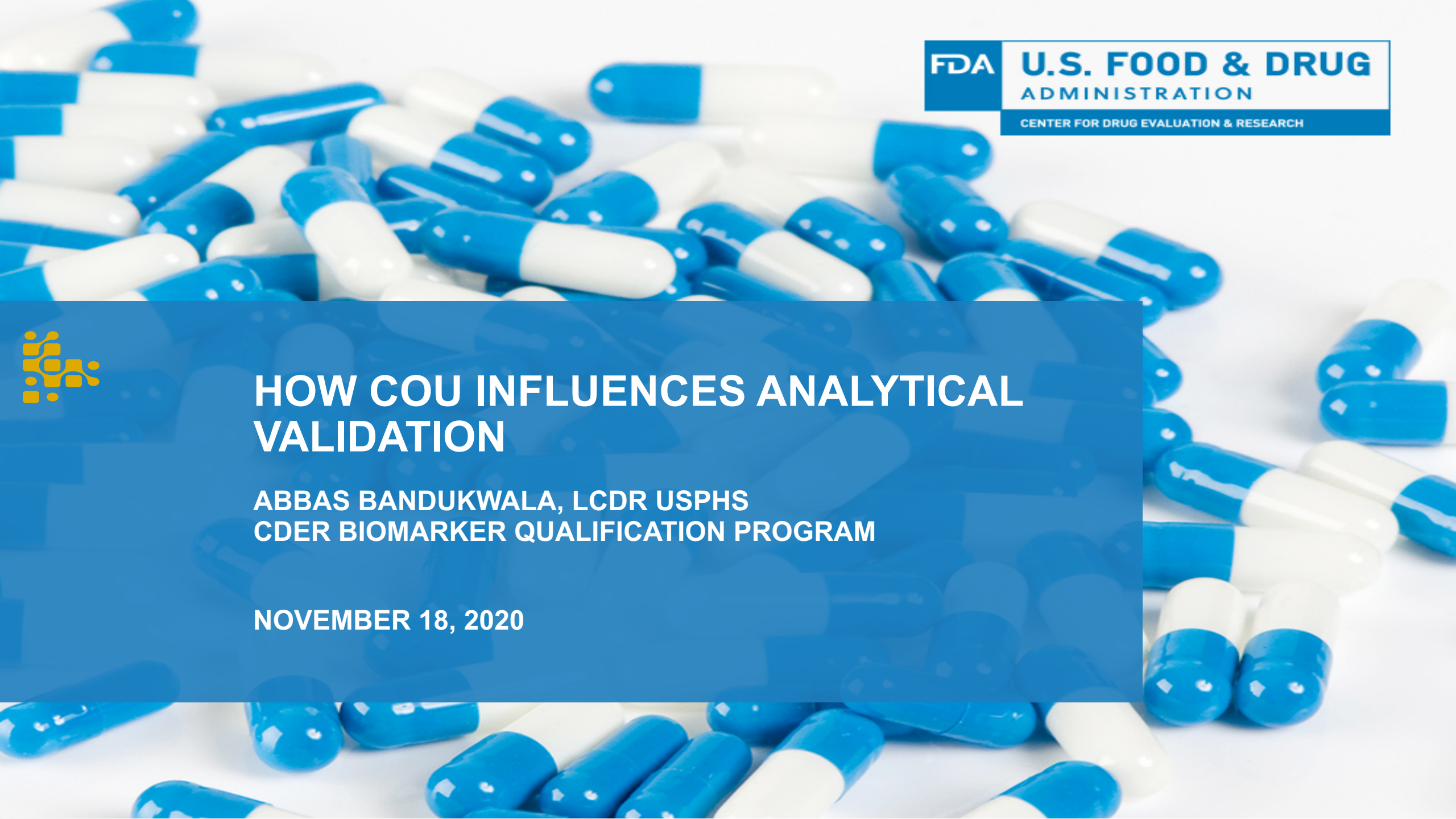


FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

HOW COU INFLUENCES ANALYTICAL VALIDATION

ABBAS BANDUKWALA, LCDR USPHS
CDER BIOMARKER QUALIFICATION PROGRAM

NOVEMBER 18, 2020

Disclaimers

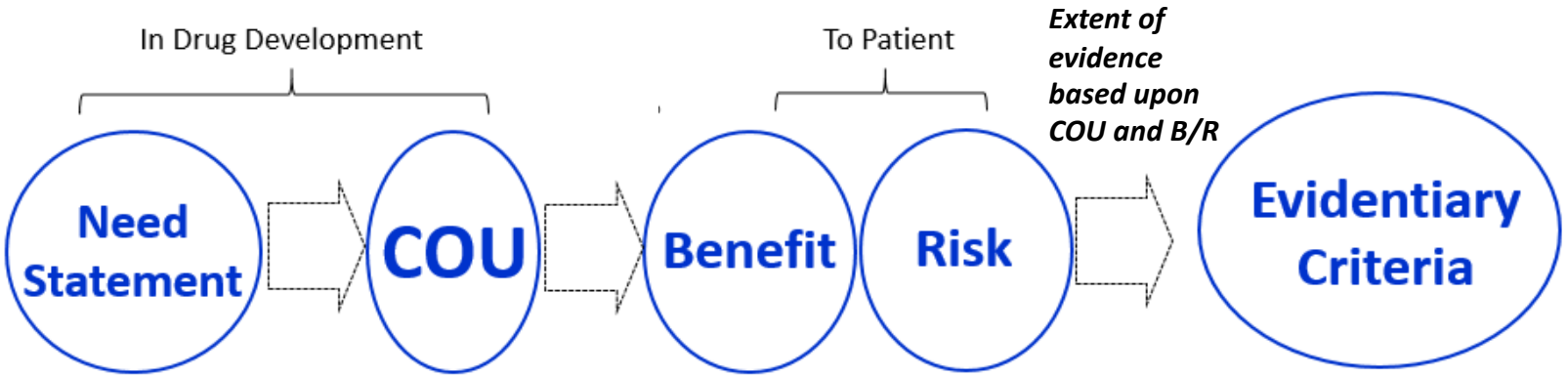
- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

- I do not have any financial disclosures regarding pharmaceutical drug products

The challenges of biomarker development

- Many disease areas with unmet needs have insufficient drug development tools to maximize trial efficiency (or even feasibility)
- Biomarker development *is a long and resource-intensive task*
  - Biomarker *discovery*: biased or unbiased screening in animal, clinical, epidemiological (include RWE)
  - Early animal *translational* models
  - Clinical or epidemiology observational studies
  - *Analytic validation* efforts: assure accuracy / reproducibility of measure
  - Interventional studies with "gold standard" endpoints compared to candidate – with multiple different treatments (different MOAs) to show that BM works across drug classes
- 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

Conceptual Framework for Biomarker Development for Regulatory Acceptance



What is the "gap" in drug development this BM can fill? What are currently available tools and their limitations?

What is the intended *use* of the BM – for what purpose ("BEST" class), in what population and setting?

What is the expected *value* of the biomarker – how does it address unmet needs?

- *Need for this tool and unmet need for treatment in target disease?*
- *How important is the impact of the BM?*

What is the consequence if the biomarker is inaccurate?

- *Used in conjunction with other endpoints or replacing other endpoints?*
- *Intended COU (e.g., enrichment vs a surrogate)?*

What is the evidence supporting the biomarkers proposed COU?

- *Where does the BM fit in the causal pathway?*
- *What is the biological rationale?*
- *What clinical data supports the relationship between the change in the BM and the clinical outcome?*
- *What are the analytic characteristics of the BM?*

https://fnih.org/what-we-do/biomarkers-consortium/programs/framework-for-safety-biomarkers

Context of Use

- From the start, COU is the foundation for the biomarker
- Helps establish and verify biomarker performance
- COU can be modified throughout the process
- Analytical performance and validation can affect COU

COU

Context of Use (COU): 1) BEST biomarker category and 2) how the biomarker impacts the clinical trial or drug development program

What question is the biomarker intended to address. Examples include:

