Opportunities to Develop Meaningful Biomarkers

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IOM Workshop

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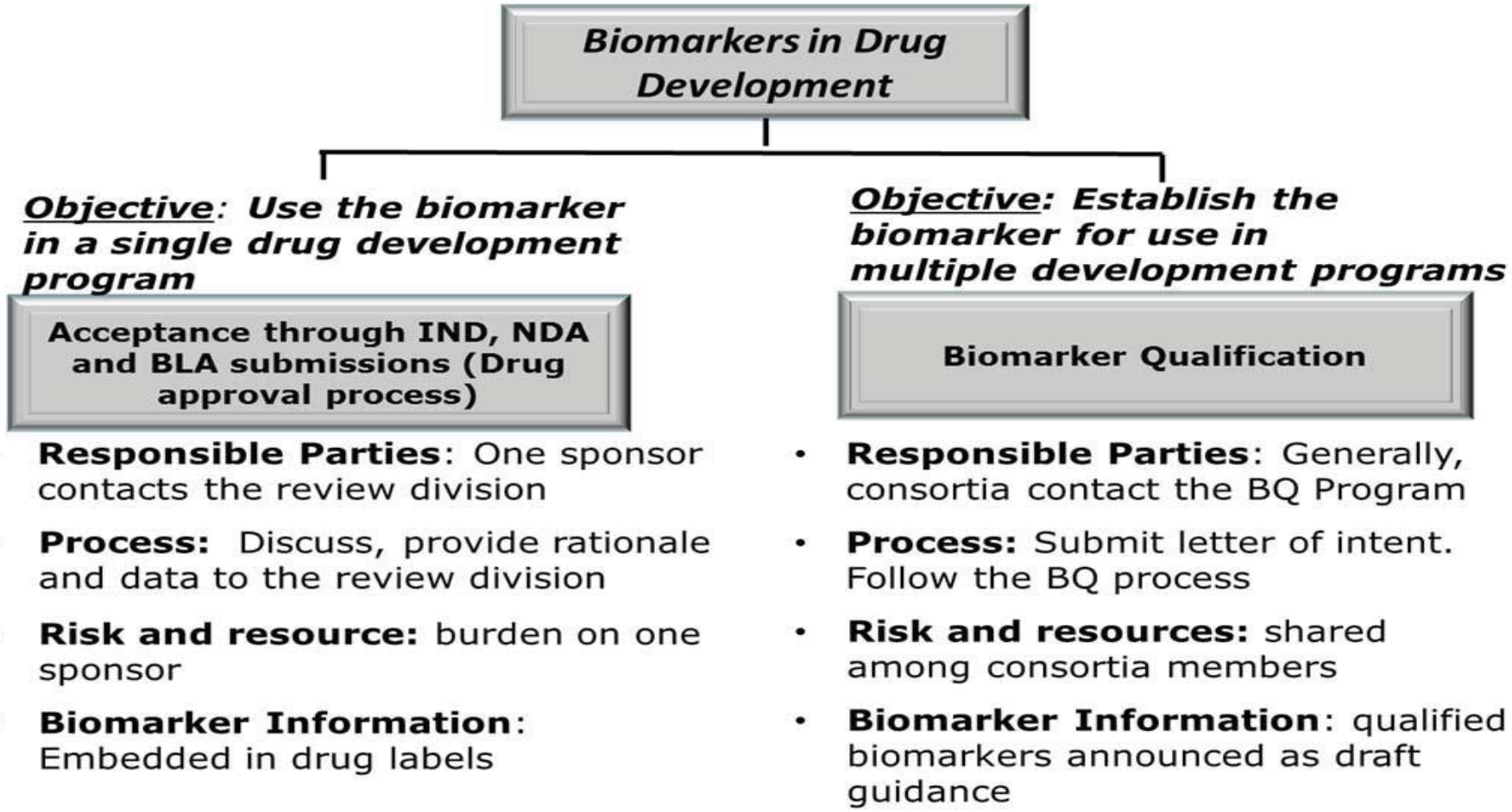
Overview

