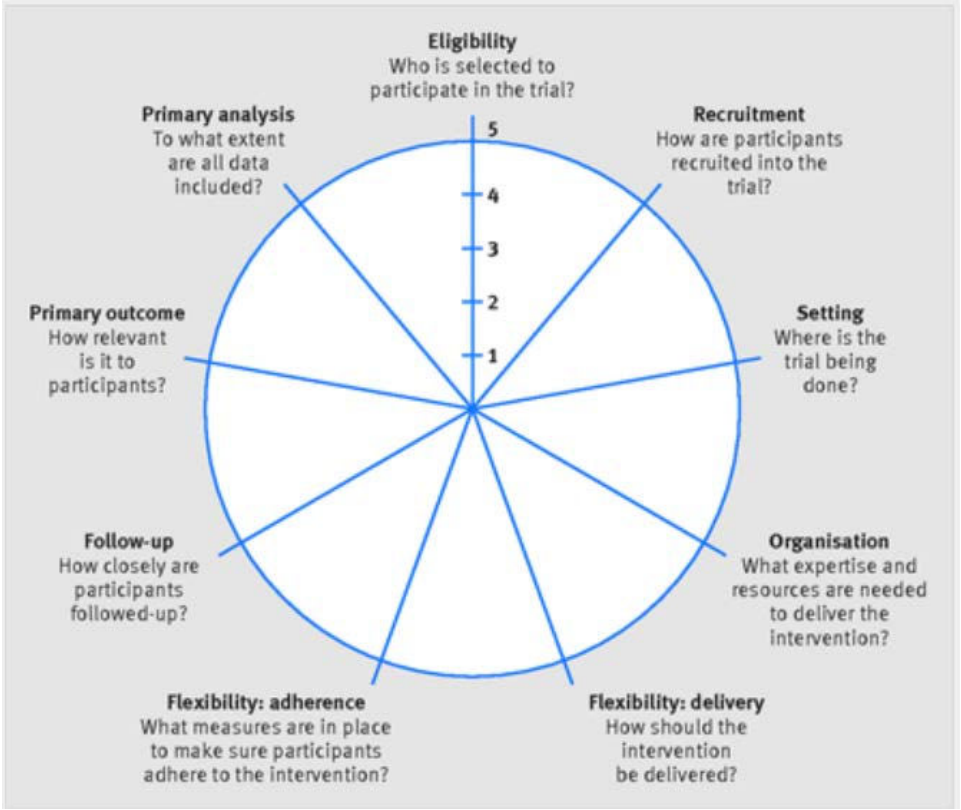
- **Much broader and diverse patient experience** vs traditional Phase 3 clinical studies
  - Includes settings and patients who will use drug post-approval
  - Patients with broader age, racial/ethnic, co-morbid disease, disease severity, concomitant medication
- **Very large sample sizes** – potential for detection of infrequent events, drug-drug interactions
- **Lower resource intensity**
  - *Observational database studies*: utilizing data from routine interactions of patients with their health care system
  - *Pragmatic clinical trials*: usually non-blinded (low cost of drug supply), data emerging from patient's usual health care - data extracted from EHR/claims, more limited eCRFs

Wide spectrum of potential uses of RWD / RWE in clinical studies



Increasing use of trials with pragmatic feature(s)

- Identification of relevant questions for practitioners and patients
- Selection of an intervention *that can be appropriately delivered* in a clinical practice setting
- For studies of approved drugs, streamline safety data collection
- Integration of clinical data across health care systems to maximize data capture
- If needed utilize mobile technologies to fill in the gaps, including the capture of patient reported outcomes



Many trials can have 'pragmatic elements' while maintaining rigorous standards for data collection and assessment

Decentralized trials and mobile devices: enhancing trial feasibility and data collection

Decentralized trials

- Enabled by mobile technologies: e.g., local collection of trial endpoints, safety monitoring
- Addresses distributed pt populations, allows greater diversity of patient populations and sites of care
- *Challenges*: applying GCP and regulatory frameworks: consent, investigator and local physician roles / responsibilities, safety monitoring, drug supply, endpoints validation, security and data integrity, data traceability

Mobile technologies: wide range of possible uses in trials, such as….