- Inclusion/exclusion criteria for prognostic or predictive enrichment?
- Alter treatment allocation based on biomarker status?
- Result in cessation of a patient's participation in a clinical trial because of safety concern?
- Result in adaptation of the clinical trial design?
- Establish proof of concept for patient population of interest?
- Support clinical dose selection for first in human or Phase 3 studies?
- Evaluate treatment response (e.g. pharmacodynamic effect)?
- Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

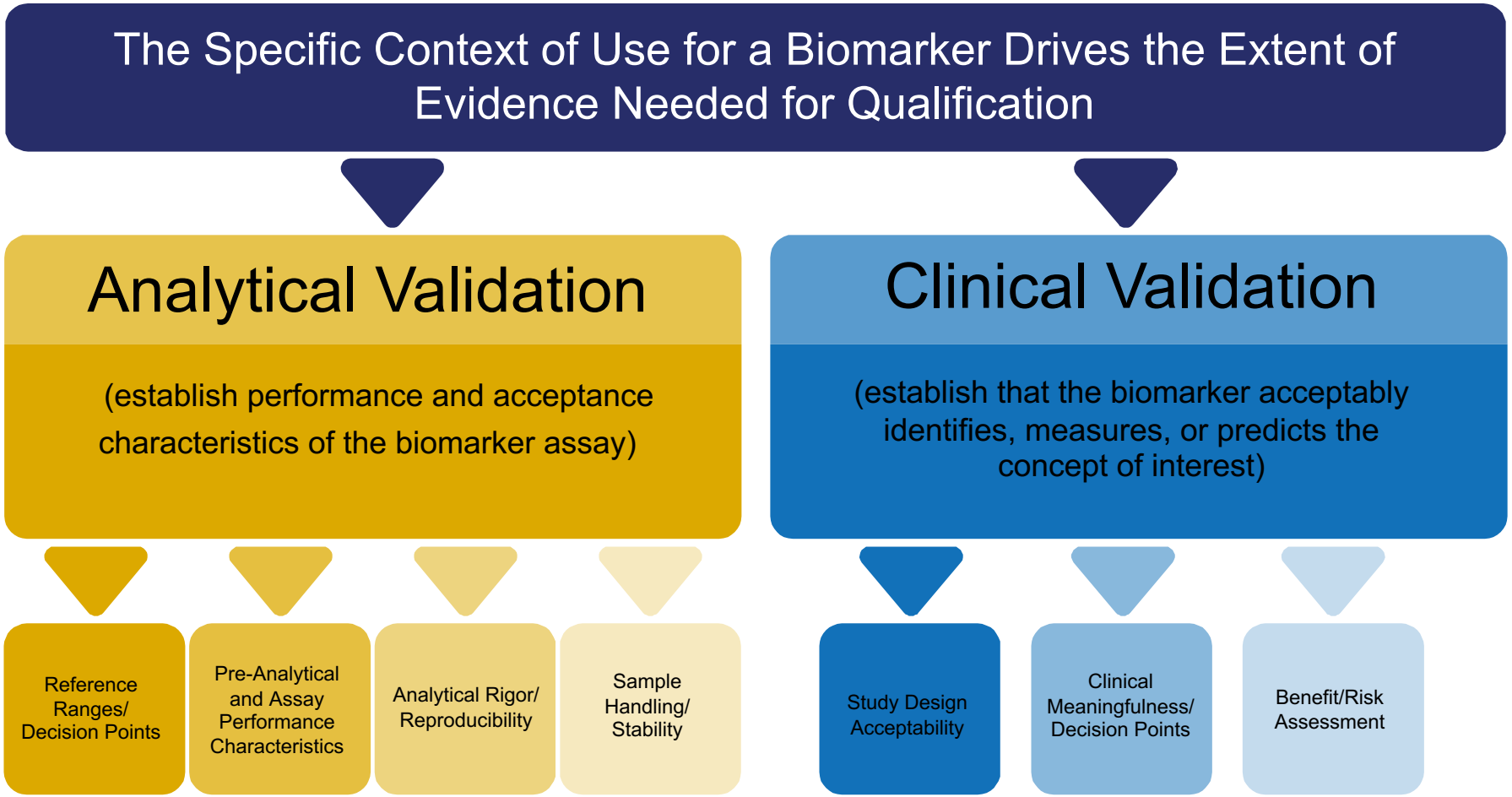
- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

