FDA's Efforts to Encourage Biomarker Development and Qualification

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OTS/CDER/FDA

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M-CERSI Symposium, Baltimore, MD

Overview

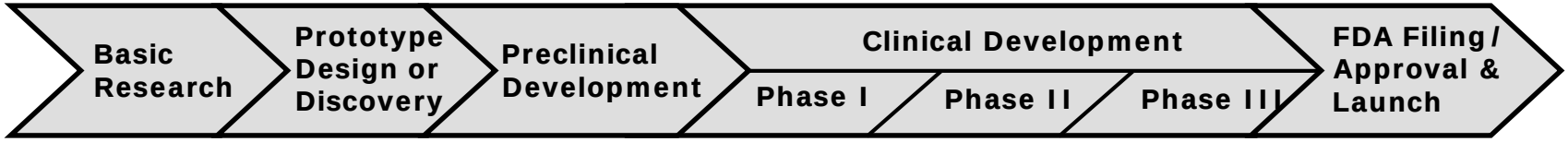
- Biomarkers in Drug Development
- Integration of biomarkers in drug development
- FDA's efforts to encourage biomarker development and qualification
- Take home points

Biomarkers

Definition: A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention"

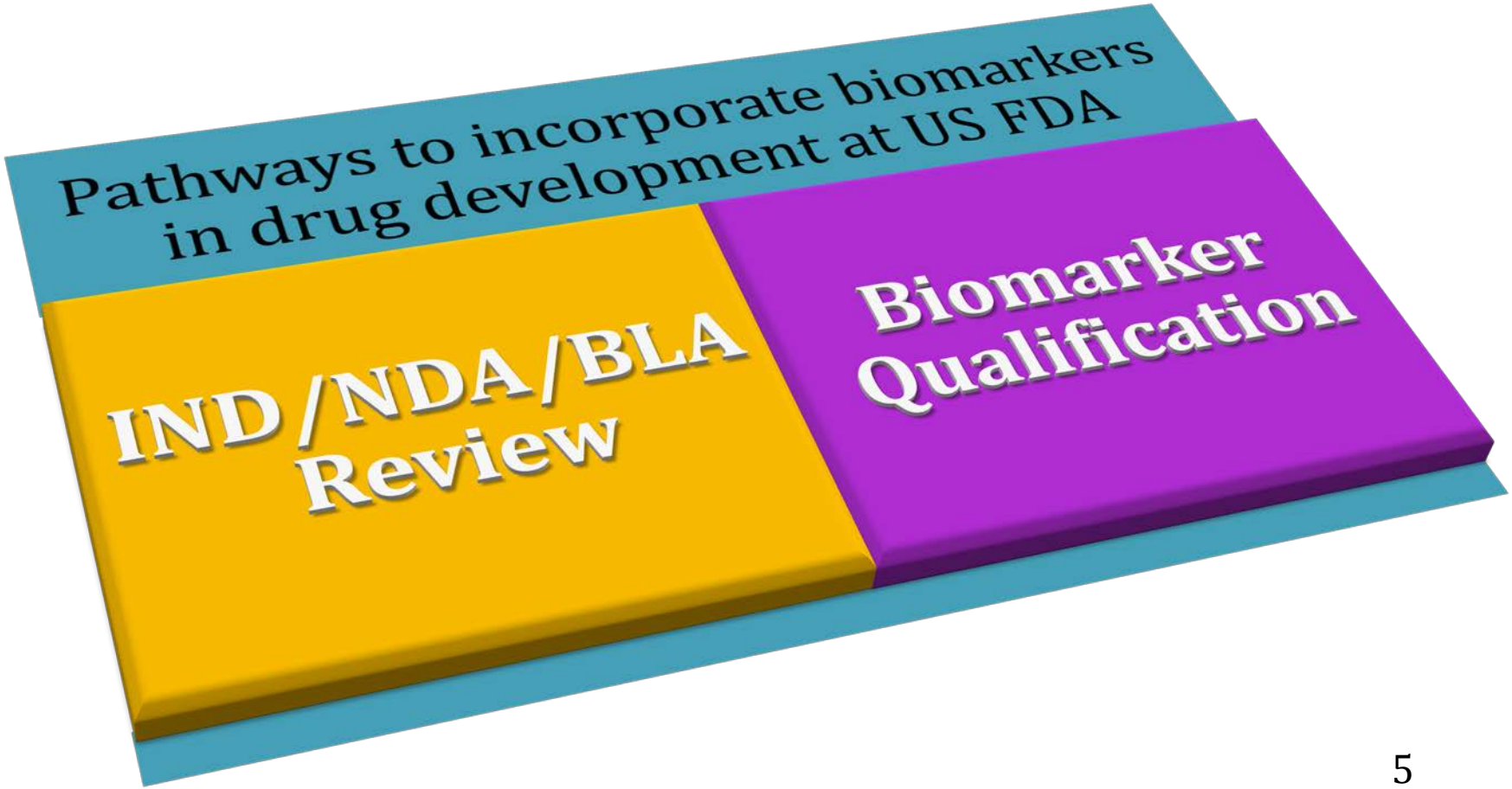
Biomarkers Definitions Working Groups: Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework. Clin. Ther. Pharmacol. 2001;69:89-95.

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

Pathways to facilitate integration of biomarkers in drug development



***Objective**: Use the biomarker in a single drug development program*

Acceptance through IND, NDA and BLA submissions (Drug approval process)

- **Responsible Parties**: One sponsor contacts the review division
- **Process:** Discuss, provide rationale and data to the review division
- **Risk and resource:** burden on one sponsor
- **Biomarker Information**: Embedded in drug labels

***Objective**: Establish the biomarker for use in multiple development programs*

Biomarker Qualification

- **Responsible Parties**: Generally, consortia contact the BQ Program
- **Process:** Submit letter of intent. Follow the BQ process
- **Risk and resources:** shared among consortia members
- **Biomarker Information**: qualified biomarkers announced as draft guidance

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

Biomarker Qualification (BQ)

