U.S. Food and Drug Administration
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Biomarkers in Drug Development

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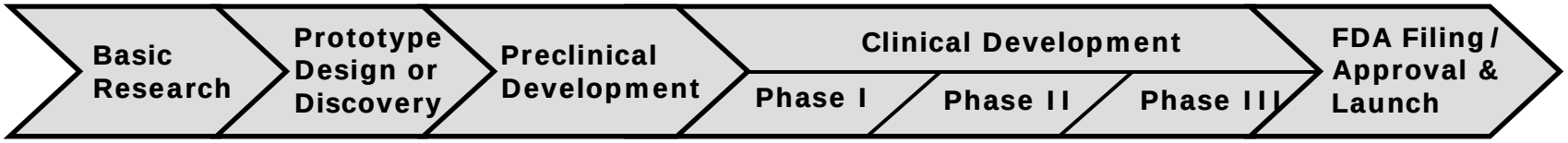
Myotonic Dystrophy Patient-Centered Therapy Development
September 17, 2015

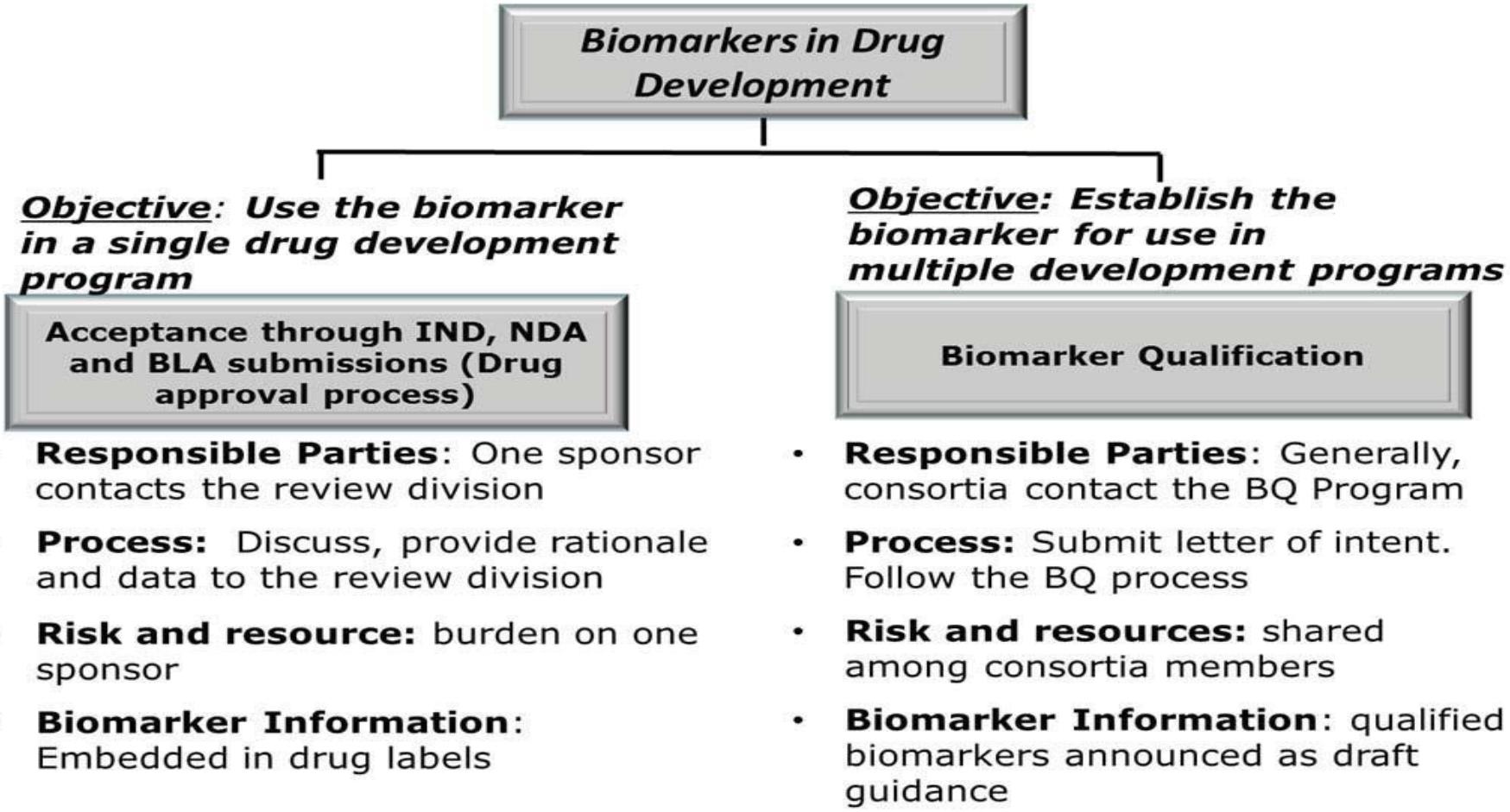
Overview

- Introduction
- Biomarker Qualification(BQ)
- Biomarker Survey
- Efforts towards developing evidentiary standards
- Take home points