Analytical Assay and Clinical Validation Considerations in Biomarker Qualification

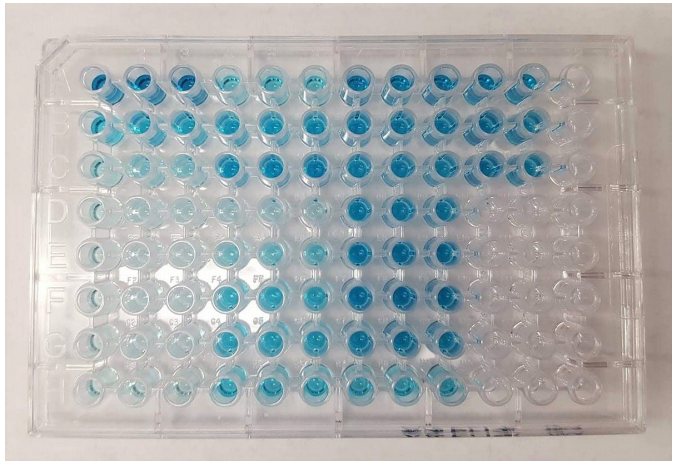


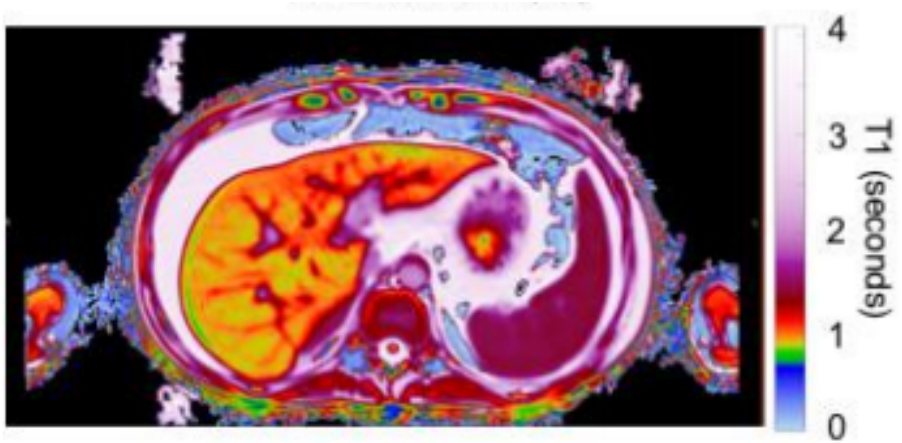
Key Analytical Performance Characteristics

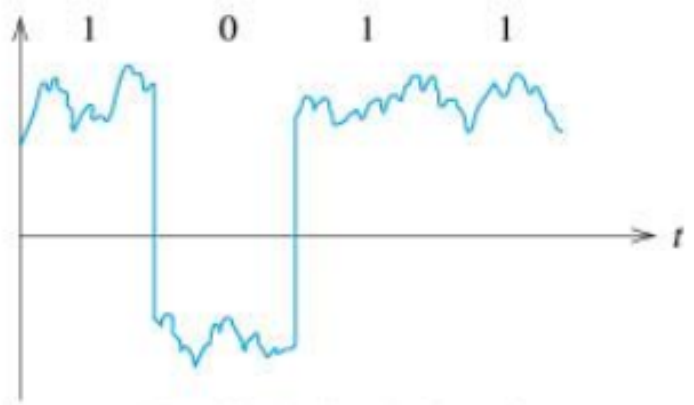
- Accuracy/Relative Accuracy
- Measurement Range
- Precision
  - Repeatability
  - Reproducibility
- Analytical Selectivity
- Limits of Detection/Limits of Quantitation

Performance characteristics

- Other characteristics may be added based on:
  - COU
  - Measurement Method Technology
    - For example Parallelism for fluid based biomarkers
  - Multiple Methods