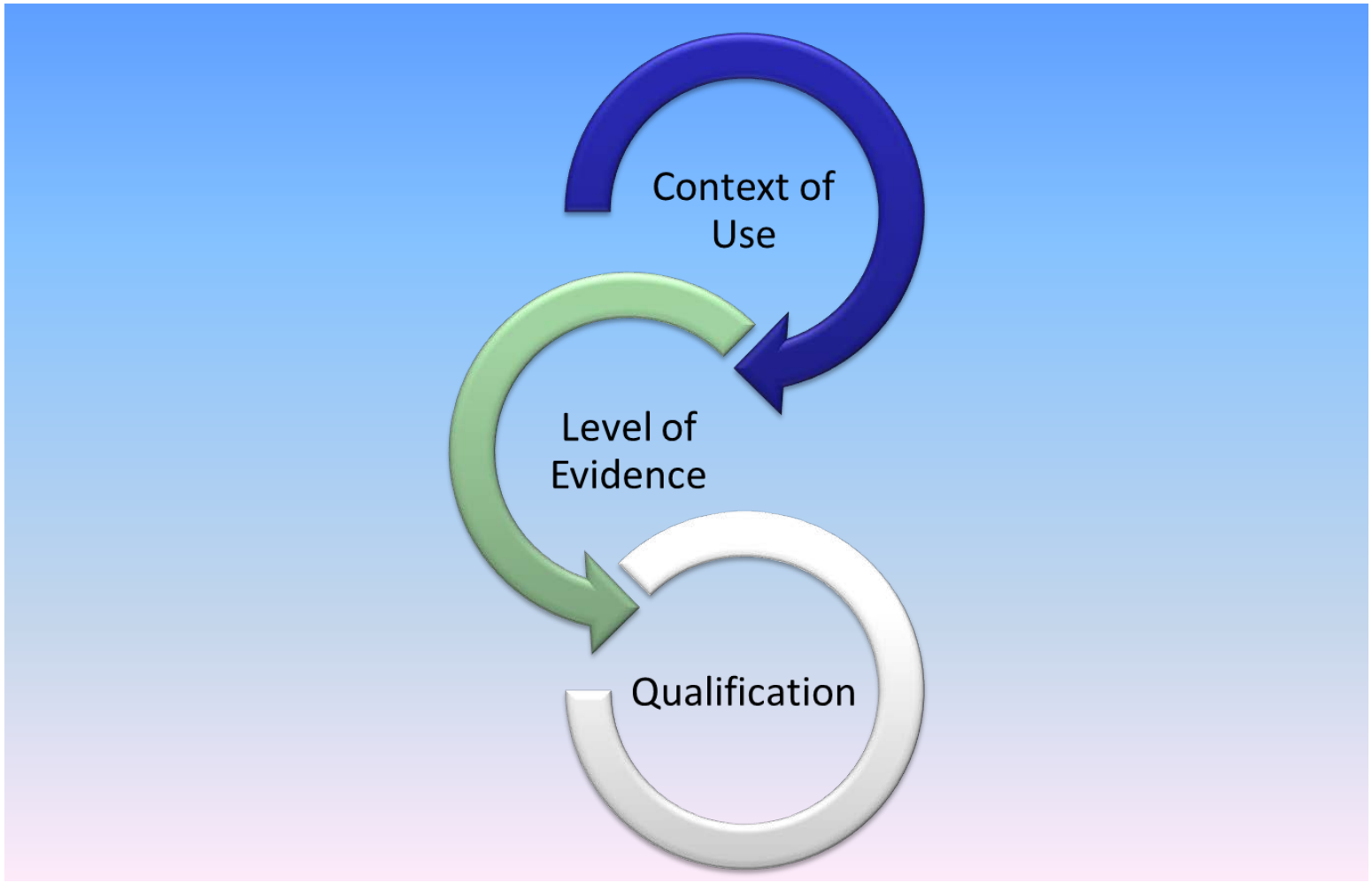
Definition:
A conclusion that within a carefully and specifically stated "context of use" the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development

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

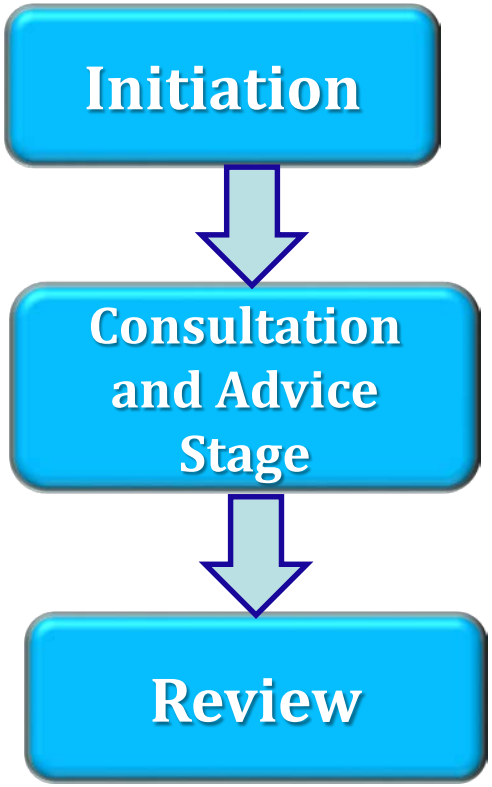
Biomarker Qualification Concept



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.

Biomarker Qualification Process



Letter of Intent (LOI) received, Biomarker Qualification Review Team (BQRT) formed, internal meeting, decision to proceed, send briefing document specifications to submitter. Biomarker Qualification Review Team (BQRT), is comprised of representatives from the appropriate review division, biostatistics, and others based on expertise needed to evaluate the submissions

Briefing document received, reviewed, internal meeting, pre-meeting comments, face-to-face Meeting- Iterative process

Full submission package received, review by BQRT, internal meetings, request additional information (if needed), qualification recommendations.

CDER Qualification Recommendation is issued as a draft guidance in federal register and posted on the FDA Guidance Web Page.

