FDA's Biomarker Qualification Program

Shashi Amur, Ph.D.

Scientific Lead
Biomarker Qualification Program
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration

Drug Development Tools for Kidney Disease Meeting,

Washington DC

September 25, 2015

Overview

DDT-KD Consortium

1. Introduction
2. Biomarker Qualification
3. Efforts to Support Biomarker Qualification
4. Take Home Points

Biomarkers

DDT-KD Consortium

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.

Biomarker Types

DDT-KD Consortium

- Diagnostic Biomarkers
  - Identify patients with a particular disease or a disease subset
- Prognostic biomarkers
  - Indicate future clinical course with respect to a specified clinical outcome, in the absence of therapeutic intervention
- Predictive biomarkers
  - Identify patients likely to respond (favorably or unfavorably) to a specific treatment

Biomarker Types

DDT-KD Consortium

- Response biomarkers

  - Indicate that biological response has occurred in a patient after having received a therapeutic intervention

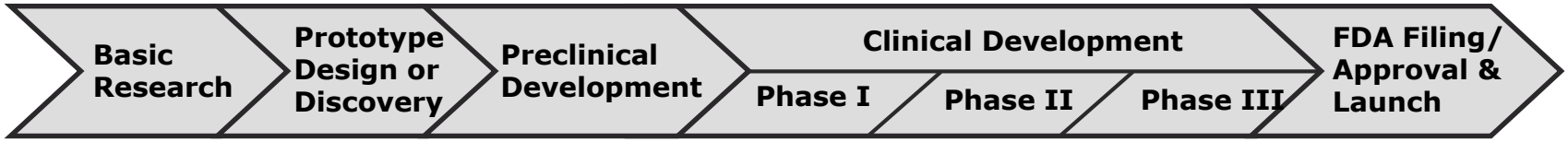
- *Pharmacodynamic biomarkers*
  - *Indicators of intended activity of the therapeutic*
  - *Not necessarily strong predictors of efficacy*

- *Efficacy-response biomarkers*
  - *Predict specific disease-related clinical outcome*
  - *Could serve as primary clinical endpoints or surrogates for a clinical end point*

- *Safety-related response biomarkers*
  - *Indicators of potential adverse drug reactions*
  - *Likely to be specific for a type of drug toxicity, usually organ specific*