- Pathways to integrate biomarkers in drug development at FDA
- Biomarker Qualification
- Qualification of Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease
- Take home points

Pathways to Integrate Biomarkers in Drug Development at US FDA

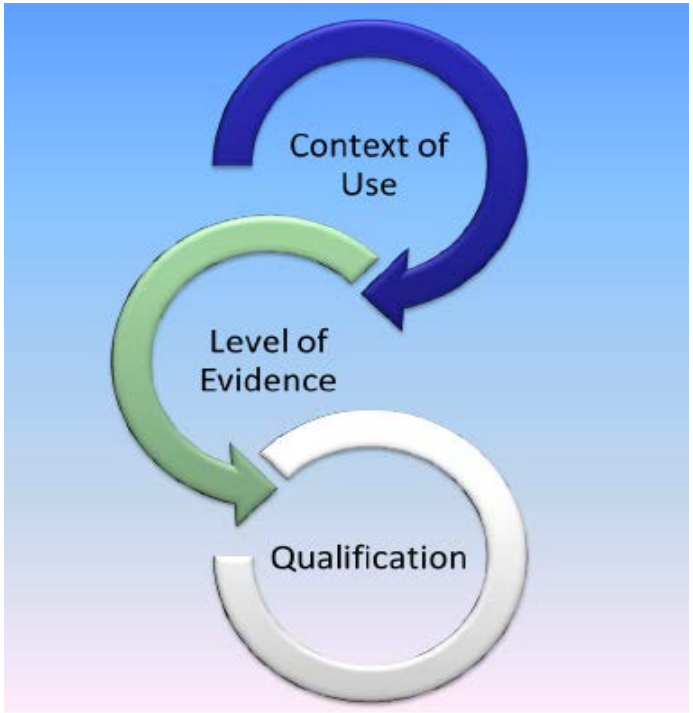


Amur et al, Clin. Pharm. Ther. 98 (1) 34-46, 2015

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



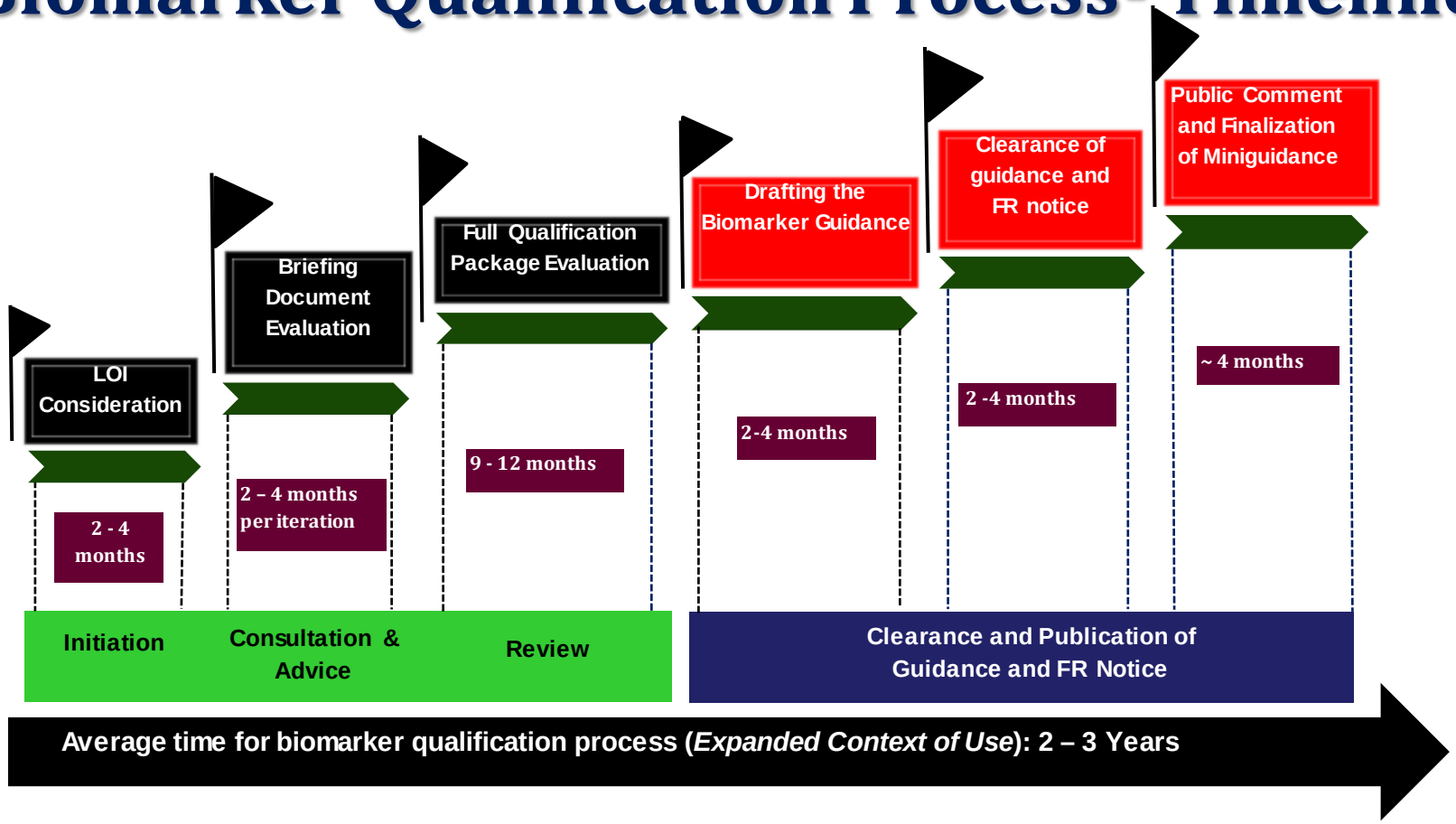
***Context of use*:**

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

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 needed depends on the type of biomarker and its COU.

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

Qualification of Total Kidney Volume (TKV) in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Joint FDA-EMA submission from Polycystic Kidney Disease Outcomes Consortium (PKDOC)

PKDOC approach

Develop standard common PKD terminology data elements (Clinical data interchange standards consortium (CDISC) data standards for ADPKD to allow for the mapping and pooling of available data into a common database)

Create new database of aggregated data from 3 patient registries and 2 longitudinal cohort studies (N= 2355 with available TKV imaging data)

Develop disease progression model

Submit qualification package to FDA

TKV BQ submission

- **Objective**: Clinical trial enrichment in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- **Stage of Drug Development for Use**: All clinical stages of ADPKD drug development, including proof of concept, dose-ranging, and confirmatory clinical trials.