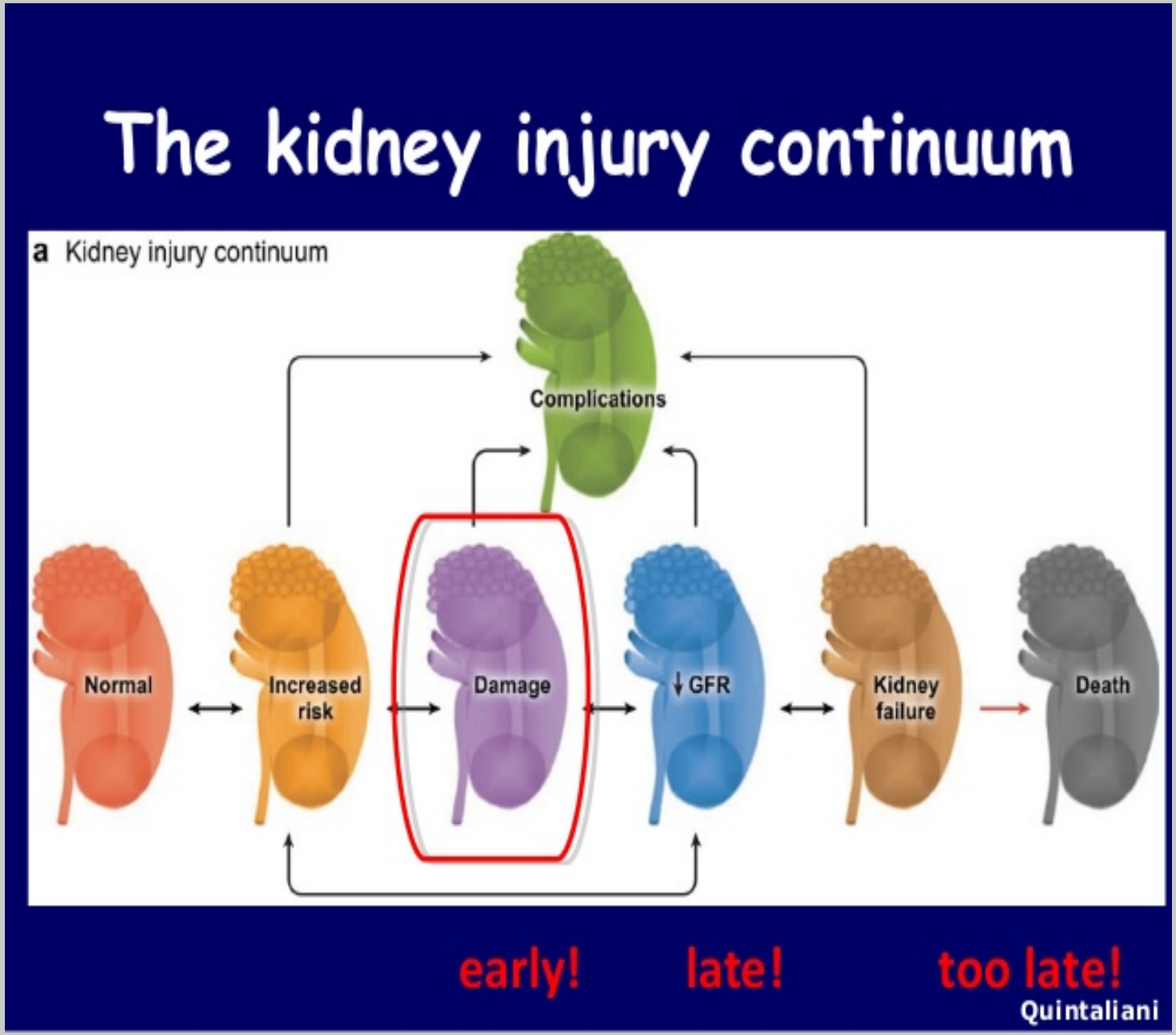






Kidney Safety Biomarkers Example

- Panel of six biomarkers
- Characterize performance of assays
- Stability data
- Analytical information for each biomarker and assay



Kidney Safety Biomarkers COU

- A safety composite biomarker panel to be used in conjunction with traditional measures to aid in the detection of kidney tubular injury in phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause renal tubular injury in humans