Public comments are received and the draft guidance revised, as needed and final guidance issued

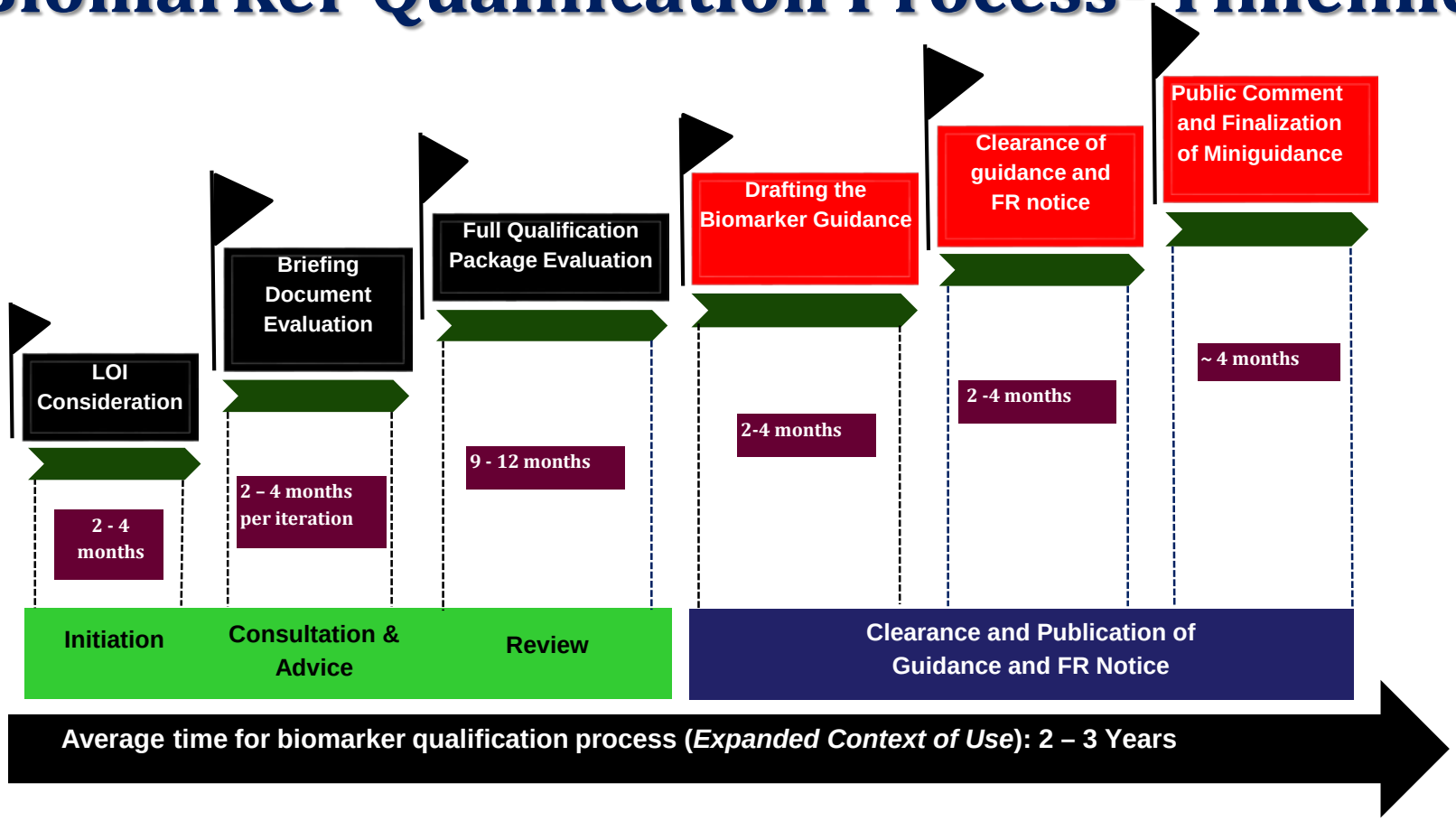
List of FDA-Qualified Biomarkers

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

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

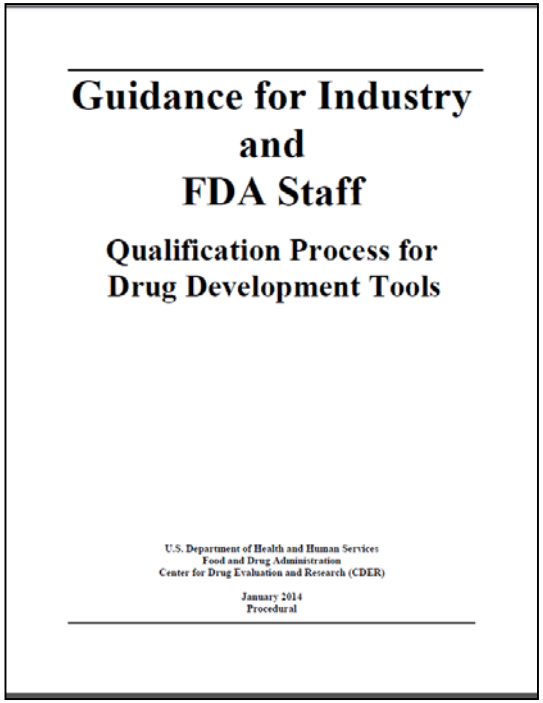
Biomarker Qualification Process- Timeline



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.*

FDA's Efforts to Encourage Biomarker Development and Qualification

Guidances



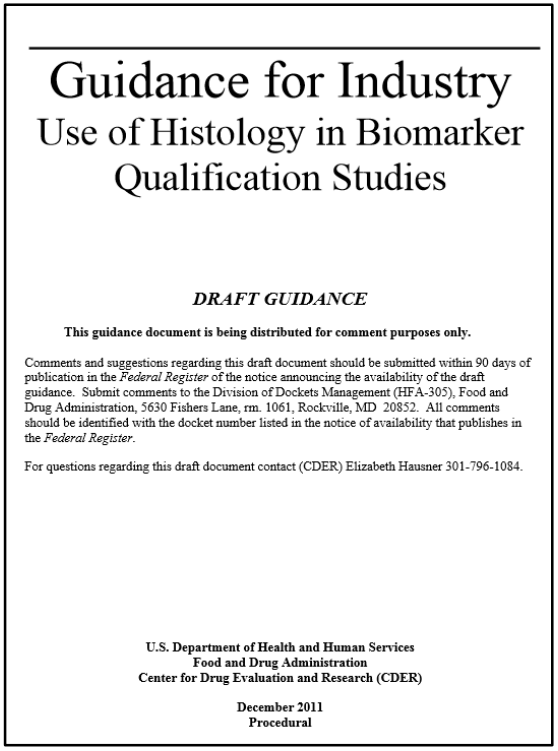
Guidance for Industry
and
FDA Staff

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.