Biomarkers in Drug Development

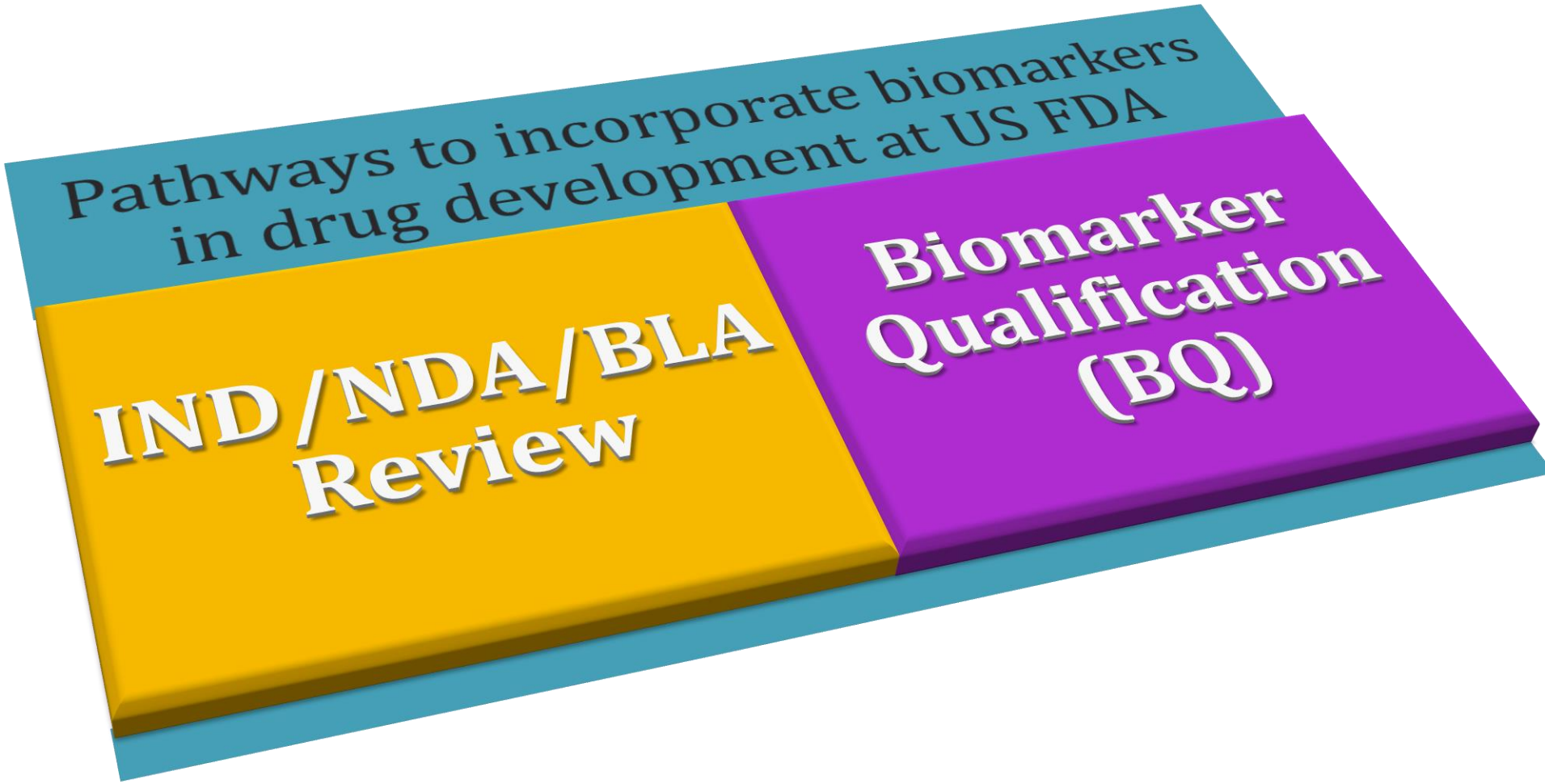
DDT-KD Consortium

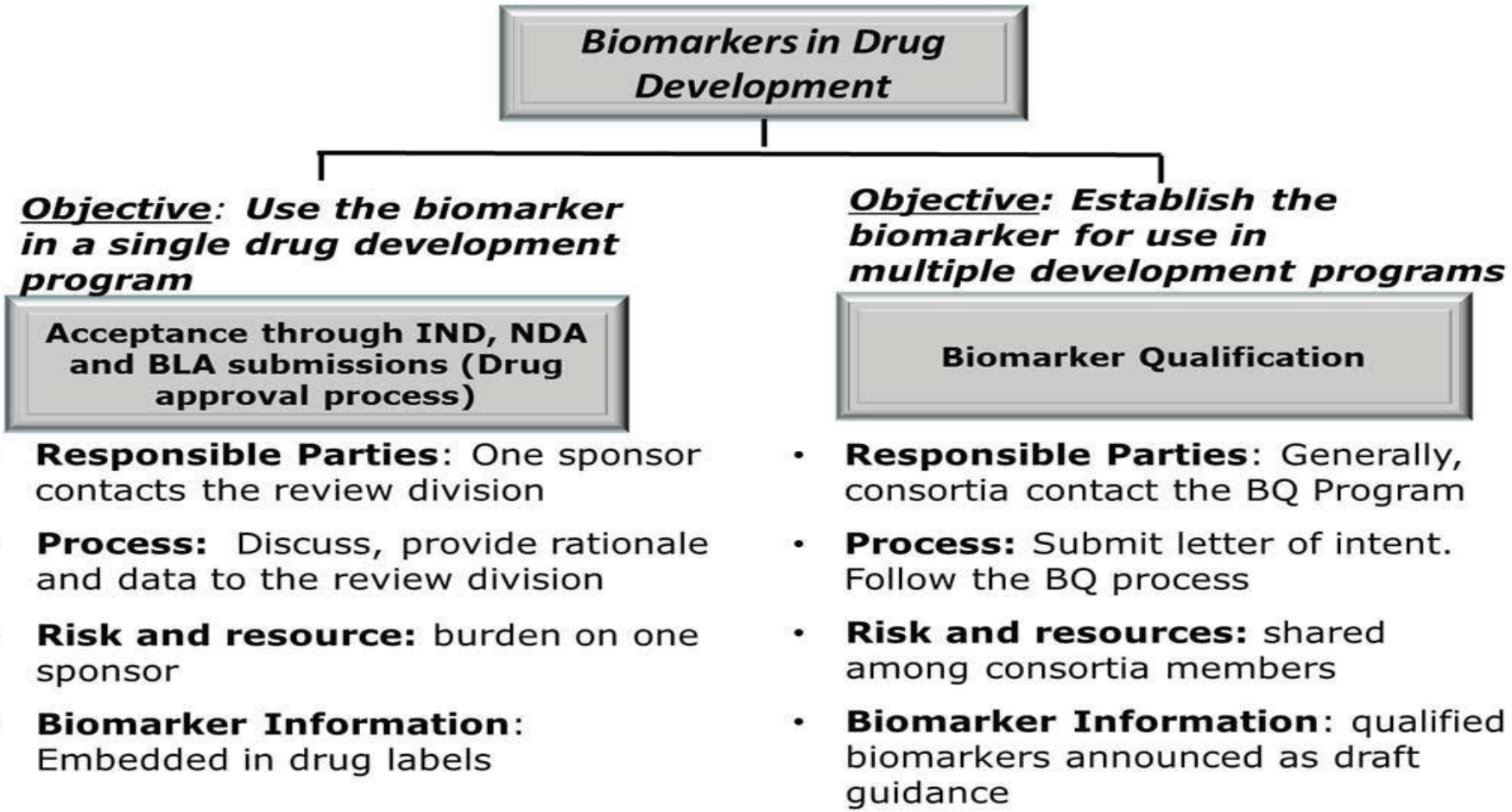


- Molecular pathways underpinning disease
- Mechanism of action of therapeutics
- Preclinical safety assessment
- Clinical trials
  - Safety Assessment
  - Dose selection
  - Stratification
  - Patient selection/enrichment
  - Surrogate end Point
- Companion Diagnostic
  - Selection of right patients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

Pathways to facilitate integration of biomarkers in drug development

DDT-KD Consortium





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

Biomarker Qualification (BQ)

DDT-KD Consortium

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:

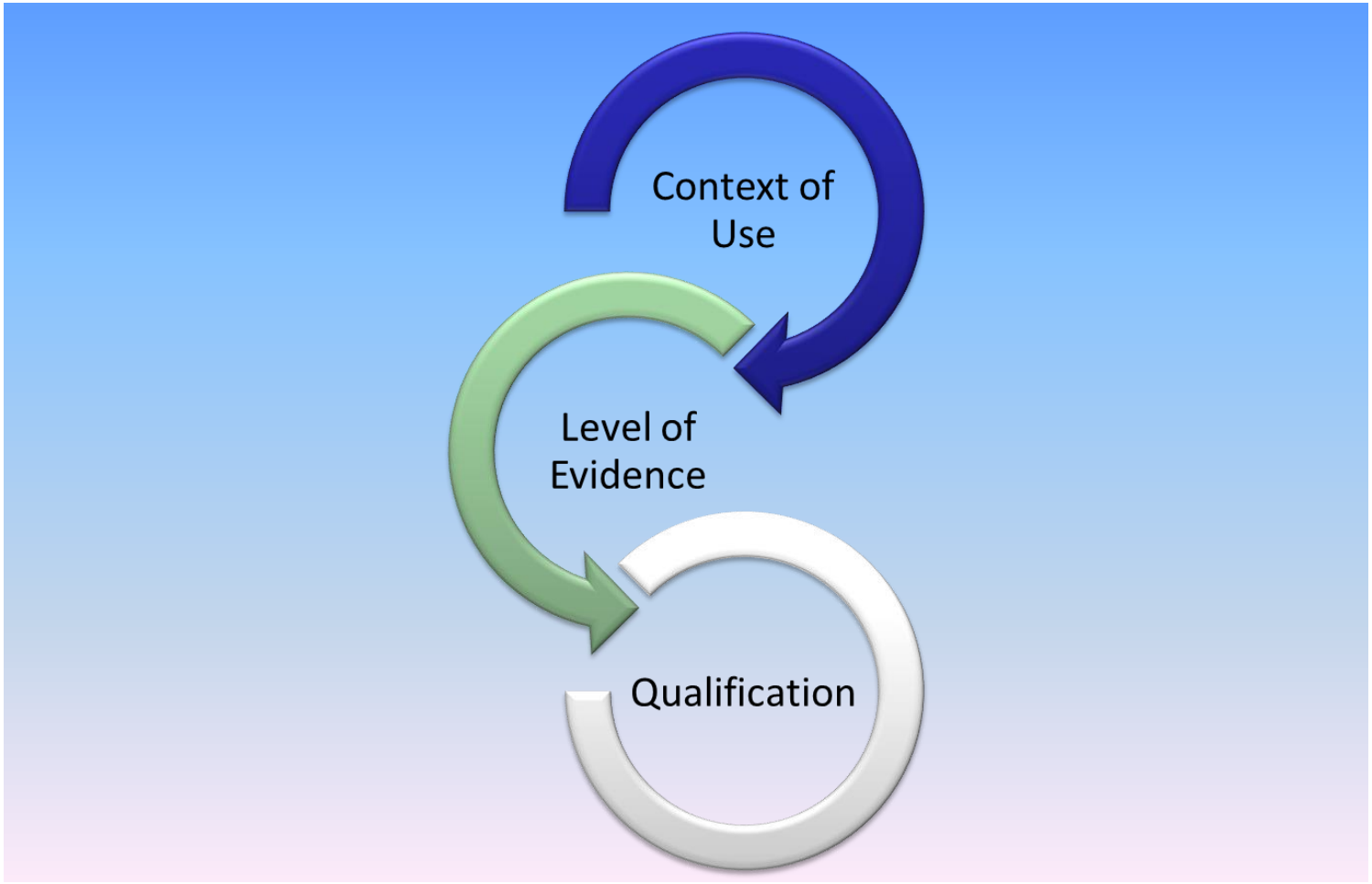
"Context of use" is a comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development.

- 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

Biomarker Qualification Concept

DDT-KD Consortium



Considerations for Biomarker Qualification

DDT-KD Consortium

- **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

DDT-KD Consortium

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 Qualification Package received, reviewed 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