- **Proposed Context of Use:** Baseline TKV can be applied as a prognostic biomarker that, in combination with patient age, can be used to help identify those ADPKD patients who are at the greatest risk of advancing in the course of their disease to a point where there is substantial decline in renal function as measured by clinically meaningful outcomes (30% worsening of eGFR , 57% worsening of eGFR (equivalent to doubling of serum creatinine), and ESRD).

eGFR: Estimated Glomerular Filtration rate; ESRD: End Stage Renal Disease

Qualification of TKV in ADPKD

FDA analysis and conclusions

- Biomarker Qualification Review Team (BQRT) conducted additional analyses and performed model development and cross validation
  - FDA analyses were **limited to patients with an eGFR ≥25 and at least 12 years of age**, which represent the population likely to be enrolled in clinical trials
  - Some subjects had imaging performed with **more than one modality.** FDA reviewers selected magnetic resonance imaging (MRI) data as the first preference, computer tomography (CT) data as the second preference and ultrasound (US) data as the last preference

Qualification of TKV in ADPKD

- Inclusion of TKV in addition to patient age and eGFR (addition of **eGFR** as a covariate suggested by FDA and EMA) in the best fit model, provided a modest improvement in predicting the risk of a confirmed 30% decline in eGFR. This finding was confirmed using cross-validation and in a separate internal dataset (**external validation**)
- There were too few ESRD and 57% decline in eGFR events over the time frame of a feasible clinical trial to perform meaningful analyses.