- Tracking adherence
- *Novel* trial endpoints: passively (e.g., ambulation, vital signs) *or* actively assessed (e.g., timed tasks or ePROs)
- Safety monitoring
- Recruitment and retention – connecting and engaging patients

Mobile technology: wide range of sources

- Smart phones: for videos, photographs of lesions, behaviors, other findings, or collection of ePROs
- Other: accelerometers, ECGs, temp sensors, EEGs, movement sensors, GPS, glucometers, spirometers

Mobile technologies: interpretation and regulatory implications - *from data to endpoints*

- Reliability of measurements: accuracy, reproducibility, data source
- Challenges of interpretation – creating meaningful endpoints: how patients *feel and function*

Drug development tool qualification at CDER

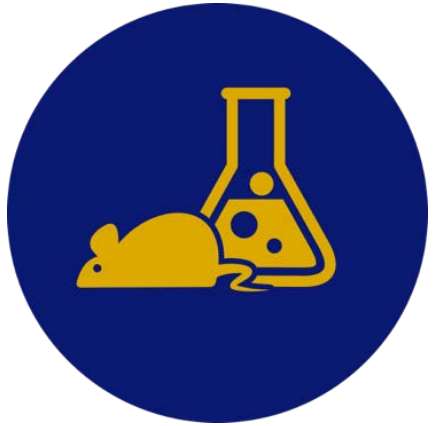
- *Qualification* is a conclusion that within the stated *context of use*, the DDT *can be relied* upon to have a specific interpretation and application in drug development and *regulatory review*
- *Types of Tools:*

Potential for wide applicability to support drug development programs:

Clinical Outcome Assessments

Biomarkers

Usually in narrow context of use (biological, radiological threats)



Animal Models (Animal Rule)

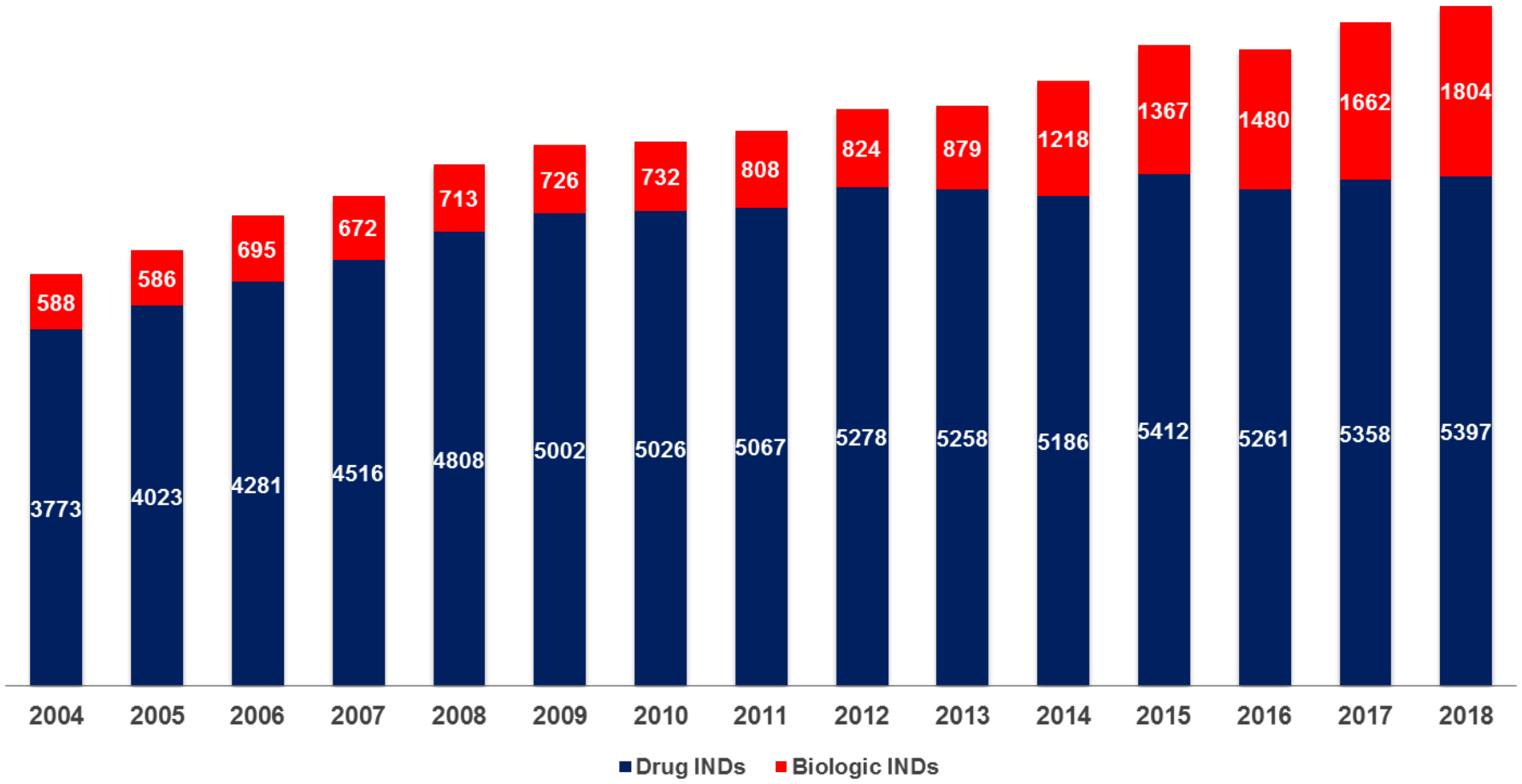
DDT integration into drug development: 3 pathways