Biomarkers in Drug Development



- Molecular pathways underpinning disease
- Mechanism of action of therapeutics
- Preclinical safety assessment
- Clinical trials
  - Safety Assessment
  - Dose selection
  - Stratification
  - Patient selection/enrichment
  - Surrogate end Point
- Companion Diagnostic
  - Selection of right patients for increased efficacy/safety



Amur et al, Clin. Pharm. Ther. 98 (1) 34-46, 2015

Biomarker Qualification (BQ)

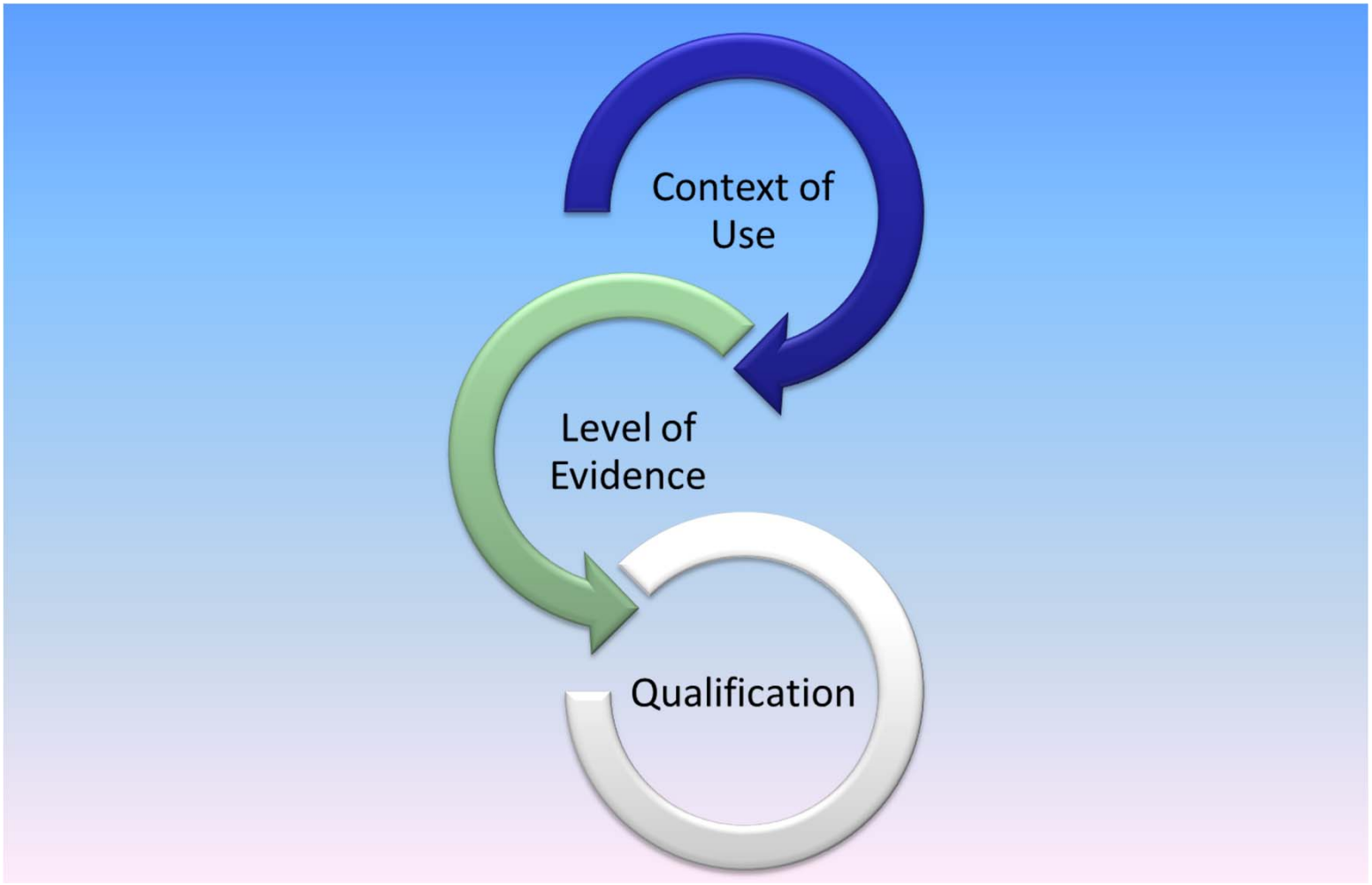
Definition:
A conclusion that within a carefully and specifically stated "context of use" the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development

Context of use:
"Context of use" is a comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development.