EMA: European Medicines Agency

Draft Guidance for TKV in ADPKD

Use Statement:

TKV, measured at baseline, is qualified as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a **confirmed 30% decline** in the patient's eGFR) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and **baseline eGFR** as an enrichment factor in these trials.

Conditions for qualified use:

1. Quantitative Imaging Biomarker
2. TKV-based selection in clinical trials:
   - Patient population
   - Patient selection
   - Measurement applicability

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf

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Drugs

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Drug Development Tools Qualification Programs

- Animal Model Qualification Program
- Biomarker Qualification Program
- Clinical Outcome Assessment Qualification Program

Reviews: Qualification of Biomarker: Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

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- Executive Summary: Biomarker Qualification Review for Total Kidney Volume (PDF - 413KB)
- Biomarker Qualification Program Office of Clinical Pharmacology Full Qualification Package Review (PDF - 358KB)
- Biomarker Qualification Review Team for Total Kidney Volume (TKV) (CDRH Consulting Review) (PDF - 436KB)
- Clinical Review of PKD Outcomes Consortium biomarker qualification submission (Division of Cardiovascular and Renal Products (PDF - 756KB)
- Statistical Review and Evaluation: Biomarker Qualification Total Kidney Volume (TKV) (PDF - 1,324KB)
- Secondary Statistical Review: Total Kidney Volume (TKV) (PDF - 350KB)

For the Executive Summary and Reviews

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm458492.htm

CPIM: Critical Path Innovation Meeting
LOS: Letter of Support

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 a voluntary process intended for biomarkers that will be used in multiple drug development programs
- Once qualified, a biomarker can be used by drug developers for other applications without re-review, for the qualified COU
- New FDA initiatives, such as LOS and limited COU qualification, can be utilized as early goal posts in biomarker development
- Early engagement with FDA on biomarker qualification encouraged

Acknowledgements

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Back-up slides

Current Challenges

- Lack of standardized methods for measuring new biomarkers and often a lack of reliable evidence about their performance
- Lack of generally-accepted evidentiary standards for qualifying new biomarkers for particular contexts of use
- Lack of public access to existing research and information on potential biomarkers
- Inadequate prioritization and coordination of the limited public and private resources available to identify and qualify biomarkers in areas of greatest unmet need
- Inadequate scientific information on the causes, biochemical pathways, and natural histories of many diseases, making identification of disease-specific biomarkers difficult

Slide from Dr. ShaAvhree Buckman-Garner

What We Are Hearing from Submitters?

- The process takes too long
- We don't have quick wins
- We don't know where the goal line is
- We are getting tired
- We are hearing conflicting views from the Review Divisions in CDER about whether qualification is even needed
- These are multi-million dollar efforts pulled together with tentative resources and we cannot afford to waste time…
- We want clearer timelines and deliverables

Slide from Dr. ShaAvhree Buckman-Garner

So, what have we done about it?