- **IND pathway**: based upon agreement with the division, in the context of a specific drug development program
- **Scientific community consensus**: broadly/widely used DDT, appropriate scientific support, generally accepted by experts in the field
- **DDT qualification programs**: review and acceptance based upon appropriate submission qualification package; available for use in any development program within approved context of use

21st Century Cures: Qualification of Drug Development Tools (Section 3011) - BQP

- Specifies the drug development tool qualification process, 3 stages
  - **Submission of LOI**
  - **Submission of qualification plan**
  - **Submission of full qualification package**
- FDA can accept or reject at each stage
- Time frames *for each review step* to be specified

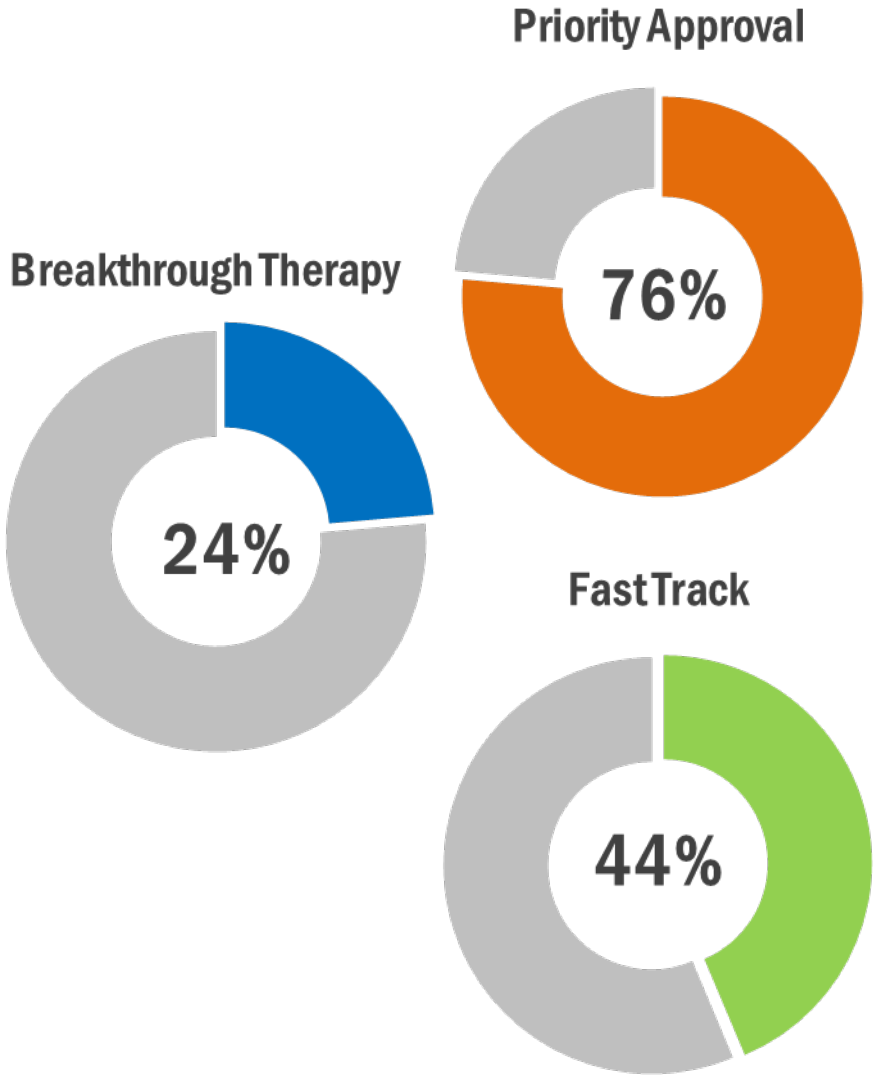
Development phase work continued to grow in 2018