DDT-KD Consortium

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

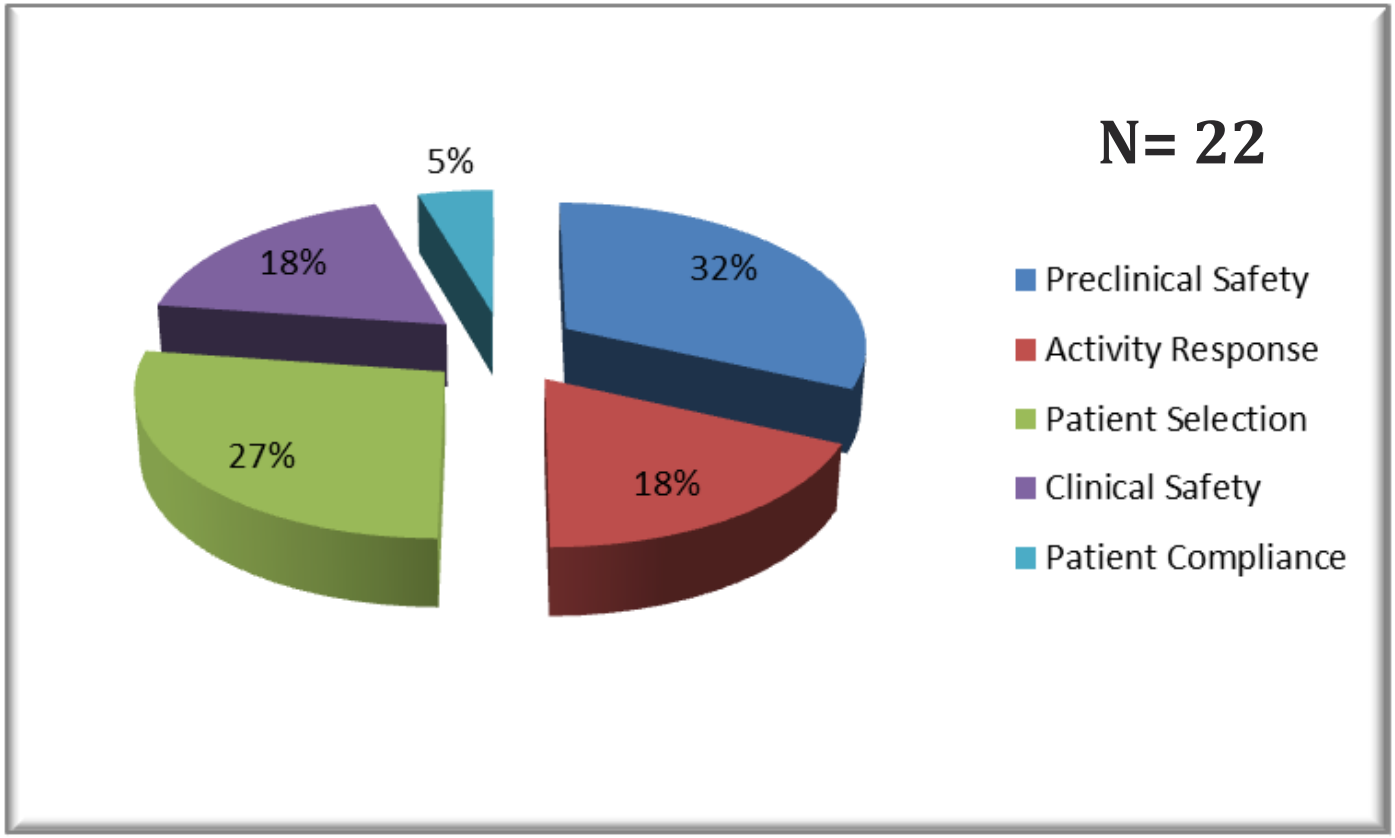
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

CRITICAL PATH INSTITUTE a decade of excellence 10 YEARS

FDA

What types of submissions are we seeing for Biomarker Qualification?

DDT-KD Consortium



Where are The Submissions in the BQ Process?