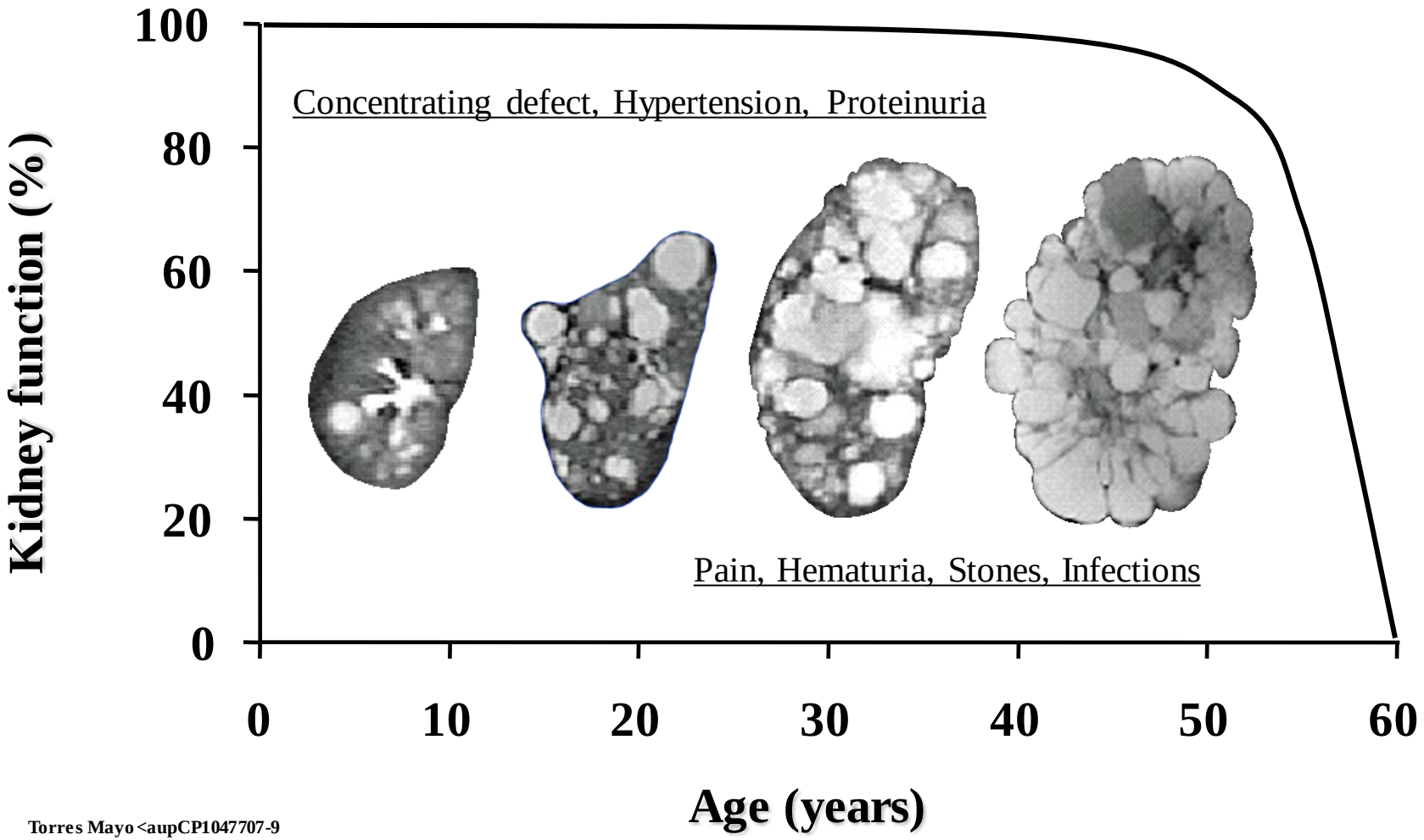
- Leadership changes for the BQ Program
- Streamlined steps in the process for BQ
- Increased focus on communication with submitters
- Increased focus on communication with CDER staff on the BQRTs
- Harmonized LOI requirements with EMA
- Set clear expectations
- Surveys to understand where biomarker development is needed
- Front loading Context of Use discussions
- New Initiatives- CPIM and Letters of Support
- Convening workshops

Slide from Dr. ShaAvhree Buckman-Garner

Qualification of Total Kidney Volume (TKV) in ADPKD

Submitter Rationale:

- No approved therapies for ADPKD
- Progression of ADPKD occurs over many decades
- Early biomarkers of disease progression are needed
- ADPKD is characterized by progressive enlargement of the kidneys due to cyst growth
- Evaluate TKV as a prognostic enrichment biomarker



Torres Mayo <aupCP1047707-9

Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

Draft Guidance for Industry

Drug Development Tool (DDT) Type: Biomarker
Referenced Biomarker(s): Total kidney volume (TKV)

TKV is defined as the sum of the volume of the left and right kidneys.

I. SUMMARY OF GUIDANCE

A. Purpose of Guidance

This draft guidance provides a qualified context of use (COU) for the biomarker TKV in studies for the treatment of autosomal dominant polycystic kidney disease (ADPKD). This draft guidance also describes the experimental conditions and constraints for which this biomarker is qualified through the CDER Biomarker Qualification Program. This biomarker can be used by drug developers for the qualified COU in submissions of investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) without the relevant CDER review group reconsidering and reconfirming the suitability of the biomarker.