Data are from the PDUFA Workload Adjuster and represent a 12 month period of July 1st - June 30th

Utilization of expedited development and review programs remains high: *so potentially shortened development times*

- Over three – quarters (76%) of the drugs approved to date in 2018 were approved under Priority Review
- Almost one out of four (24%) of the drugs approved to date in 2018 received Breakthrough Therapy designation
- About four out of ten (44%) of the drugs approved to date in 2018 received Fast Track designation



The challenges of COA and biomarker development

- Many disease areas with unmet needs have insufficient drug development tools to maximize trial efficiency (or even feasibility)
- Biomarker and COA development *is a long and resource-intensive process*
  - Going from initial description or identification, to refining, to validation – several year or longer process
- Many stakeholders in the mix:
  - Academic investigators at multiple institutions, US and ex-US
  - Often several academic societies in disease area with different viewpoints and membership
  - Different companies – both drug and device-focused may be working in the area
  - May be different patient stakeholder organizations
- The challenge: how to *prioritize* biomarker needs, *focus* resources, and *integrate* efforts across stakeholders
- And…in a changing development landscape: *COAs for rare diseases, new platforms, incorporating the patient voice, mobile technologies, and in real world settings, and with faster timelines*

CLINICAL OUTCOME ASSESSMENT QUALIFICATION PROGRAM UPDATE

Michelle Campbell, PhD

COA Staff

- Associate Director:
  - Elektra Papadopoulos, MD, MPH
- Regulatory Project Managers:
  - Kim Chiu, PharmD
  - Kristina Luong, PharmD
- DDT Qualification Scientific Coordinator:
  - Elektra Papadopoulos, MD,MPH
- Team Leads:
  - Selena Daniels, PharmD, MS
  - Wen-Hung Chen, PhD
  - Sarrit Kovacs, PhD
- Reviewers:
  - Yasmin Choudhry, MD
  - Ebony Dashiell-Aje, PhD
  - Oneyka Illoh, OD, MPH
  - Julia Ju, PharmD, PhD
  - Susan Pretko, PharmD, MPH
  - Christopher St.Clair, PharmD (Detail)
  - Hongling Zhou, PhD (Detail)
- ORISE Fellows:
  - Parima Ghafoori, PharmD
  - Yujin Chung, PharmD

Congratulations

- **Qualification of Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)** demonstrated adequate evidence of content validity and cross-sectional measurement properties (i.e., internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of asthma in the context of use described below.

- **COA Concept of Interest :**The concept of interest is the severity of the core defining symptoms (difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough) of asthma

- **Context of Use :**The appropriateness of the ADSD and ANSD as primary or secondary endpoint measures has not been established. This qualification statement supports the ADSD and ANSD as measures of asthma symptoms in drug development. Further evaluation is needed on the instruments' longitudinal measurement properties (e.g., ability to detect change) and the interpretation of clinically meaningful within-patient change in scores. This information can be obtained in early phase studies in drug development programs.

Submissions and Letters

	Type	CY 2018
Received	Letters of Intent (LOIs)	10 (9)*
	Qualification Plans (QPs)	2 (0) *
	Full Qualification Packages (FQPs)	2 (2) *
	Updates	13
	Information Request (IR) Responses	17
	Meeting Requests	7
Sent	Response Letters	19
	Response Emails	2
	Referrals to the Critical Path Institute	11
	Qualification Statements	1

* Number of submissions reviewed by the COAQP

Meetings (CY 2018)

	Meeting Type	Number
External	Teleconferences between the QRT and requestor(s)	10
	Teleconferences between the COAQP and requestor(s). This includes interest calls with potential requestors.	18
Internal	Internal COA Meetings	20
	QRT Meetings	40
	DDT Committee Meetings	5

Additional Initiatives and Projects

- Organize, review and create the first postings to meet the transparency provisions of the 21 CC.
- Lead our drug development tool (DDT) Qualification Program (QP) counterparts in the effort to revamp and update joint DDT webpages.
- Participated, planned and coordinated the December Public Meeting to discuss the DDT program.
- Participate with bioinformatics meetings to identify and pilot solutions that will increase the efficiency of receiving submissions and document management.
- Participate in regular meetings discuss legal issues related to COAQP and 21 CC.