- Considerations when using these biomarkers were provided.
  - Cohort of patients
  - Composite Measure for normal healthy volunteers

Biomarker	Albumin	Clusterin	Creatininee	Creatinine	Cystatin-C	KIM-1	NAG	NGAL	Osteopontin	Protein (Total)
Platform	Roche Modular P	R&D ELISA	Modified Jaffé	Roche Modular P	R&D ELISA	R&D ELISA	Roche Modular P	BioPorto ELISA	R&D ELISA	Roche Modular P
Detection	Turbidometric	Colorimetric	Colorimetric	Colorimetric	Colorimetric	Colorimetric	Enzymatic colorimetric	Colorimetric	Colorimetric	Turbidometric
Precision WIR – L	2.6 %	10.5 %	0.7 %	1.0 %	3.9 %	8.3 %	4.3 %	5.4 %*	3.2 %	6.9 %
Precision WIR – M	1.4 %	6.3 %	1.0 %	2.4 %	3.0 %	1.1 %	2.5 %	8.8 %*	3.0 %	0.9 %
Precision WIR – H	1.1 %	5.8 %	0.8 %	0.7 %	4.3 %	5.3 %	1.9 %	8.7 %*	3.9 %	1.2 %
Precision BTR – L	4.6 %	14.5 %	2.2 %	0.9 %	1.3 %	11.3 %	5.6 %	-	12.5 %	8.5 %
Precision BTR – M	2.2 %	4.3 %	2.7 %	2.9 %	6.7 %	14.6 %	4.5 %	-	7.7 %	1.6 %
Precision BTR – H	1.5 %	4.7 %	2.2 %	1.5 %	5.8 %	15.8 %	2.5 %	-	10.0 %	1.4 %
Precision BTR – Mean (CV)	<5%	< 15%	-	< 3%	< 12%	< 16%	< 6%	< 7%	< 13%	<9%
Units	**mg/L**	**ng/mL**	**mg/dL**	**mg/dL**	**ng/mL**	**pg/mL**	**U/L**	**ng/mL**	**ng/mL**	**mg/dL**
Precision WIR – L Sample Value	5.64	16	-	49.2	14.2	169	0.86	4.2	807	6.9
Precision WIR – M Sample Value	31.53	105	-	97.4	27.2	579	2.41	20	1775	53.2
Precision WIR – H Sample Value	105.09	238	-	146.1	79.4	1161	9.9	44.5	4524	181.3
LLOQ	3.0	10 (Incl. PAD)	0.8	3.6	1.31	11.6	0.31	0.004 (Incl. PAD)	44 (Incl. PAD)	3.5
ULOQ	400	800	600	900	100	2000	55.25	100	8,800	200
Upper reportable limit	4,400	3,200	19,200	16,864	6,400	64,000	2,210 U/L	6,400	281,600	10,800
Recovery range	ND	90-107.5%	-	103.5-107.9%	83.8-104.2%	96.6-118%	99.1-104.5%	93.3-109.4%	97.9-101.5%	104.1-118.8%
Reference interval (normalized to uCr)	ND	35-383 ng/mg	-	40.0-278 mg/dL (M); 29.0-226 mg/dL (F)	0.014-0.058 µg/mg	<1.191 ng/mg	<0.78 U/mmol	<41.8 ng/mg	495-2029 ng/mg	1.3 – 10.1 mg/mg (x100)
Dilutional range	≤11-fold	≤4-fold (Pre-Diluted)	≤32-fold	≤32-fold	≤64-fold	≤32-fold	≤40-fold	≤64-fold (Pre-Diluted)	≤32-fold (Pre-Diluted)	≤54-fold
Dilutional linearity	±13.8%	±20%	±8.3	±4.9 %	±19.6%	±18.0%	±12.1%	ND	±8.3%	±20.3%
Procedural Dilution	-	4	-	-	-	-	-	100	440	-

Analysis of Analytical data

- Characterize the performance of the assay for each of these biomarkers
- Differences in process for how clinical samples and analytical samples processed and measured
- Stability data for some biomarkers

Plasmodium falciparum 18S rRNA/rDNA (copies/mL) Malaria Biomarker

- Malaria
- Original context of use – Monitoring
- Additional context of use
- Different analytical data needed for different COU

Malaria Monitoring Context of Use

- A monitoring biomarker, that when positive, informs initiation of treatment with an anti- malarial drug >6 days following controlled human malaria infection (CHMI) with P. falciparum sporozoites in healthy subjects (18-50 years old) from non-endemic areas enrolled in clinical studies for vaccine and/or drug development.