B. Application of Guidance

This guidance applies to the use of TKV in studies for the treatment of ADPKD. It does not change any regulatory status, decisions, or labeling of any medical imaging device used in the medical care of patients.

TKV use in drug development outside of the qualified COU will be considered by FDA on a case-by-case basis in regulatory submissions. In such cases, additional information relevant to the expanded use may be requested by the CDER product review team.

DDT Tracking Number: [DDTBMQ-000021]

II. CONTEXT OF USE

A. Use Statement

This draft guidance provides qualification recommendations for the use of TKV, measured at baseline, as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a *progressive decline* in renal function (defined as a confirmed 30% decline in the patient's estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and baseline eGFR as an enrichment factor in these trials.

B. Conditions for Qualified Use

1. *Quantitative Imaging Biomarker*

TKV should be calculated from the left and right kidneys measured with a validated and standardized image acquisition and analysis protocol within the trial. (Please see supporting documentation for details at Biomarker Qualification Program: Qualified Biomarkers and Supporting Information.)

2. *TKV-Based Patient Selection in Clinical Trials*

a. PATIENT POPULATION

Patients with ADPKD should be at least 12 years of age

b. PATIENT SELECTION

Baseline TKV can be used in combination with the patient's age and baseline eGFR as an enrichment factor in ADPKD clinical trials to select ADPKD patients at high risk for a *progressive decline* in renal function. (Please see supporting documentation for details at Biomarker Qualification Program: Qualified Biomarkers and Supporting Information.)

c. MEASUREMENT APPLICABILITY

Various imaging modalities and post-processing methods are available to determine TKV. These modalities have different levels of precision. For patients with ADPKD at high risk for a confirmed 30% decline in their eGFR, TKV was qualified based on a collection of data from multiple study sites, as well as on results from imaging modalities (i.e., magnetic resonance imaging (MRI), computed tomography (CT), or ultrasound (US)) and from analysis methodologies (i.e., stereology and ellipsoid calculations).

FR Notice- Survey

"Identifying Potential Biomarkers for Qualification and Describing Contexts of Use to Address Areas Important to Drug Development."

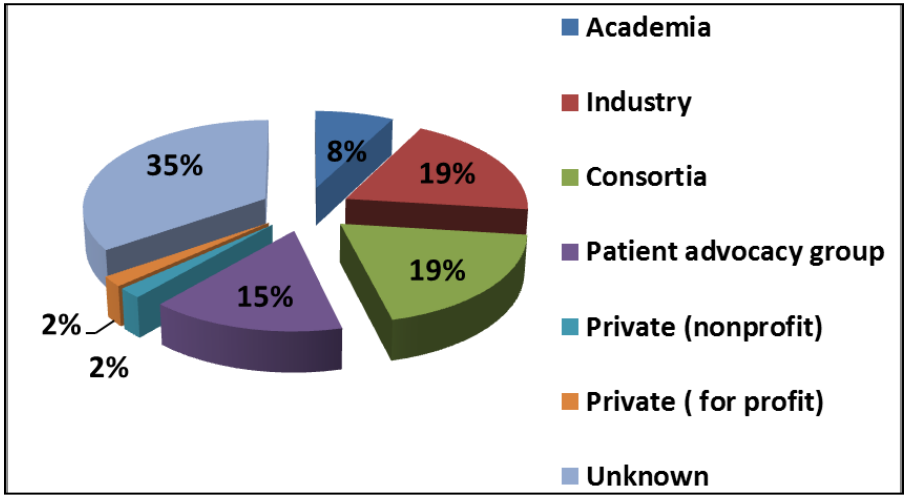
- **Goal**: To seek public input to facilitate development and qualification of biomarkers in areas related to human drug therapeutics
- **Logistics**: Published on February 13, 2015 with a deadline of April 14, 2015. Extended to May 15, 2015
- 14 Questions asked
- Two options given for providing responses
  - Docket (34 responses received)
  - Online Survey Tool (38 responses received)