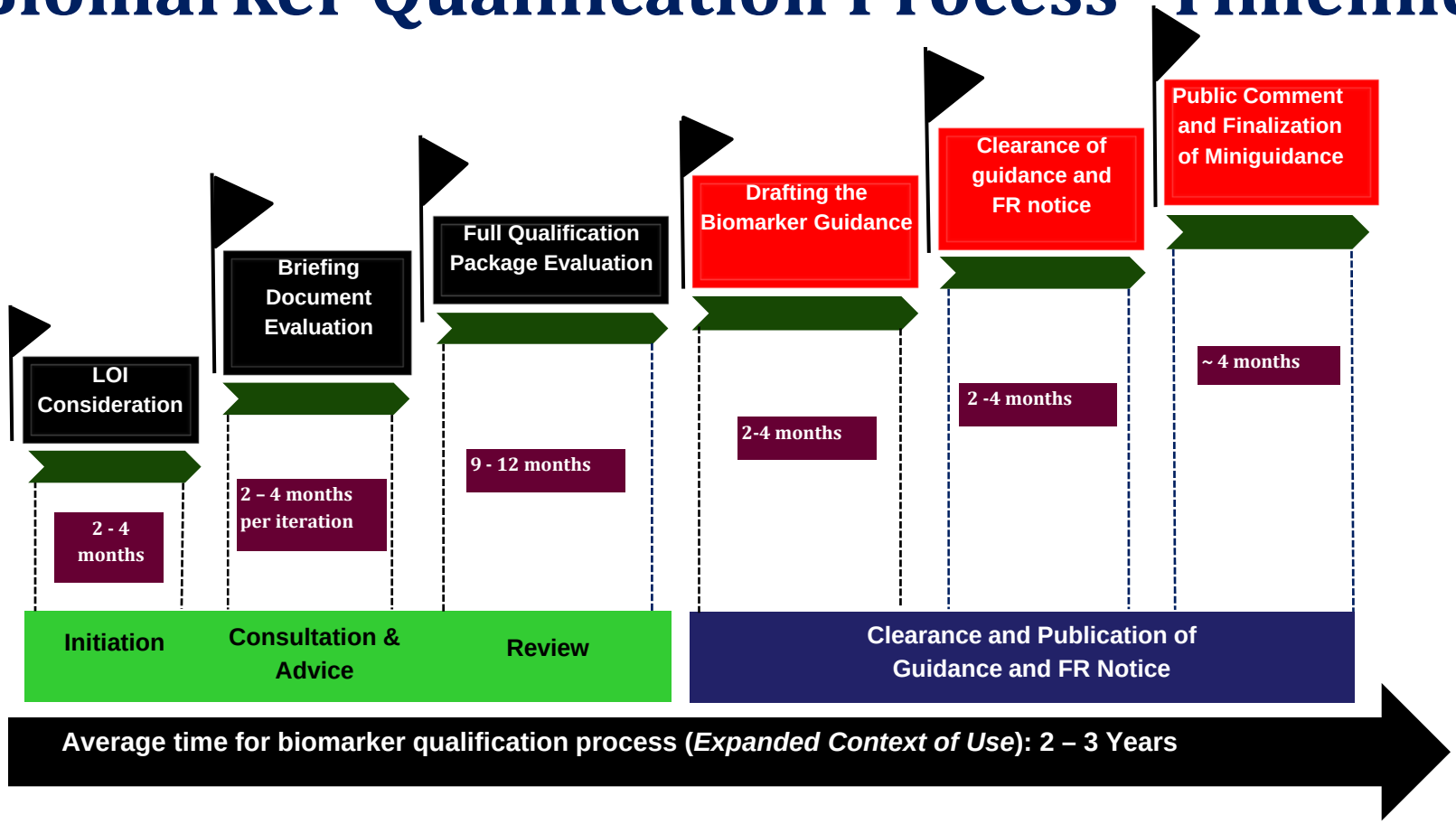
- Use Statement:
  Name, identity and purpose of use of the biomarker in drug development

- Conditions for qualified use:
  Comprehensive description of conditions and boundaries for the biomarker to be used in the qualified setting

Biomarker Qualification Concept



Biomarker Qualification Process- Timeline



Note: *The timeline is based on our experience to date and may vary. This timeline does not capture the time needed by submitters to generate the data and submit the necessary documents (LOI, Briefing document, and Final Qualification Package) or requested additional information.*

List of FDA-Qualified Biomarkers

Qualified Biomarkers and Supporting Information:

General Area	Submitter	Biomarker(s) Qualified for Specific Contexts of Use	Issuance Date with Link to Specific Guidance	Supporting Information
Nonclinical	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary biomarkers: Albumin, β2- Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil factor-3	4/14/2008 Drug-induced Nephrotoxicity Biomarkers	Reviews
Nonclinical	International Life Sciences Institute (ILSI)/ Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)	9/22/2010 Drug-induced Nephrotoxicity Biomarkers	Reviews
Nonclinical	PJ O'Brien, WJ Reagan, MJ York and MC Jacobsen	Serum/plasma biomarkers: Cardiac troponins T (cTnT) and I (cTnI)	2/23/2012 Drug-induced Car-diotoxicityBiomarkers	Reviews
Clinical	Mycoses Study Group	Serum/bronchoalveolar lavage fluid biomarker: Galactomannan	10/24/2014 Patient selection biomarker for enrollment in Invasive Aspergillosis (IA) clinical trials	Reviews
Clinical	Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)	Plasma biomarker: Fibrinogen	7/6/2015 Prognostic biomarker for enrichment of clinical trials in Chronic Obstruction Pulmonary Disease (COPD)	Reviews
Clinical	Polycystic Kidney Disease Outcomes Consortium	Imaging Biomarker: Total Kidney Volume (TKV)	8/17/2015 Prognostic biomarker for enrichment of clinical trials in Autosomal Dominant Polycystic Kidney Disease.	Reviews