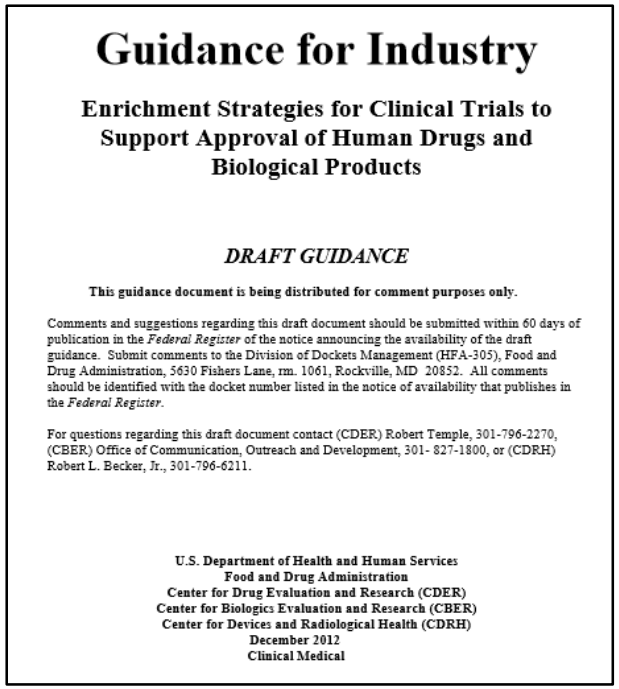
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers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

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.

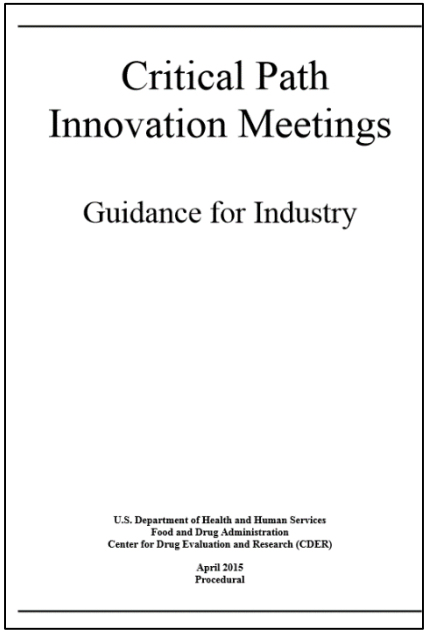
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical

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

New Initiatives

CPIM (Critical Path Innovation Meeting)

- Discussion of the science, medicine, and regulatory aspects of innovations in drug development; nonbinding
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers & clinical outcome assessments, natural history studies, technologies (not manufacturing), clinical trial designs and methods
- Outcomes include CDER perspective on role of innovation in drug development; proposals for future collaborations


Critical Path
Innovation Meetings

Guidance for Industry

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

April 2015
Procedural

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417627.pdf

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

Letters of Support

This is a letter issued to a submitter that briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation. **This letter does not connote qualification of a biomarker**. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.

Issued Letters of Support

Submitter	Biomarkers	Area(s) for Further Evaluation	Issuance Date with Link to Letter of Support	Submitter Contact
Critical Path Institute's (C-Path) Predictive Safety Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary Biomarkers: Osteopontin and Neutrophil Gelatinase-associated Lipocalin (NGAL)	Early Clinical Drug Development	8/20/2014: Letter of Support (PDF)	Refer to Predictive Safety Testing Consortium Web Site
C-Path, PSTC, Skeletal Muscle Working Group (SMWG)	Serum and Plasma Biomarkers: Myosin Light Chain 3 (Myl3), Skeletal Muscle Troponin I (sTNI), Fatty Acid Binding Protein 3 (FABP3), Creatine Kinase, Muscle Type (CK-M, the Homodimer CK-MM)	Early Clinical Drug Development	1/22/2015: Letter of Support (PDF)	Refer to Predictive Safety Testing Consortium Web Site
C-Path, Coalition Against Major Diseases Consortium (CAMD)	Cerebral Spinal Fluid (CSF) Analyte Biomarkers: $A\beta_{1-42}$, Total tau, Phosphotau	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer's Disease Clinical Trials	2/26/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, CAMD	Magnetic Resonance Imaging Biomarker: Low Baseline Hippocampal Volume	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer's Disease Clinical Trials	3/10/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, CAMD	Molecular Neuroimaging Biomarker: Dopamine Transporter (DAT)	Exploratory Prognostic Biomarkers for Enrichment in Early Stage Parkinson's Disease Clinical Trials	3/16/2015: Letter of Support (PDF)	Refer to Coalition Against Major Diseases Web Site
C-Path, Polycystic Kidney Disease (PKD) Outcomes Consortium	MRI, Computerized Tomography (CT), or Ultrasound (US) Biomarker: Total Kidney Volume (TKV)	Exploratory Prognostic Biomarker for Enrichment in Autosomal Dominant Polycystic Kidney	4/23/2015: Letter of Support (PDF)	Refer to Polycystic Kidney Disease Outcomes Consortium Web Site

6 letters issued to date

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm434382.htm

Joint FDA-EMA LOI

Joint FDA/ EMA Letter of Intent (LOI) Submissions for Biomarker and Clinical Outcome Assessment Qualification Programs

A Joint Letter-of-intent (LOI) template to enable efficient parallel submissions to the US FDA and EMA for Drug Biomarker Qualification or Clinical Outcome Assessment Qualification.

The United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are launching a joint letter of intent (LOI) template to encourage parallel submissions to these agencies for qualification of biomarkers or clinical outcome assessments. As noted in the template, some sections of the form are specific for the FDA or EMA. This joint template is intended to reduce the submitter's preparation time. However, it is not a requirement for joint submission to FDA and EMA—the submitter may still choose to send in the agency-specific form for the LOI to each agency.