DDT-KD Consortium

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

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

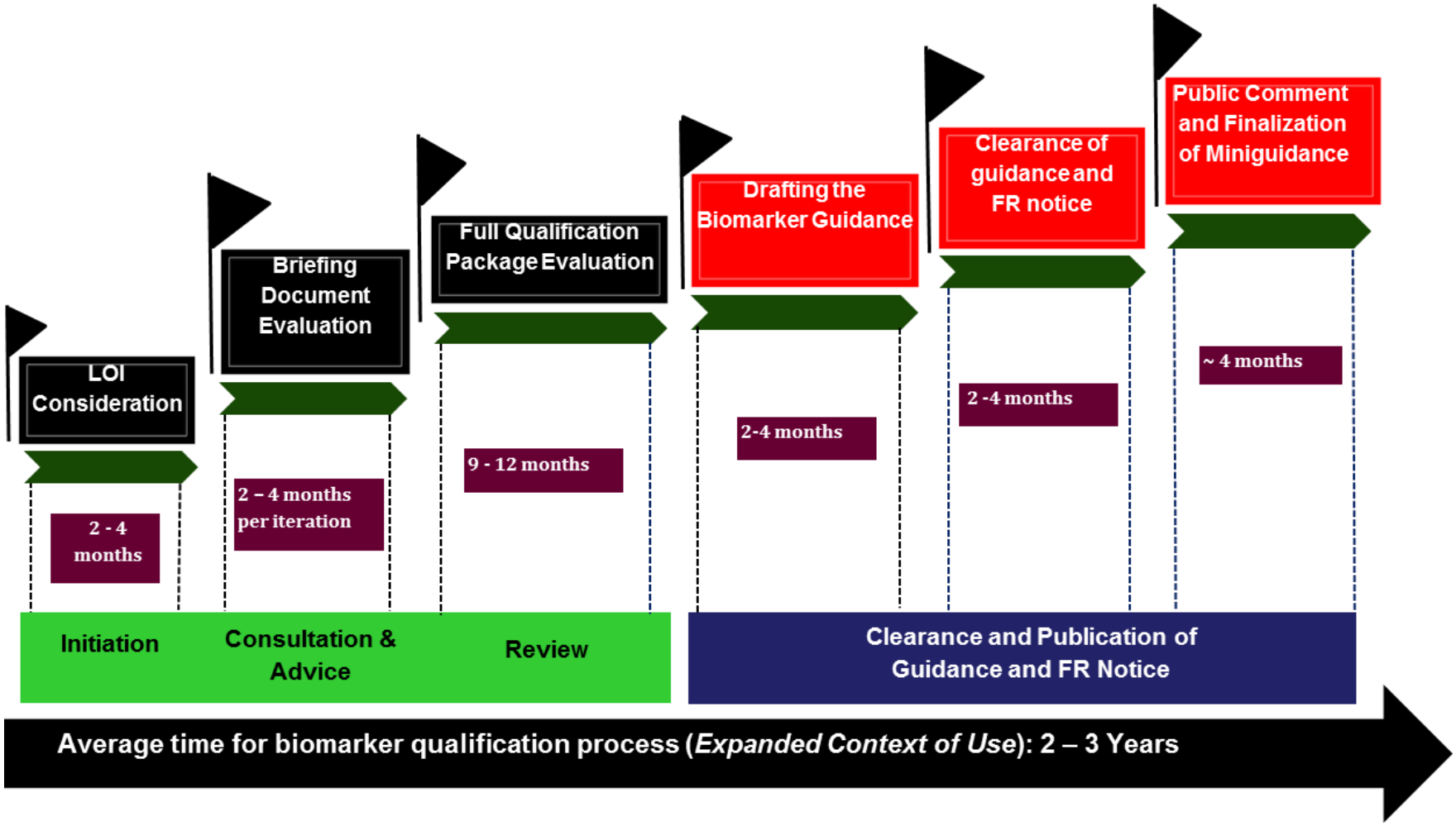
Biomarker Qualification (BQ) Submissions

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

CRITICAL PATH INSTITUTE
a decade of excellence
10 YEARS

Biomarker Qualification Process-Timeline

DDT-KD Consortium



CRITICAL PATH INSTITUTE a decade of excellence 10 YEARS

FDA

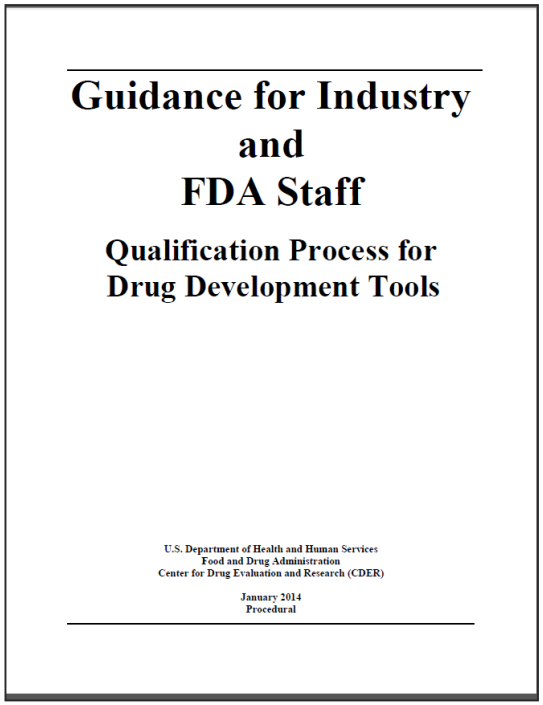
In Preparation for Biomarker Qualification