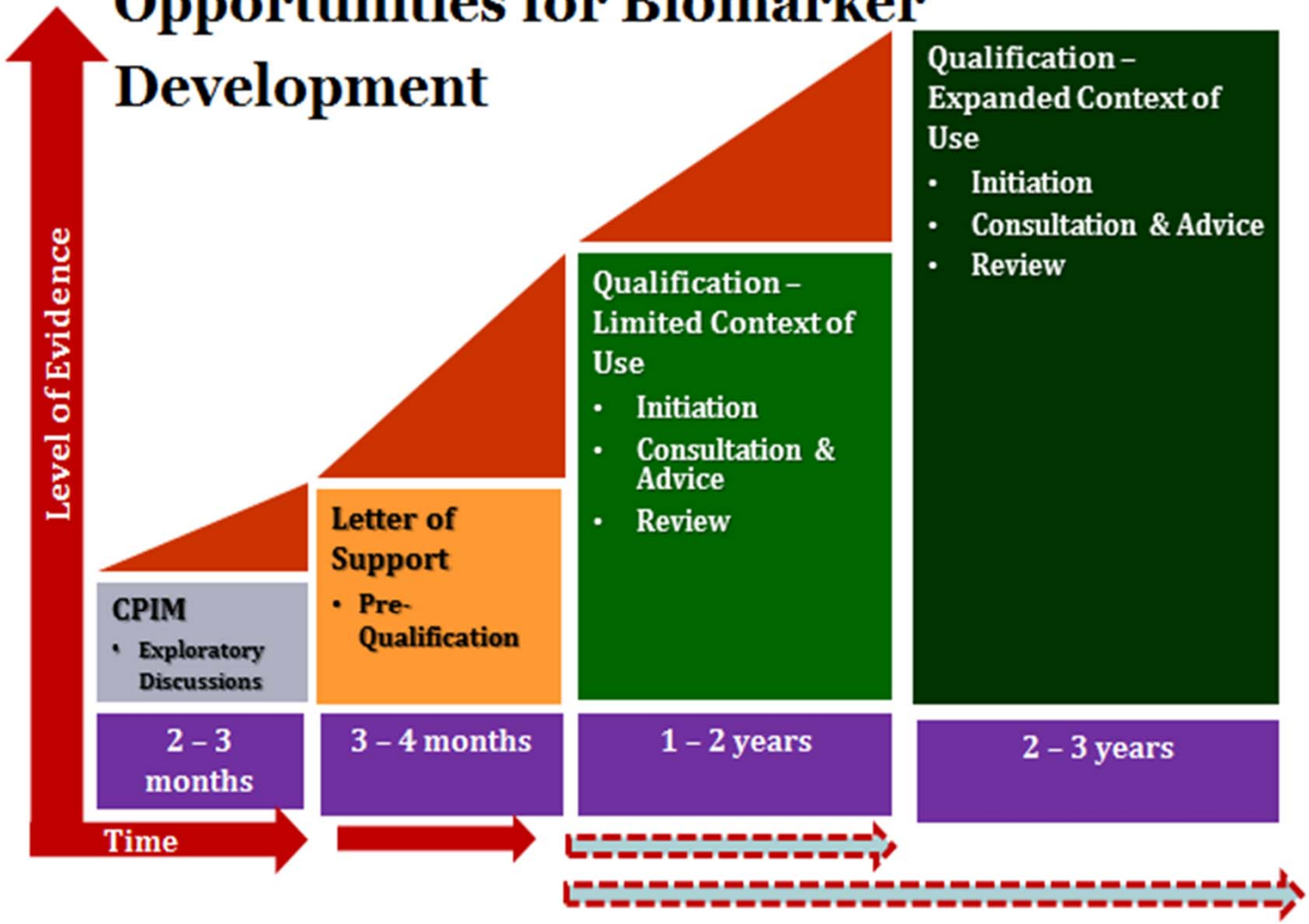
Submitters: Can be Individuals or groups; e.g., Academia, Consortia, Disease foundations, Patient advocacy groups