When joint LOIs for DDT qualification are submitted to FDA and EMA, the two agencies share scientific perspectives, advice, and response letters for the submitters.

There are three stages in the DDT qualification process at both the agencies, with minor differences in nomenclature as shown in the table below:

Stage	FDA	EMA
1	Initiation	Pre-submission
2	Consultation and Advice	Consultation and Advice by the Secretariat
3	Review	Review by the Scientific Advice Working Party

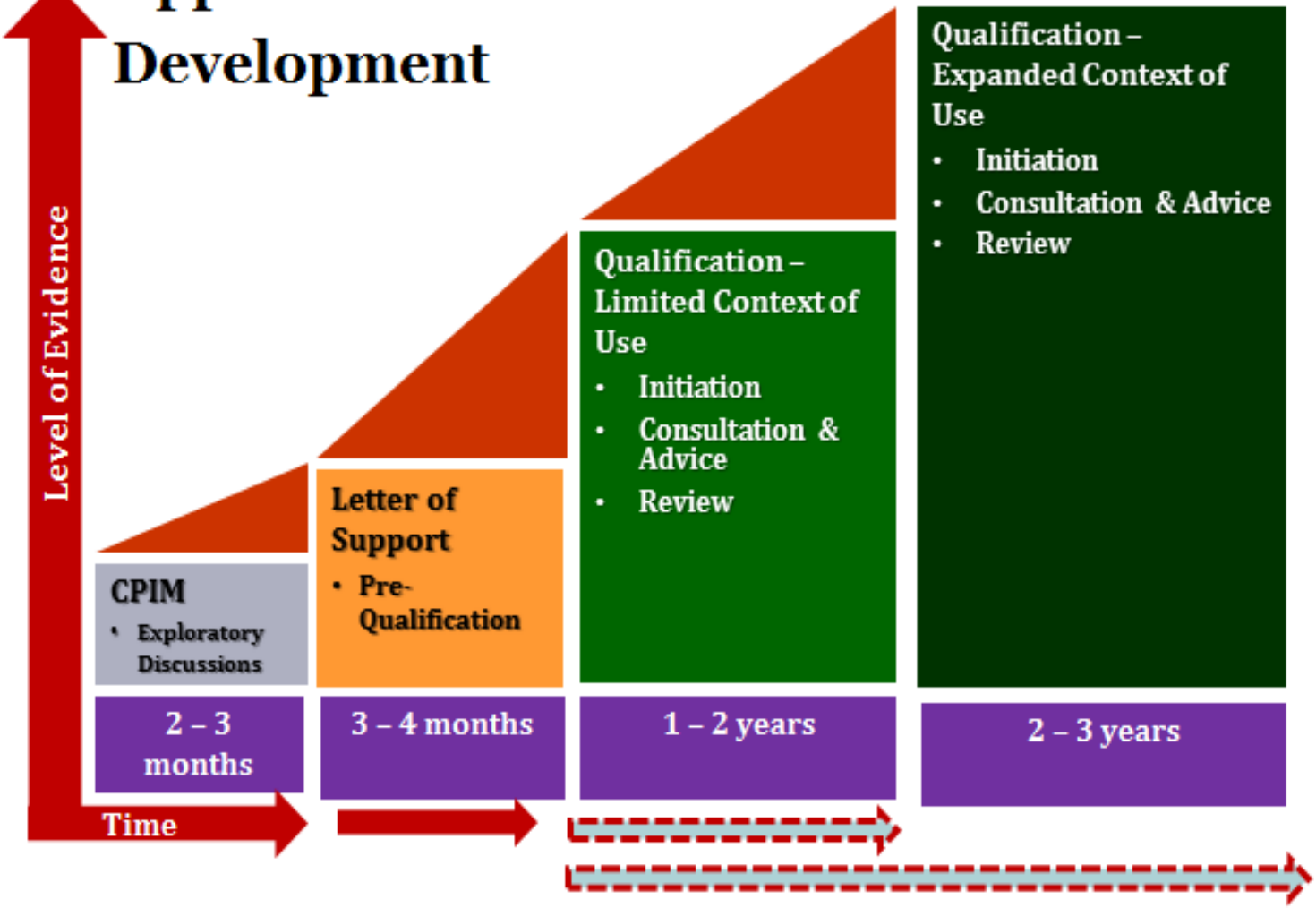
Joint LOI template submissions for FDA should be submitted via the following process:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm422888.htm

Limited COU

CDER provides an avenue to qualify a biomarker for a "limited" context of use in order to expedite the integration of the biomarker in drug development and to possibly generate additional data that can help in qualifying the biomarker for the "expanded" context of use.

Opportunities for Biomarker Development



Communication

Communication

- Enhanced interaction with submitters
- Frontloading COU discussions
- Enhanced interactions with consortia, NCATS, FNIH, and Critical Path Institute
- International interactions (EMA/IMI)
- Presentations
- Publications
- FDA webpage- Information for submitters

FDA Webpage
Information for the Submitters

- Contact Information and Submission Procedures
- Submission Help
  - Cover letter template
  - LOI template
  - FDA-EMA Joint LOI template
  - Briefing Document template
  - Biomarker Qualification Submissions Checklist
  - Context of Use explanation
  - COU example for a hypothetical biomarker
  - FAQs
- Additional Information
  - BQ Presentation (recorded)
  - Relevant BQ-related Publications

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

June, 2015 Update

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	87	7	24	56
Number in Initiation Stage	26	4	1	21
Number in Consultation and Advice Stage	54	3	18	33
Number in Review Stage	7	0	5	2
Number Qualified	5	0	4	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