“Limited Context of Use”

- No longer using exploratory qualification
- Context of Use are now described based on the data provided
- “Limited Context of Use”- demonstration of content validity and cross-sectional measurement properties

Last 10 Years

- 5 Qualifications
  - 3 from PRO Consortium
- Developed a Process Guidance
- Passage of 21st Century Cures
  - New process and transparency
- Strong relationships with Review Divisions and Office of Biostatistics
- More communication with the Agency

In the Future

- Revised Process Guidance
- Online Portal Based Submission System
- More qualifications ☺

UPDATES IN PATIENT-FOCUSED DRUG DEVELOPMENT INITIATIVES: PAST, PRESENT AND FUTURE

Elektra Papadopoulos, MD, MPH

Happy 10th Anniversary!!

Patient-Focused Outcomes

Those outcomes important to patients' survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by providers and caregivers when patients cannot report for themselves

Donald L. Patrick, Ph.D., MSPH
May 20, 2013

Pillars of Patient-Focused Drug Development

- Collaboration
- Science and innovation
- Communication and transparency

COLLABORATION

If you want to go fast, go alone.

If you want to go far, go together.

African proverb

Collaborations

- Public Private Partnerships, including
  - Critical Path Institute
  - CTTI (FDA and Duke University)
- Government agencies
  - Other domestic and international agencies
  - NIH (including pain, addiction, aging, rare diseases)
  - Internal-FDA cross collaborations
- Academia, including
  - Centers of Excellence in Regulatory Science and Innovation (CERSI)
    - Yale/Mayo, UCSF/Stanford, Univ of Maryland, Johns Hopkins University
- Patient Groups
- Others

PRO Consortium

- COA instruments
  - Three qualified from PRO Consortium
    - Symptoms of major depressive disorder (adults) (2017)
    - Non-small cell lung cancer symptoms (2018)
    - Asthma symptoms (adults and adolescents) (2019)
  - One in qualification review (IBS-C)
- Science
  - Publications, participation in expert workshops, others
- Learnings
  - Continuous learning can help shape policies and practices

SCIENCE AND INNOVATION

- Section 1. Modernize Toxicology to Enhance Product Safety: Strategic Plan for Regulatory Science
- **Section 2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes: Strategic Plan for Regulatory Science**
- Section 3. Support New Approaches to Improve Product Manufacturing and Quality: Strategic Plan for Regulatory Science
- Section 4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies, Strategic Plan for Regulatory Science
- **Section 5. Harness Diverse Data through Information Sciences to Improve Health Outcomes: Strategic Plan for Regulatory Science**
- Section 6. Implement a New Prevention-Focused Food Safety System to Protect Public Health: Strategic Plan for Regulatory Science
- Section 7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security: Strategic Plan for Regulatory Science
- Section 8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products: Strategic Plan for Regulatory Science

Regulatory science is unique

- Science to support regulatory decision-making, including shaping policy and communication strategies
- Science of patient input is a key component of regulatory science

Science of Patient Input

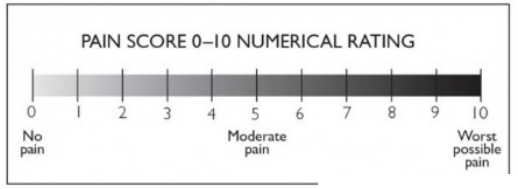
- The generation and use of patient experience data is an evolving science
- Multidisciplinary, collaborative approach needed
- Rigor needed to ensure evidence is fit for regulatory decision-making

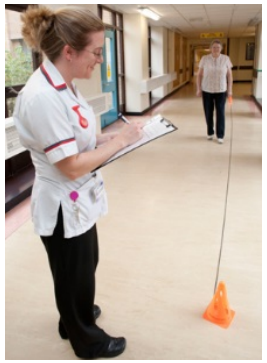
Emerging data sources: Social media & other online sources

- Potential rich data source of patient experience
- Semantic analysis can be used to extract meaningful information from unstructured and unsolicited data sources
- Potential to inform regulatory decisions including:
  - Patient-focused measurement strategy
  - Endpoint selection; including COAs
  - Benefit:risk assessment

How do we measure how patients feel and function?