FDA Biomarker Survey

- **Areas** that have a critical need for biomarkers to assist drug development
- The **names of the biomarkers**
- The proposed **context of use (COU)** for the biomarker (if known)
- **Rationale** for use of the biomarker for the specific COU in drug development
- Any **evidence** that should be developed to support qualification of the biomarker
- Any **groups** currently positioned to address these needs
- Any **barriers** that preclude engagement or investment in biomarkers for these priority areas

Preliminary Evaluation of Survey Data

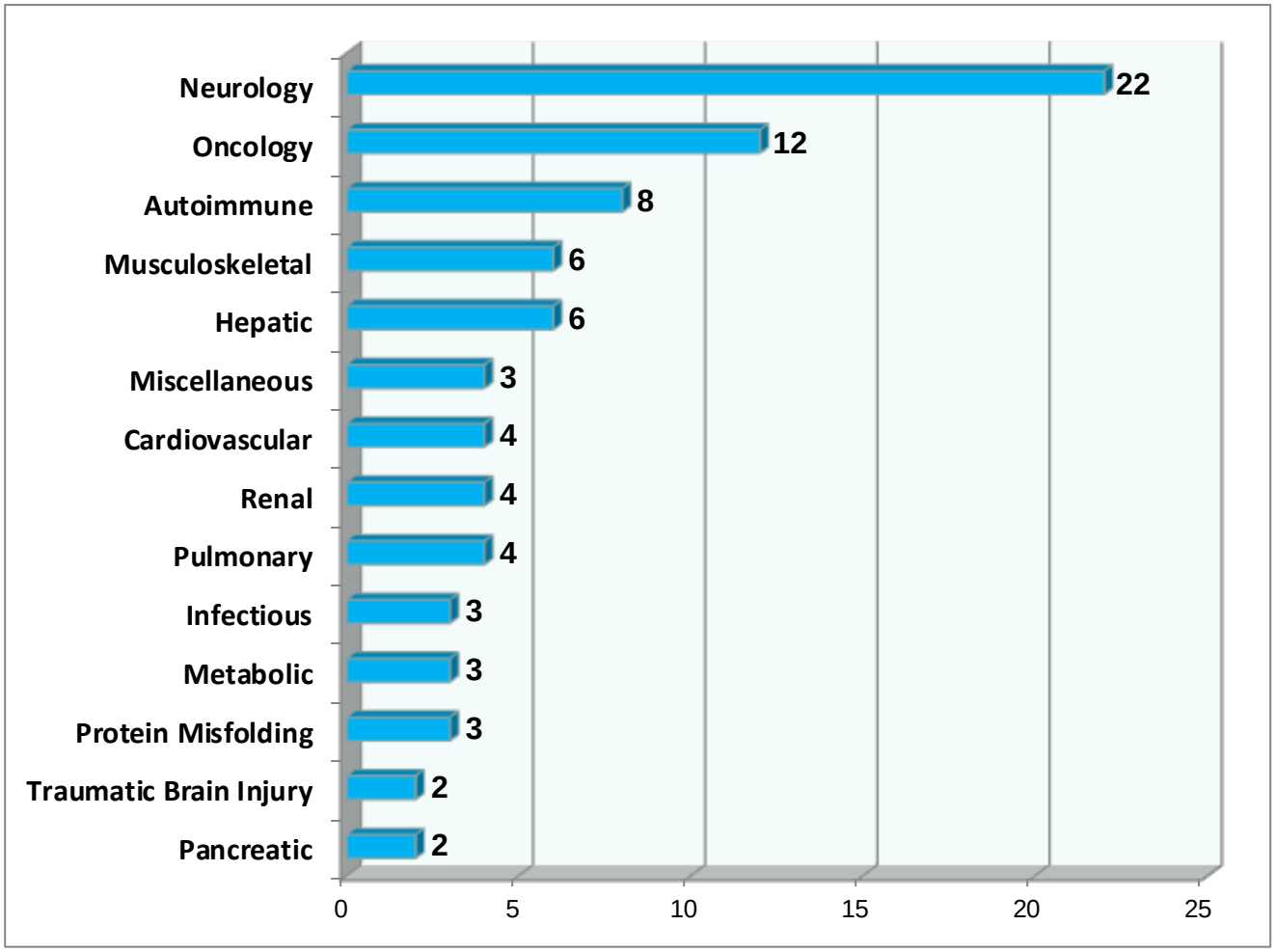
- Submissions to the survey came from academia, industry, consortia, patient advocacy groups and private entities