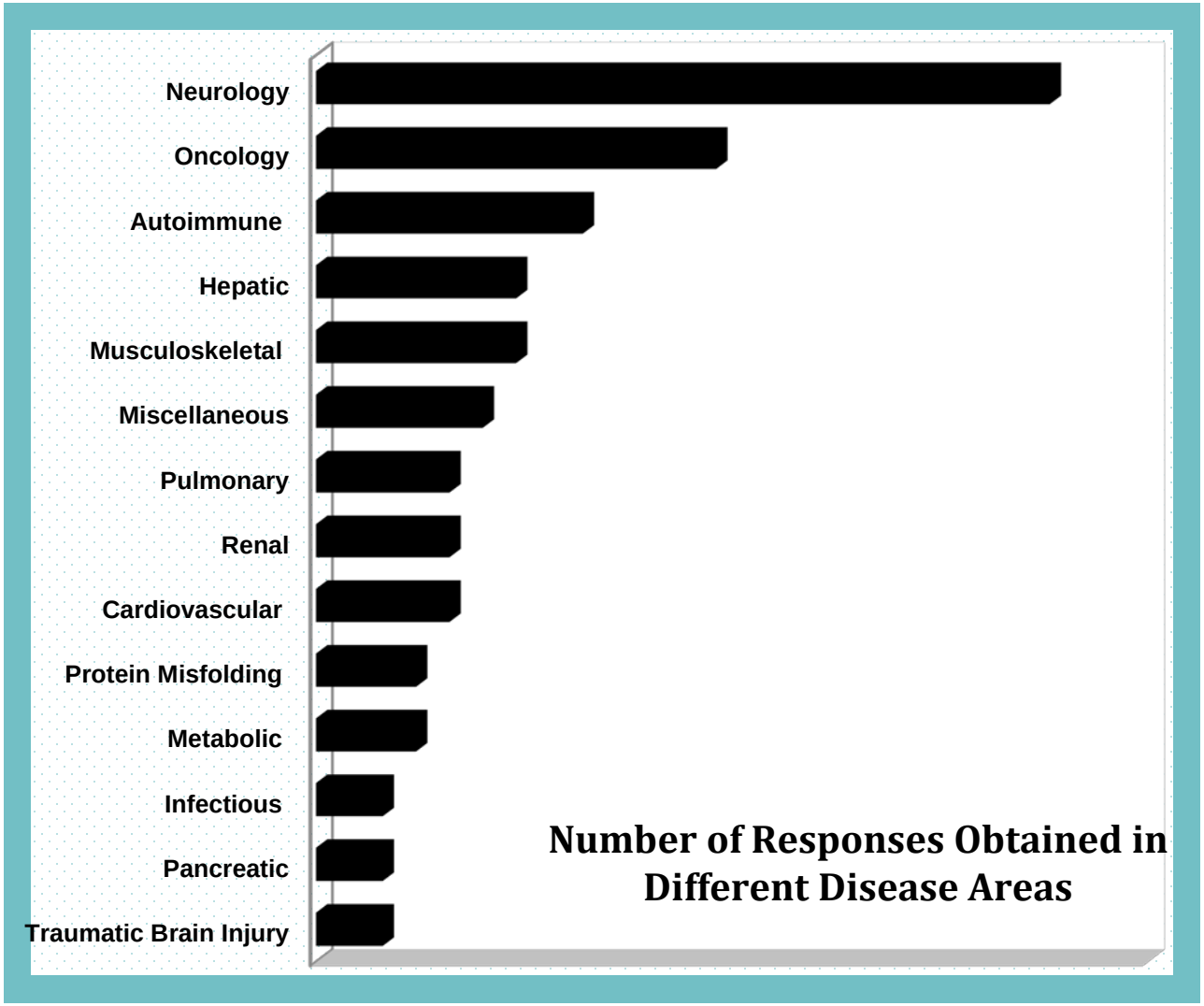
Submitter	Biomarker	Date Accepted into BQ Program	Type of Biomarker	Proposed Biomarker Utility	Qualification Stage
Critical Path Institute (C-Path), Predictive Safety Testing Consortium, (PSTC), Skeletal Muscle Working Group (SKM WG) Contact: John-Michael Sauer	Drug-Induced Skeletal Muscle Injury Biomarkers	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

Survey to identify biomarkers needed in drug 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



Survey Results

Disease area/Organ toxicity	Specific Areas in Critical Need for Biomarker Developmemt	Biomarker Names	Context of Use	Why Is The Biomarker Useful in Drug Development?
Neurological and Neuropsychiatric Diseases	Alzheimer's disease, Mood Disorders, Epilepsy, Huntington's disease, Alcohol Dependence, Schizophrenia and Parkinson's disease.	Tau imaging markers.	Diagnosis, stratification and outcome measures.	AD diagnosis and staging; progression monitoring, PD measurement.
		Genetic & epigenetic biomarker signatures (AD and Mood		Disease risk
		Screening biomarkers for AD, Mood disorders (blood tests, neurofunctional and behavioral		Patient enrichment for clinical trials.
		Novel strategies to approach outcome measures (different than patient reported outcomes).		n.d.
		Biomarkers of functional outcome measures.		Objective measures for motor dysfunction.
		Imaging measures (PET, tMRI) and physiological (EEG).		For stratification purposes in CNS disorders in general.
		Translocator Protein (TSPO) PET ligand.	Patient Selection.	Neuroinflammatory biomarkers such as the TSPO PET Ligand should thus be considered in the context of expei;imental medicine to potentially enrich clinical study designs and improve the testing of clinical hypotheses.
		Utilizing composite biomarker.	Identification of target population based on disease biology and/or drug target for predicting drug efficacy /response.	The field acknowledges that given the heterogeneity and complexity of CNS disorders, a single biomarker (e.g.. Gene, SNP,micro RNA, protein or metabolite) will be unlikely to identify a subpopulation and/ or explain
		Phosphodiesterase(PDE)-10A PET ligand	Diagnostic, Dose selection.	The PDE10A PET ligand will serve multiple purposes. Firstly it will confirm that a given drug enters the CNS, reaches and binds to the PDE10A enzyme. Furthermore, the PET ligand will enable the establishment of plasma exposure of a drug to target occupancy. This will be critical in determining the therapeutic dose range.
	Alzheimer's Disease biomarker to identify subjects "at risk", which would help in patient stratification.	n.d.	Treatment Response.	n.d.
	Multiple Sclerosis	n.d.		n.d.
Oncology	i) Cardio-vascular system, liver, kidney for safety(toxicity) biomarkers. ii) Efficacy biomarkers based on genomics are largely studied in oncology.	i) Patient stratification biomarkers. ii) Drug efficacy and safety biomarkers.	i) Proof of concept (POC) using pharmacodynamic biomarkers. ii) Patient stratification in enrollment using drug efficacy (also subset of pharmacodynamic and safety biomarkers). iii) Monitoring clinical safety using safety biomarkers.	n.d.