DDT-KD Consortium

- 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

Guidances

DDT-KD Consortium



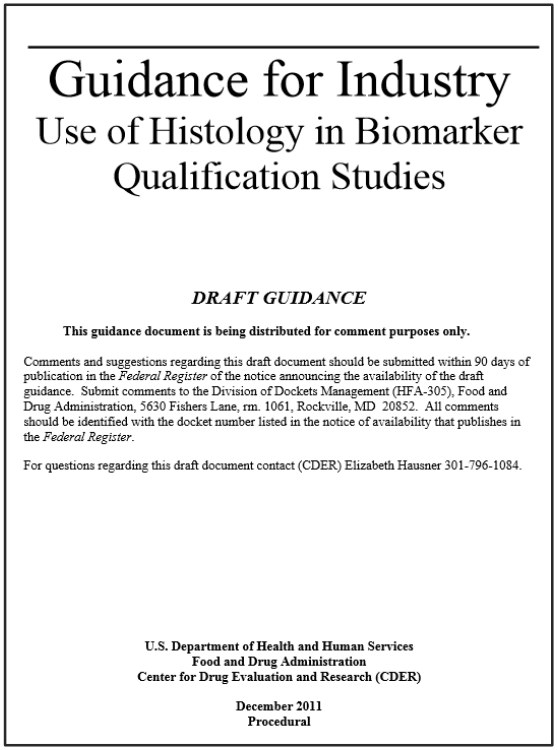
Guidance for Industry and FDA Staff

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.

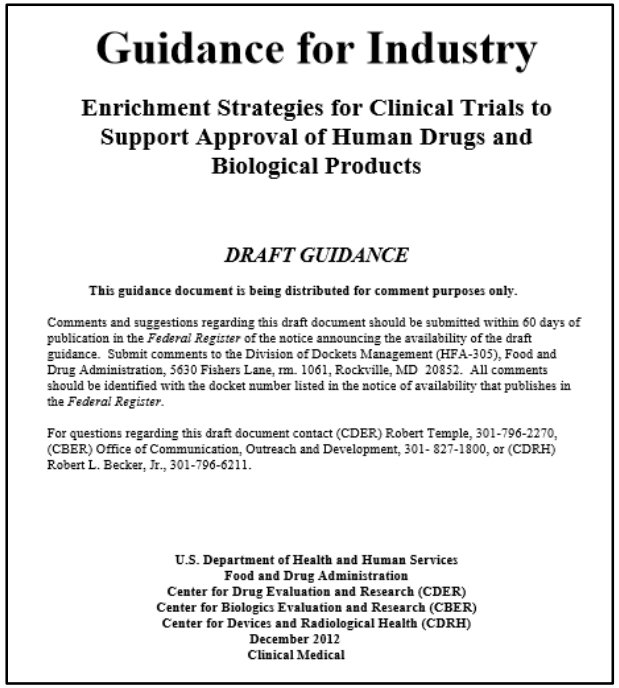
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers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