- Most of the responders did not answer all the questions
- Amount of detail provided varied
  - specific biomarkers not provided, but responded that biomarkers for a specific disease area needed
  - biomarker names not provided, but responded that a specific type of biomarkers for a specific disease area are needed
  - biomarker names provided, but not the context of use
- Biomarkers for a number of different disease areas (including rare diseases) and organ toxicities were provided

Disease Area	•Specific Area for Biomarker Development
Neurology	•Neurodegenerative: Alzheimer's, Parkinson's, Huntington's Disease. •Neuromuscular: Duchenne muscular dystrophy Becker muscular dystrophy , Facioscapulohumeral muscular dystrophy and Amyotrophic Lateral Sclerosis, Myotonic dystrophy, Friederich's Ataxia. •Neuropsychiatric: Mood Disorders, Epilepsy, Alcohol Dependence, Schizophrenia and Parkinson's disease.
Oncology	•Cancer (all types) - Non-small-cell lung carcinoma, pancreatic, solid tumors.
Auto-Immune & Inflammatory	•Systemic Lupus Erythematosus, Systemic Lupus Erythematosus, Rheumatoid Arthritis, Crohn's disease, Ulcerative colitis, Ankylosing Spondylitis, Acute Immunotoxicity.
Hepatic	•Liver pathology: Non-Alcoholic Steatohepatitis, Non-Alcoholic Fatty Liver Disease, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Viral Hepatitis B and C, Hepatocellular Carcinoma, Alcoholic Liver Disease, Autoimmune hepatitis, Safety biomarkers for acute and chronic Hepatotoxicity.
Musculoskeletal	•Imaging biomarkers for Osteoarthritis and Osteoporesis.
Pulmonary	•Chronic Obstructive Pulmonary Disease, Cystic fifrosis.
Renal	•Acute and Chronic nephrotoxicity, Autosomal dominant polycystic kidney disease
Cardiovascular	•Therapies in acute and chronic heart failure with reduced or preserved ejection fraction, Safety biomarkers for acute and chronic cardiotoxicity, heart failure.
Protein Misfolding	•Amyloid Light-chain amyloidosis, Transthyretin amyloidosis including disease-related dysfunction of the heart, kidneys and liver.
Metabolic	•Type I Diabetes, Diabetic Nephropathy.
Infectious Disease	•Vaccines against Pneumococcal disease, Acute Bacterial Skin and Skin Structure Infections, Community-Acquired Bacterial Pneumonia, Hospital-Acquired Bacterial Pneumonia and Ventilator Associated Bacterial Pneumonia (VABP).
Pancreatic	•Safety biomarkers for accute and chronic pancreatic toxicity.
Traumatic Brain Injury	• Brain magnetic resonance imaging
Miscellaneous	•Nutrigenomics /Nutritional medicine, Immuno-Oncology, Pain medicine, chronic kidney disease, Fall detection, Psychiatry.

Number of Responses Obtained in Different Disease Areas (N = 72)



Survey Results (Short version)

Disease area/Organ toxicity	Specific Areas in Critical Need for Biomarker Development	Biomarker Names	Context of Use	Why Is The Biomarker Useful in Drug Development?
Neurological and Neuropsychiatric Diseases		Biomarkers of functional outcome measures		Objective measures for motor dysfunction.
		Imaging measures (PET, tMRJ) 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/A	Treatment Response.	N/A
	Multiple Sclerosis	N/A		N/A
Oncology	i) Cardio-vascular system, liver, kidney for safety(toxicity) biomarkers.	i) Patient stratification biomarkers ii) Drug efficacy and safety biomarkers	i) Proof of concept (POC) using pharmacodynamic biomarkers ii) Patient stratification in enrollment using	N/A

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