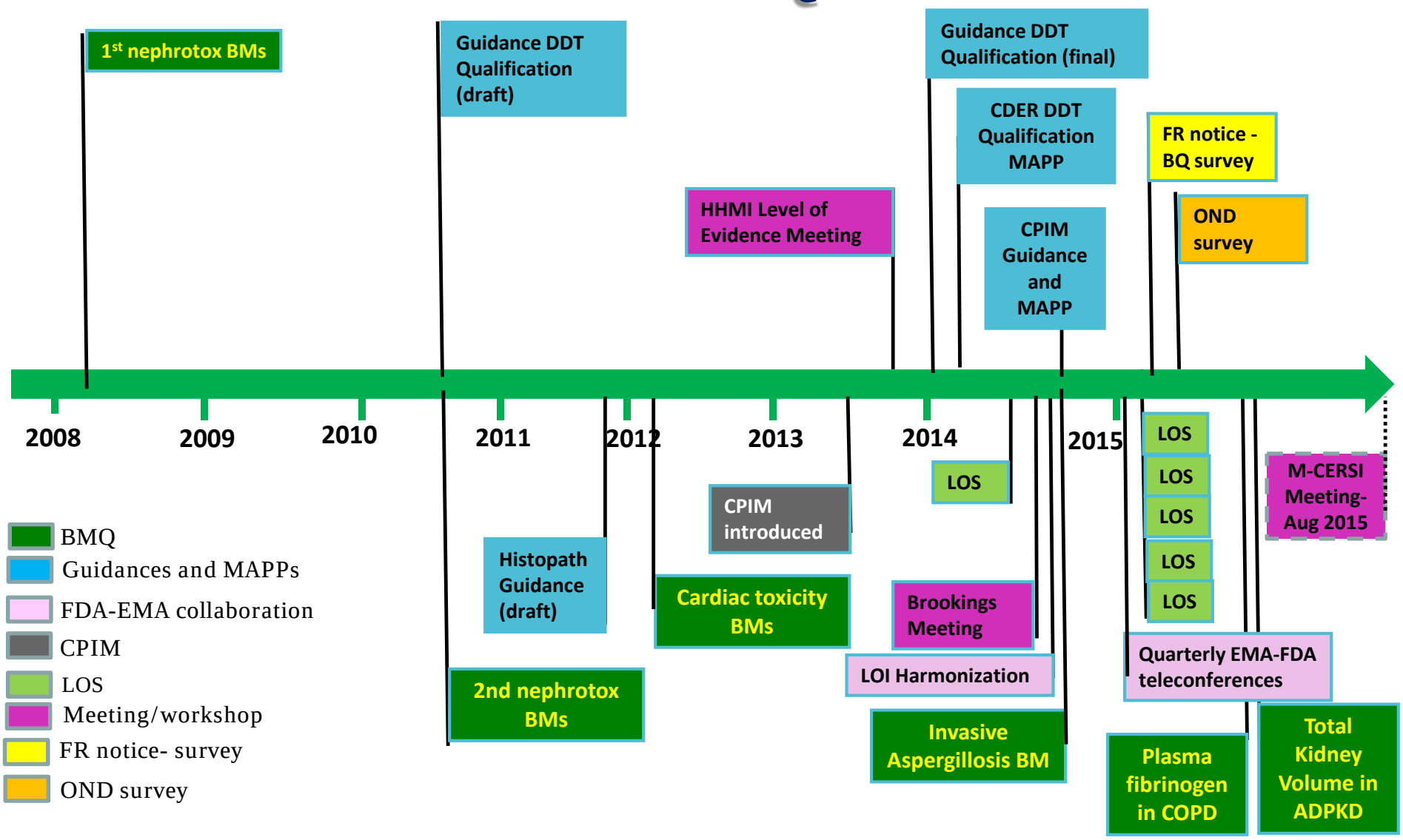
Initiating collaborative efforts aimed at developing evidentiary standards

Discussions on Evidentiary Standards

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

Timeline for Salient BQ-related Efforts



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

Take Home Points contd....

- Early engagement with FDA on biomarker qualification encouraged
- CDER has streamlined the BQ process, to improve communication both internally and externally and has launched new initiatives to encourage biomarker development and qualification
- CDER has conducted a survey to identify potential biomarkers for qualification in areas important to drug development

Acknowledgements

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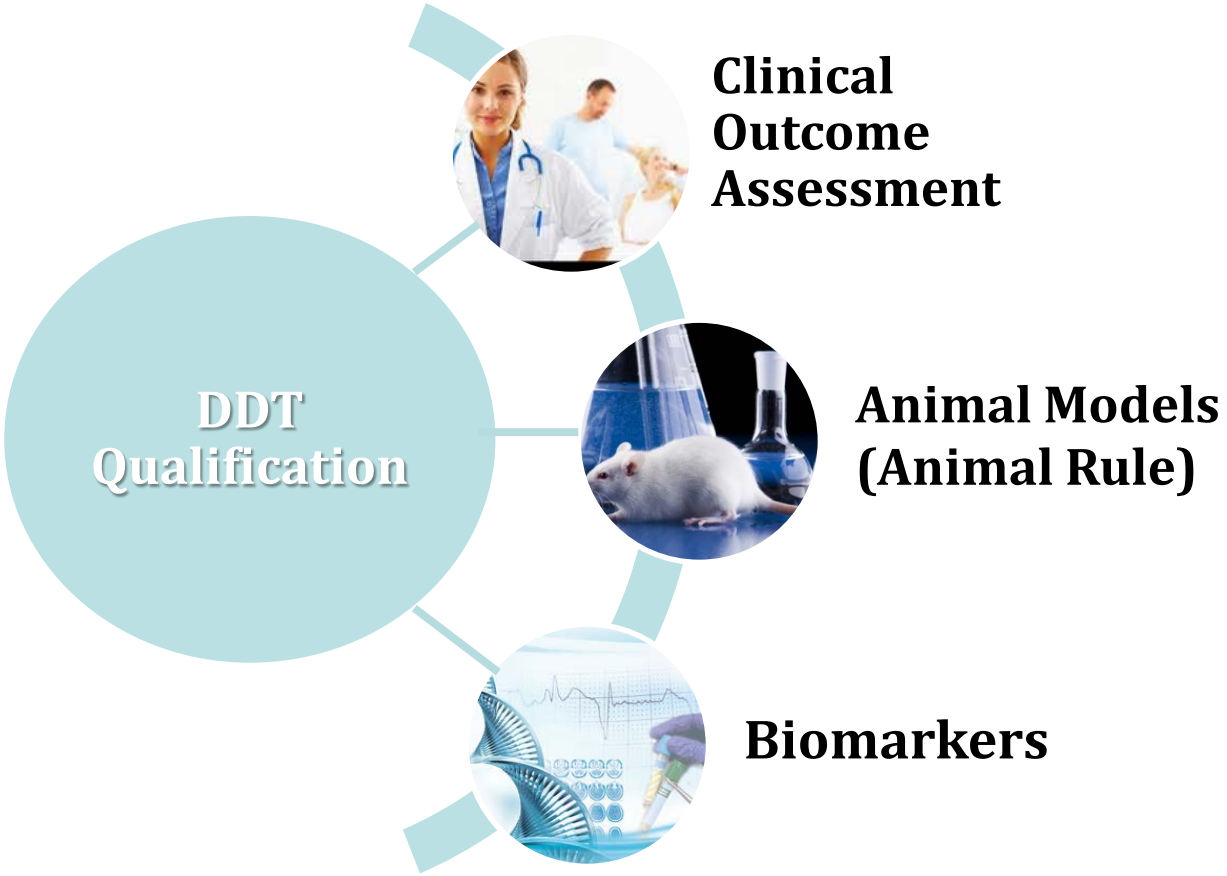
Sarmistha Sanyal