Traditional Approaches





Novel Approaches

FDA's Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation

August 29, 2018

By: Scott Gottlieb, M.D.

- *"Electronic capture of PRO data (ePRO) is also becoming standard, providing a rich pipeline of structured clinical data.*
- *...mobile wearable technologies can complement traditional PRO surveys by generating objective, continuous activity and physiologic data.*
- *Obtaining reliable wearable device data on activity level, coupled with direct patient report on their ability to carry out important day to day activities, can provide information on physical function that is directly relevant and important...."*

https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm619119.htm

Some potential impacts of endpoints collected via remote data capture

- Enhancement of endpoints that matter to patients in daily life (e.g., information of patients' experiences between clinic visits)
- Reduced participation burden/fewer barriers to clinical trial participation (e.g., travel)
- Larger, more inclusive, and more generalizable trials

Adapted from: Clinical Trials Transformation Initiative's Mobile Clinical Trials – Novel Endpoints Project

COMMUNICATION/TRANSPARENCY

COA Terminology*

- Where we were in 2010:
  - PROs, Caregiver reports and ClinROs
- Where we are today:
  - Clinician-reported outcome instruments
  - Observer-reported outcome instruments
  - Patient-reported outcome instruments
  - Performance outcome instruments
- Next:
  - “Digital health technology tool” COA?

*BEST (Biomarkers, EndpointS, and other Tools) Resource
https://www.ncbi.nlm.nih.gov/books/NBK338448/

COA Compendium Expansion

- **Coming soon!**
- Communication tool:
  - Includes COAs that have been previously labeled and may serve as a starting point for consideration and discussion between drug developers and FDA
- We heard your recommendations:
  - Added drug's name and approval date corresponding to the labeling
  - Will omit COAs in development/review in the COA DDT Qualification Program
    - Ongoing qualification projects are listed on the public COA Qualification website

New COA Compendium Format

Division of Metabolism and Endocrinology Products (DMEP)				
Disease/Condition	Concept	COA Tool & Type	COA Context of Use	Drug Name/ Approval Date/ Qualification Link
Human immunodeficiency virus (HIV)-related lipodystrophy	Body image	Belly appearance distress score: PRO	Adult patients with HIV-related lipdystrophy	Egrifta (tesamorelin) November 10, 2010

COA Core Sets Pilot Program: Purpose

- Develop publicly available standard core set(s) of COAs and their related endpoints for specific disease indications
- The standard core set(s) can include different types of COAs (i.e. PRO, ClinRO, ObsRO, PerfO instruments) and their related endpoints that assess *a minimum list of impacts that matter most to patients, are likely to demonstrate change, should be reported in a clinical trial and inform FDA's assessment of drug safety and effectiveness*
- A standard core set might be relevant across several disease populations or subgroups or be focused on attributes of a specific disease

COA Core Sets Pilot Program: Disease Areas or Disease Impacts of Interest

- **Gastrointestinal diseases/conditions**, specifically for use across gastrointestinal diseases/conditions with overlapping signs and symptoms
- **Physical/functional status** including, but not limited to, **standardized assessment of activities of daily living dependent on gross and fine motor function** (including upper and lower limb function) across a range of diseases and populations
- **Migraine** trials, including functional impact or disability from migraine
- **Opioid sparing drugs intended to treat acute pain**
- **Schizophrenia trials**, including shortened versions of current instruments, as appropriate

FDA is also interested in applications for disease areas or disease impacts that are not represented on this list.

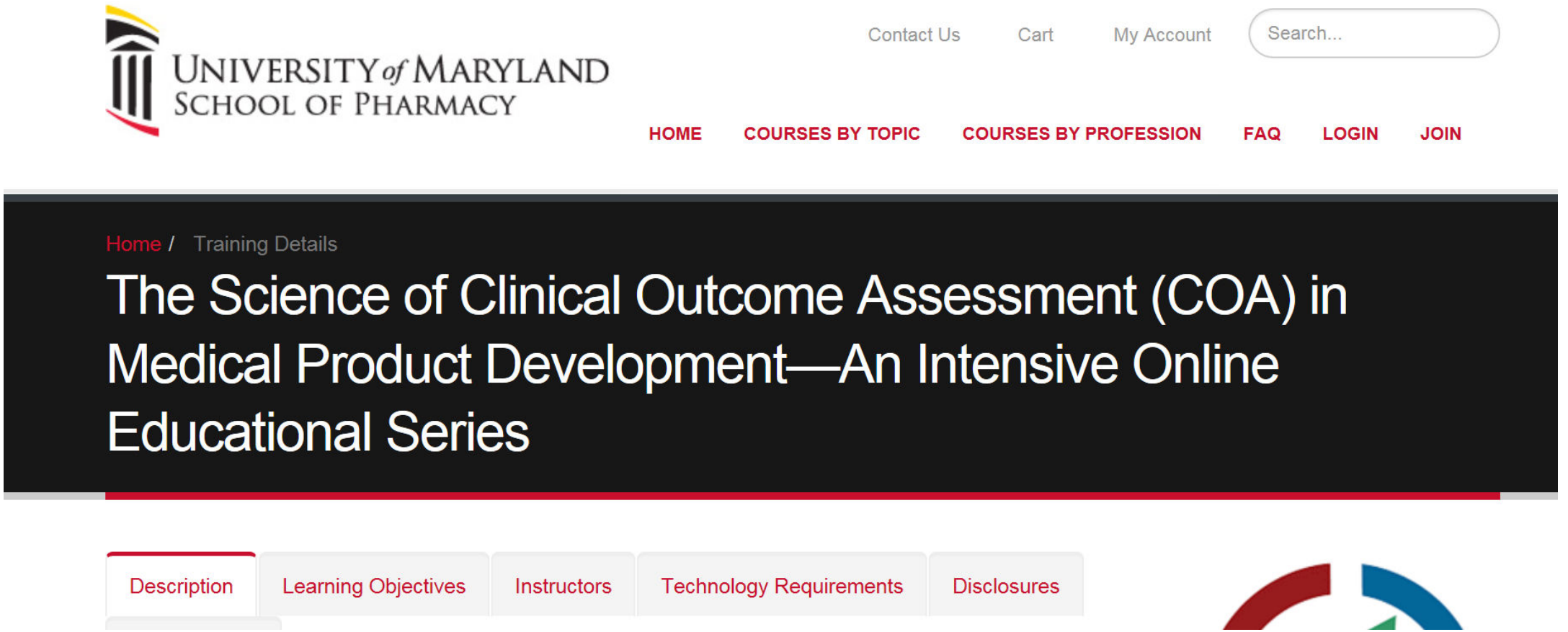
COA Core Sets Pilot Program: Deadline for applications

- Application Due Date:
  - **May 31, 2019, by 11:59 PM Eastern Time**

- Apply early; No late applications will be accepted

https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-19-006.html

New COA course now available!



https://ce.pharmacy.umaryland.edu/ProductDetails.aspx?ProductID=311

Overview of PFDD Guidance Development: 21st Century Cures and PDUFA VI

- Guidance 1: Identifying research questions and developing a sampling strategy to collect representative patient input; operationalizing data collection, management and analysis (Draft guidance issued: June 2018)
- Guidance 2: Methods to elicit detailed, unbiased, and comprehensive input from patients, patient groups, and caregivers (Public Workshop held Oct 15-16, 2018)
- Guidance 3: Using patient input to develop or identify appropriate COAs for use in clinical trials (Public Workshop held Oct 15-16, 2018)
- Guidance 4: Developing COA-related clinical trial endpoints based upon patient input; interpreting those endpoints

Future

- Capacity building—COA Staff is hiring!
- Knowledge management
  - COAs being used in trials, including use of qualified instruments
  - Submission and use of patient-experience data
- Continued growth of the DDT Qualification Program—with greater efficiency and transparency
- PFDD guidance development
- Continued multi-stakeholder and cross-disciplinary collaboration
- Research and innovation
  - Use of social media and other online data sources
  - Increased experience with use of digital health technology tools (e.g., activity monitors)
  - Measurement research and COAs in rare diseases, children and in heterogeneous populations
  - COA Toolboxes
  - Collection, interpretation and communication of patient experience data
  - Others

Thank you!

AUDIENCE Q&A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