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

Considerations for Biomarker Qualification

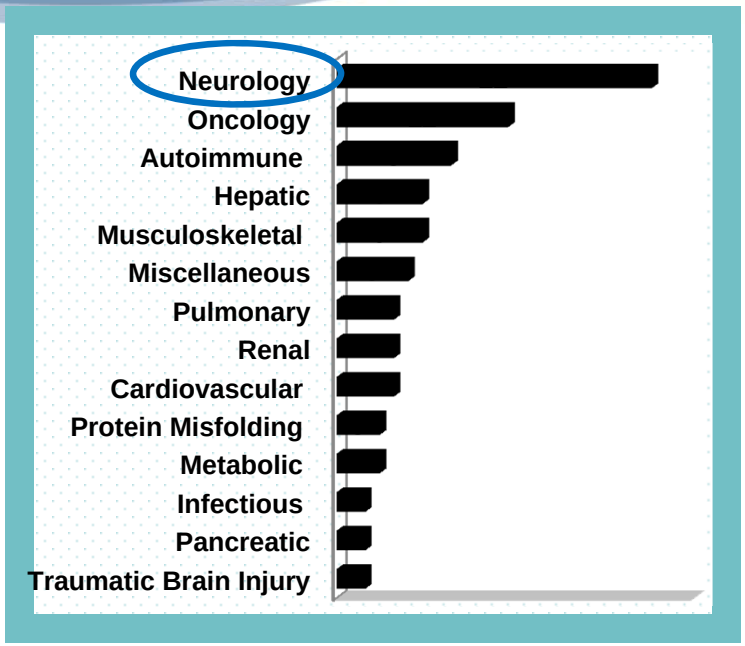
- **Type and COU of the biomarker** for use in drug development
- **Biological rationale** for use of the biomarker (if available)
- Characterizations of the various **relationships** among the biomarker, the clinical outcomes, and the treatment (where applicable) required for the proposed COU.
- **Assay considerations** (analytically validated method and understanding of potential sources of variability in the measurement).
- **Type of data available** to assess the strength of association of the biomarker with its proposed clinical outcome: retrospective or prospective, registry data, and/or randomized controlled trial (RCT) data.
- **Reproducibility of data** (need for test dataset and confirmatory dataset).
- Use of appropriate, **pre-specified statistical methods** to demonstrate the hypothesized relationships for the COU.
- **Strength of evidence**: the level of evidence depends on the type of biomarker and its COU.

Opportunities for Biomarker Development



FR Notice- Survey

- **Goal**: *Identifying Potential Biomarkers for Qualification and Describing Contexts of Use to Address Areas Important to Drug Development*
- **Logistics**: Published on February 13, 2015 with a deadline of April 14, 2015. Extended to May 15, 2015
- Two options given for providing responses
  - Docket (35 responses received)
  - Survey Monkey (38 responses received)



Survey Results

Number of responses received in the survey

Disease	Biomarkers
Duchenne's Muscular Dystrophy (DMD)	• Dystrophin • Skeletal MRI • The assessment of upper extremity function based on the concept of 3-dimensional reachable workspace
Duchenne muscular dystrophy (DMD), Facioscapulohumeral muscular dystrophy (FSHD), Becker muscular dystrophy (BMD), and Amyotrophic Lateral Sclerosis (ALS).	A scalable and sustainable remote measurement platform for upper extremity function.
Myotonic dystrophy (DM)	• Biomarkers for cardiac and central nervous system. • Predictive genetic biomarkers. CELF1 protein (upregulated in DM1 tissues, particularly in heart).

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm459144.htm
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM459168.pdf

Efforts at Developing Evidentiary Standards

A Multiple stakeholder effort:

Workshops

- PhRMA-FDA workshop in 2007
- Institute of Medicine Workshop on Biomarker Qualification in 2009
- FDA-cosponsored "Biomarkers workshop" with HHMI in 2013
- FDA-cosponsored Brookings meeting on "Advancing the Use of Biomarkers and Pharmacogenomics" in 2014
- FDA-cosponsored workshop with M-CERSI and PSTC "Evidentiary Considerations for Integration of Biomarkers in Drug Development "held today (August 21, 2015)
- NIH-FDA Workshop planned for October, 2015
- FNIH-FDA Workshop planned for 2016

Take Home Points

- Biomarkers can be integrated into drug development through either of the two pathways:
  1. Regulatory submissions for drug approval in the context of a single drug or
  2. Biomarker qualification
- Biomarker Qualification is intended for biomarkers that will be used in multiple drug development programs
- Biomarker Qualification is a voluntary process
- Early engagement with FDA on biomarker qualification encouraged