Thank You!

Shashi.amur@fda.hhs.gov

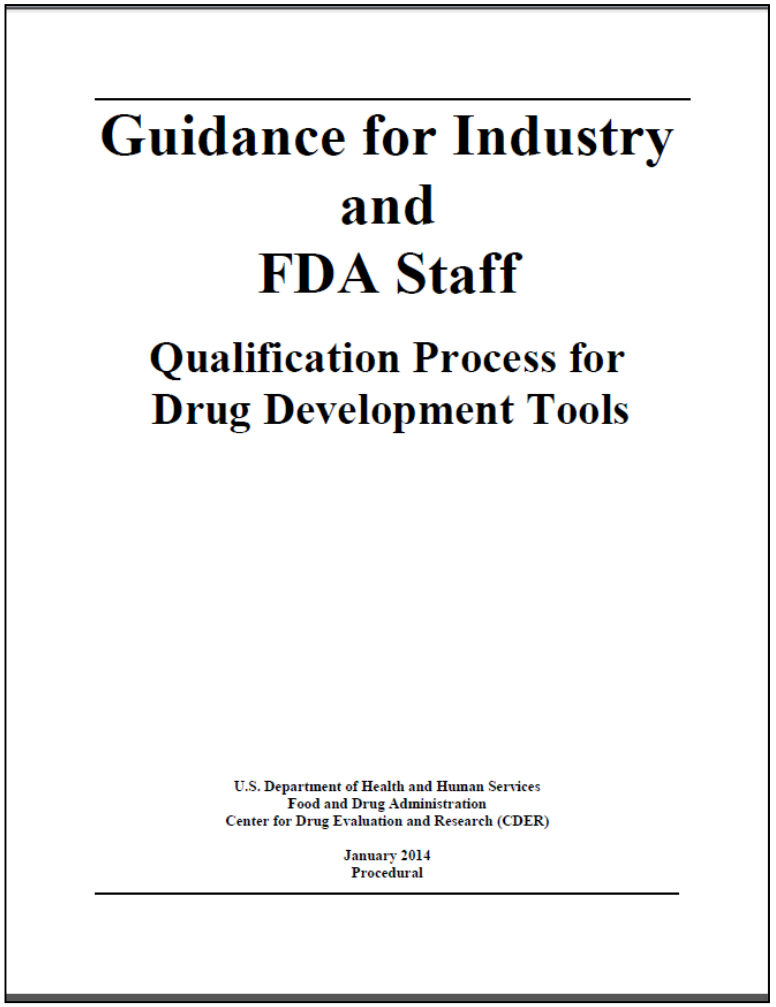
Back-up Slides

Drug Development Tools (DDT) Qualification at CDER, FDA



DDTs are methods, materials, or measures that aid drug development

DDT Qualification at CDER, FDA



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

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Drugs

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Development & Approval Process (Drugs)
- Drug Development Tools Qualification Program
- Animal Model Qualification Program
- Biomarker Qualification Program
- Clinical Outcome Assessment Qualification Program

Resources for You
- DDT Frequently Asked Questions (FAQs)
- DDT Glossary
- DDT Contacts and Submission

Drug Development Tools (DDT) Qualification Programs

The Drug[1] Development Tools (DDTs) Qualification Program was created by CDER as part of the FDA's Critical Path Initiative (CPI) to provide a framework for development and regulatory acceptance of scientific tools for use in drug development programs. DDT qualification programs currently exist for biomarkers, clinical outcome assessments (COAs), and animal models for use under the Animal Rule.

The Drug[1] Development Tool (DDT) Qualification Programs allow CDER to work with submitters to guide them as they develop or refine a DDT for a specific context of use. CDER then will rigorously evaluate the submission for use in the regulatory process. Qualifying a DDT will allow sponsors to use the DDT in the qualified context of use during drug development without requesting that CDER reconsider and reconfirm the suitability of the DDT for the qualified context of use.

Mission and Objectives
- To qualify and make DDTs publicly available for a specific context of use to expedite drug development and review of regulatory applications
- To provide a framework for scientific collaboration to facilitate DDT development
- To facilitate integration of qualified DDTs in regulatory review
- To encourage development of DDTs for contexts of use with unmet needs
- To encourage the formation of collaborative groups to undertake DDT development programs to increase the efficiency and lessen the individual resource burden incumbent with DDT development
- To encourage innovation in drug development

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

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

MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 4130.1

POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

Drug Development Tool Qualification Programs

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http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407254.pdf