Plasmodium falciparum 18S rRNA/rDNA Analytical Data Provided

- Analytical sensitivity
- Correlation
- Accuracy
- Precision
- Reference interval
- Analytical specificity
- Reportable range
- Analyte stability
- Carryover

Plasmodium falciparum 18S rRNA/rDNA Analytical Data

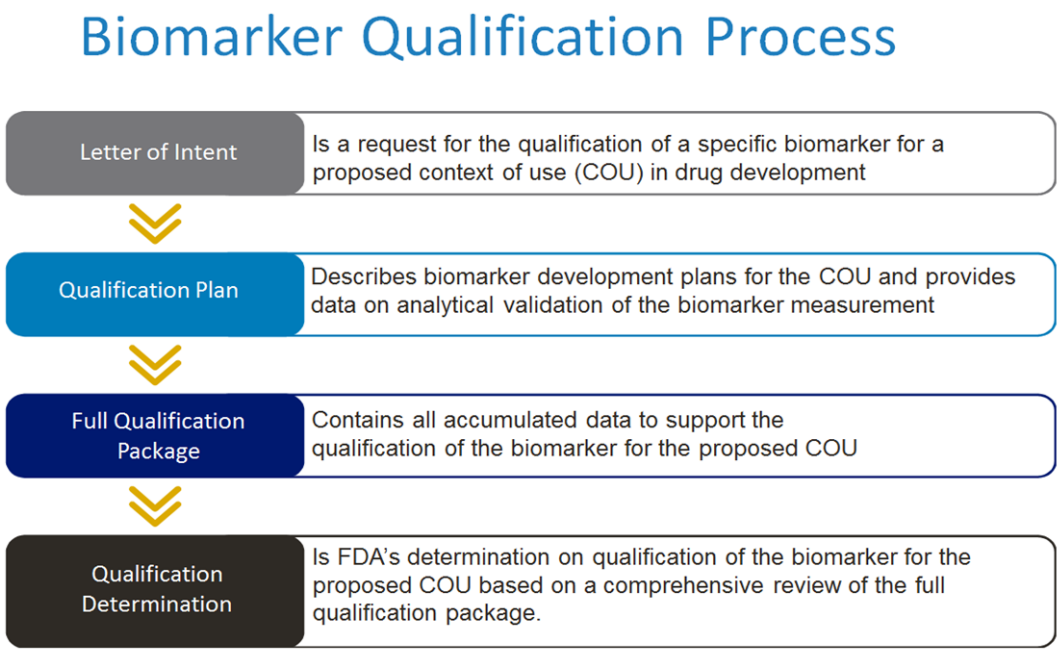
- Small Sample size
- No WHO Reference Material Standard
- Actionable decision point
- Quantitation is a separate claim from detection and qualitative (yes/no) decision point

Future Malaria Biomarker Context of Use

- Monitoring biomarker in endemic areas
- Endpoint biomarker to evaluate drugs and vaccines in endemic areas
- Both COU will require additional analytical data to support the COU
- Slight change to assay
- Additional interference from parasites in endemic areas
- Analytical data around thresholds

21st Century Cures (CC) 507 DDT Qualification

- 21st CC and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role



- FDA submission decision: Accept or Not Accept
- A transparent process – so all stakeholders are aware of tools in development, stage, and FDA determinations/recommendations

BQP Resources

- Guidance documents
  - Evidentiary Framework guidance
  - Biomarker Qualification Program Analytical Validation Guidance
    - (Not the same as the Bioanalytical Validation Guidance)

- CDER BQP Website
  - Current projects
  - List of Qualified Biomarkers
  - https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program

Thank you for your attention