Acknowledgements

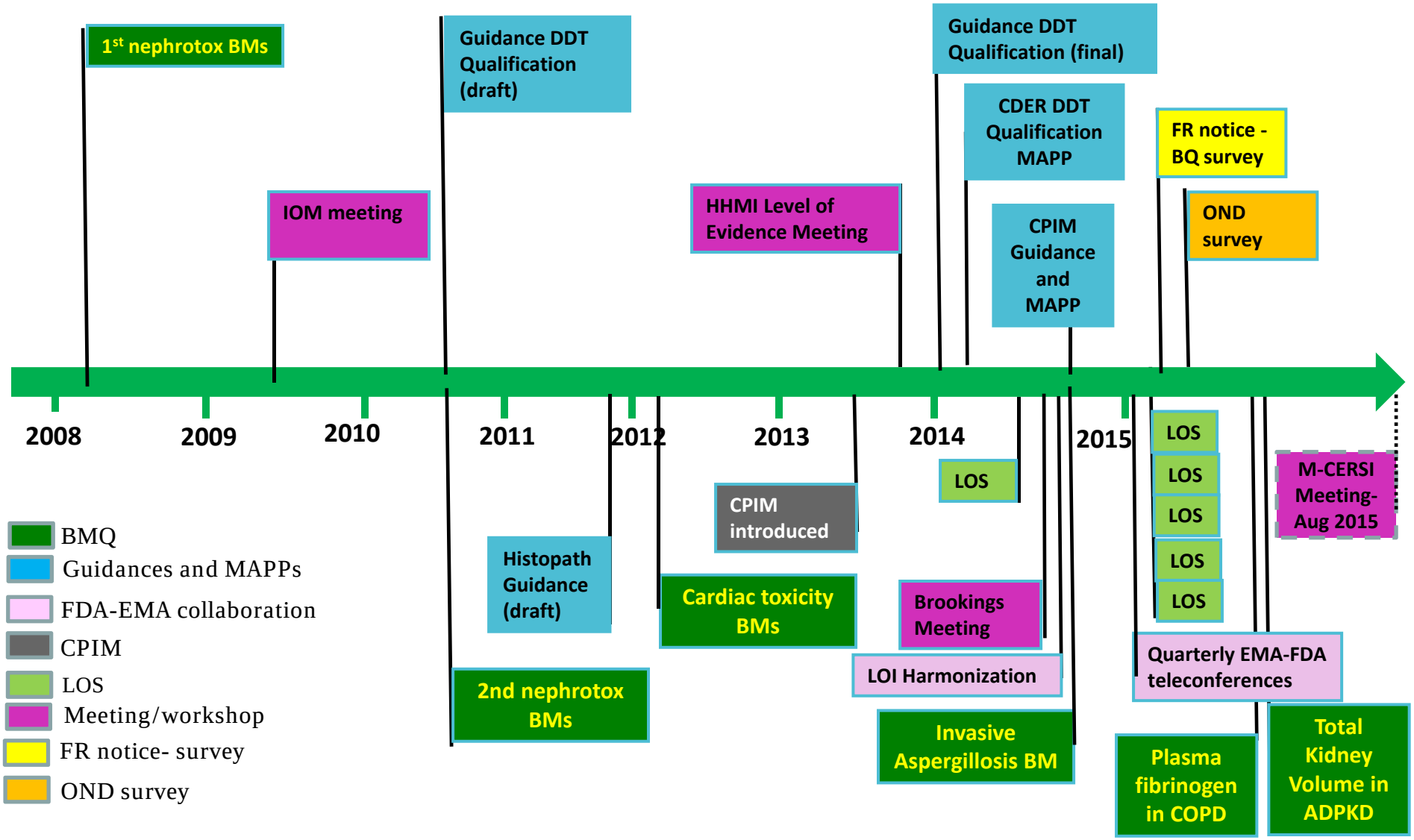
Janet Woodcock
ShaAvhrée Buckman-Garner
Chris Leptak
Suzie McCune
Marianne Noone
Sarmistha Sanyal

Back up slides

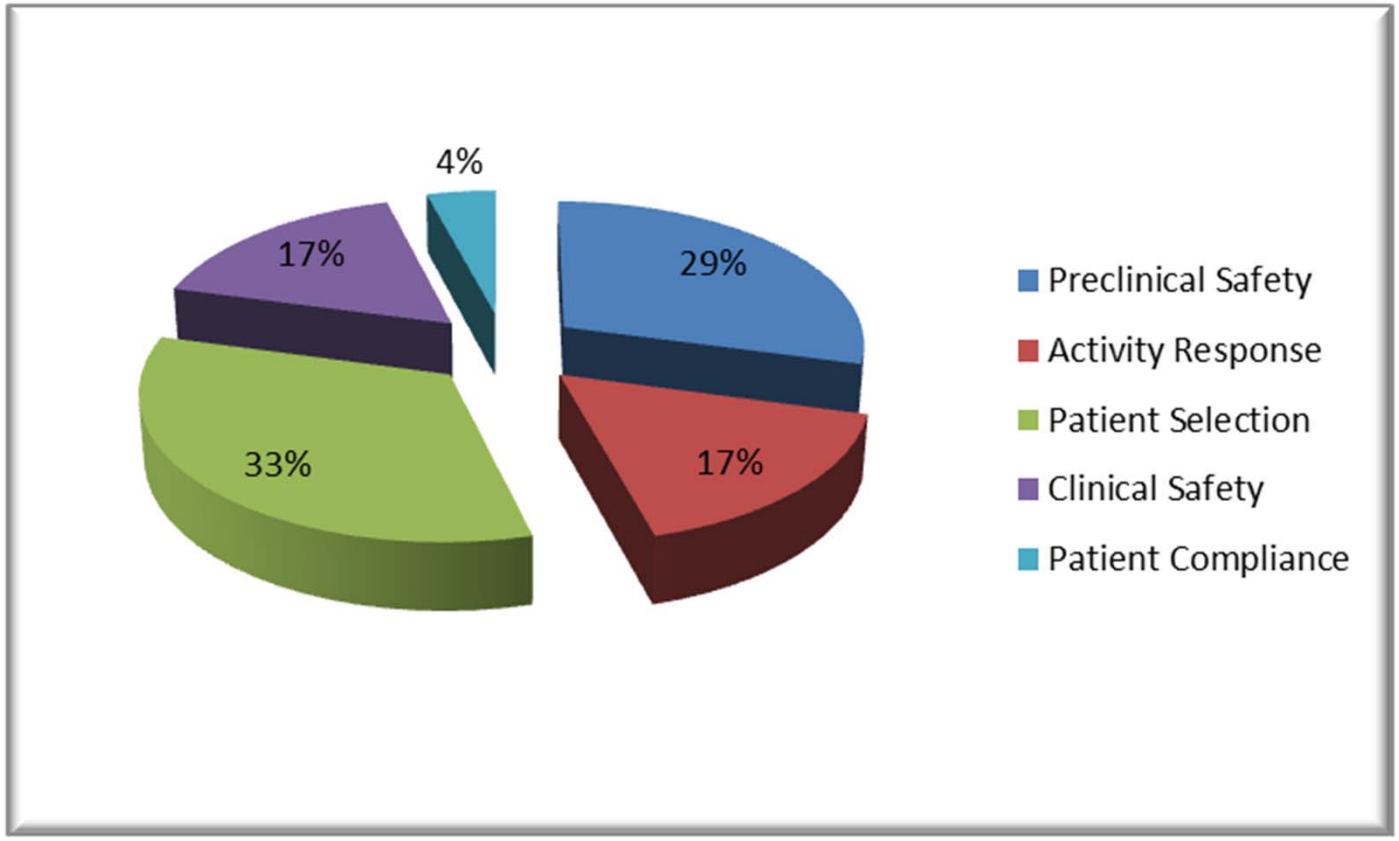
In Preparation for Biomarker Qualification