CRITICAL PATH INSTITUTE
a decade of excellence
10 YEARS

FDA

Efforts to Support Biomarker Qualification

Joint FDA-EMA LOI

DDT-KD Consortium

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

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

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

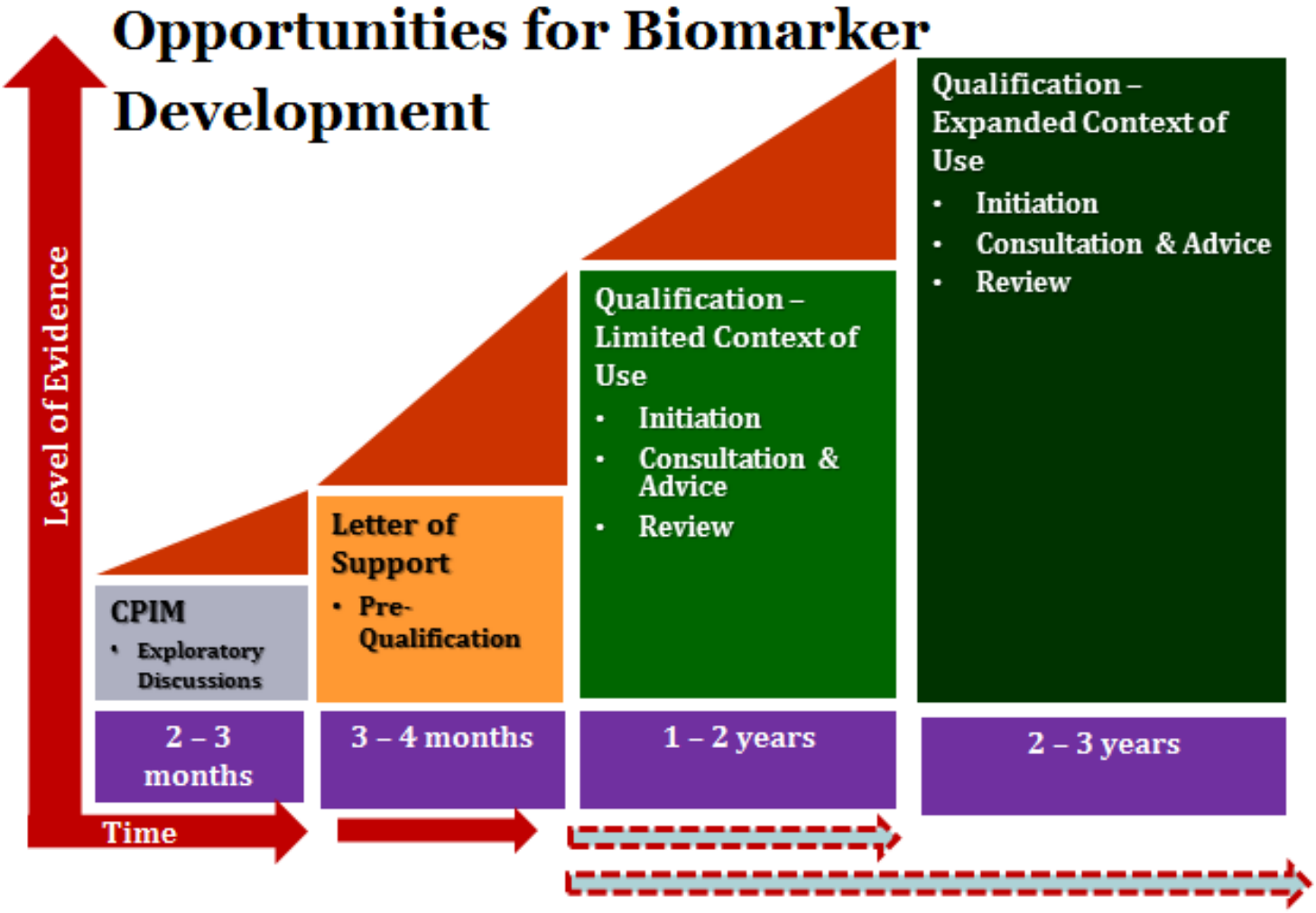
Joint LOI template submissions for FDA should be submitted via the following process:

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

Limited COU

DDT-KD Consortium

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
Level of Evidence
Time
CPIM
• Exploratory Discussions
2 – 3 months
Letter of Support
• Pre-Qualification
3 – 4 months
Qualification – Limited Context of Use
• Initiation
• Consultation & Advice
• Review
1 – 2 years
Qualification – Expanded Context of Use
• Initiation
• Consultation & Advice
• Review
2 – 3 years

Take Home Points

DDT-KD Consortium

- 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 a voluntary process intended for biomarkers that will be used in multiple drug development programs

Take Home Points contd….

DDT-KD Consortium

- Once qualified, a biomarker can be used by drug developers for other applications without re-review, for the qualified COU
- Early engagement with CDER on biomarker qualification encouraged
- CDER has streamlined the BQ process, improved communication both internally and externally and has launched new initiatives to encourage biomarker development and qualification

Acknowledgements

DDT-KD Consortium

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

Thank You!

Shashi.amur@fda.hhs.gov