- Identify promising biomarkers potentially useful in drug development
- Availability of a reliable method to measure the biomarker (preferably analytically validated at this stage)
- Context of Use of the biomarker- How (manner and purpose of use) can the biomarker(s) be used in drug development programs?
- Collect available data, evaluate gaps in the knowledge
- Usefulness of available data for qualification (retrospective data acceptable); which studies to select and why
  - Additional studies needed? Plan studies- consult FDA early
  - Consider resources needed
- Consider Design principles, data standardization, and data sharing needed
  - Prospective statistical analysis plan
  - Testing/confirmatory data sets

Timeline for Salient BQ-related Efforts



What types of submissions are we seeing for Biomarker Qualification?



Where are The Submissions in the BQ Process?

August, 2015 Update

Drug Development Tool (DDT) Qualification Projects at CDER, FDA

This Table provides the current[1] number of active CDER Drug Development Tool (DDT) Qualification projects overall and by Program. Numbers are also provided by stage. Refer to DDT Contacts and Submitting Procedures for contact information for each DDT Program.

	All Drug Development Tool (DDT) Qualification Programs	DDT - Animal Model Qualification Program	DDT - Biomarker Qualification Program	DDT - Clinical Outcome Assessments
Total Number of Active Projects	91	8	22	61
Number in Initiation Stage	30	5	1	24
Number in Consultation and Advice Stage	55	3	18	34
Number in Review Stage	5	0	3	2
Number Qualified	7	0	6	1

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm409960.htm

16/24 submitters agreed to add their Submission information to the FDA webpage

Biomarker Qualification (BQ) Submissions

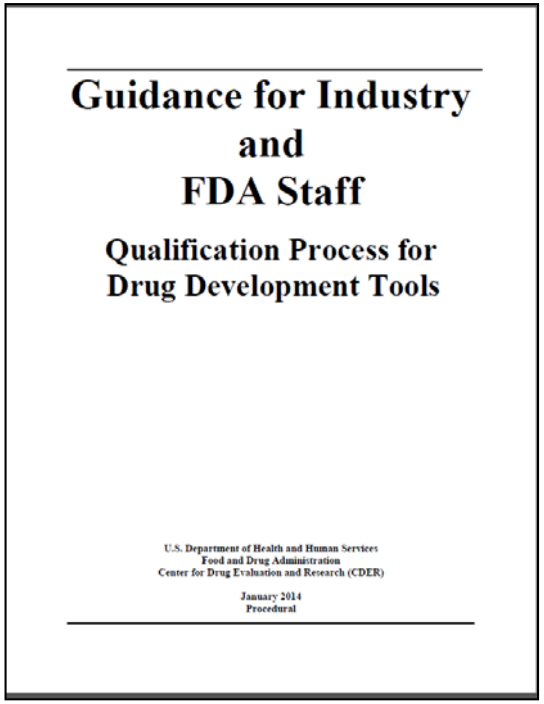
Submitter	Biomarker	Date Accepted into BQ Program	Type of Biomarker	Proposed Biomarker Utility	Qualification Stage
Critical Path Institute (C-Path), Predictive Safety Testing Consortium, (PSTC), Skeletal Muscle Working Group (SKM WG) Contact: John-Michael Sauer	Drug-Induced Skeletal Muscle Injury Biomarkers	12/19/2009	Safety	Safety Assessment	Consultation and Advice
C-Path, PSTC, Hepatotoxicity Working Group (HWG) Contact: John-Michael Sauer	Drug-Induced Liver Injury Biomarkers	11/13/2009	Safety	Safety Assessment	Consultation and Advice
International Life Sciences Institute (ILSI) /Health and Environmental Sciences Institute (HESI) Contact: Raegan O'Lone	Genomic Biomarker Approach for Positive Findings in the In vitro Chromosome Damage Assays in Mammalian Cells	3/11/2010	Safety	Pre-Clinical Safety	Consultation and Advice
C-Path/ Coalition Against Major Diseases (CAMD) Contact: Diane Stephenson	Cerebral Spinal Fluid (CSF) Markers in Alzheimer's Disease	1/25/2011	Prognostic	Patient Selection	Consultation and Advice
C-Path/ CAMD Contact: Diane Stephenson	Baseline Hippocampal Volume Measured by MRI in Alzheimer's Disease	1/25/2011	Prognostic	Patient Selection	Consultation and Advice
C-Path PSTC Nephrotoxicity Working Group (NWG) Contact: John-Michael Sauer	Drug-Induced Non-Clinical Kidney Injury Biomarkers	1/26/2011	Safety	Safety Assessment	Consultation and Advice
C-Path PSTC NWG/ Foundation for the National Institutes of Health (FNIH)	Drug-Induced Clinical Kidney Injury Biomarkers	2/24/2011	Safety	Safety Assessment	Review

Opportunities for Collaboration

- **Develop evidentiary standards for context-of-use-specific biomarker qualification**
- **Prioritize specific diseases and respective biomarkers whose development and qualification would advance drug development and satisfy unmet medical needs**
- Expand qualification by developing and maintaining an accessible database for collecting biomarker data, and a repository for samples
- Develop standards for biomarker measurement tools…Reproducibility initiatives…
- Encourage and fund biomedical research that is necessary as the basis for development of new biomarkers
- Coordinate existing partnerships and consortia so that they effectively direct their efforts toward development and qualification of priority biomarkers
- Train investigators on regulatory considerations for biomarker development

Slide from Dr. ShaAvhree Buckman

Guidances



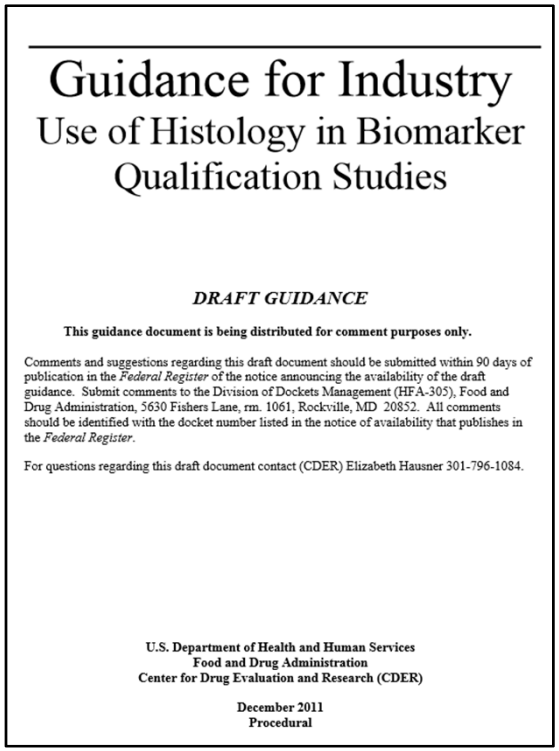
Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

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

January 2014
Procedural

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



Guidance for Industry
Use of Histology in Biomarker Qualification Studies

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

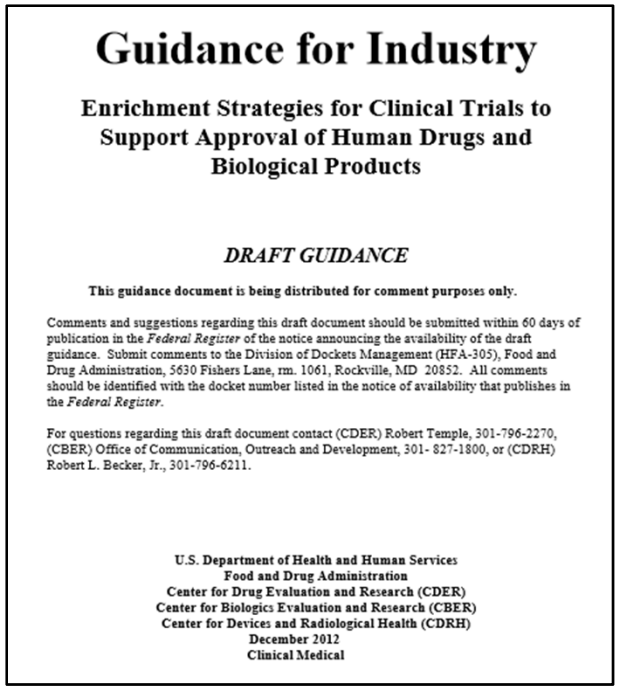
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers 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) Elizabeth Hausner 301-796-1084.

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

December 2011
Procedural

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285297.pdf



Guidance for Industry

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

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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

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf