FDA WORKSHOP:
Title: "EVIDENCE-BASED TREATMENT DECISIONS IN TRANSPLANTATION"
Subtitle: "THE RIGHT DOSE & REGIMEN FOR THE RIGHT PATIENT/INDIVIDUALIZED TREATMENT"
September 27 and 28, 2018
White Oak Campus, Silver Spring, Maryland
Great Room

AGENDA	

BACKGROUND - Why are we holding this workshop?

GOALS: The current workshop is focused on the patient and utilizing biomarkers during the drug development process to determine the right treatment regimen to prevent long-term rejection of the patient's allograft.

During the INTRODUCTORY session, attendees will learn about the formation of the Transplant Therapeutics Consortium (TTC) and the role of public-private partnerships in catalyzing drug development.

Day 1: Background on Biomarker Qualification Versus Clinical Practice; Potential Biomarkers to Assess Patient Level Immunologic Risk and Rejection; and Data to Support Biomarker Qualification

- Session 1 –The Difference Between Biomarker Implementation in Clinical Practice and Biomarker Qualification for use in Drug Development
- Session 2 - Potential Biomarkers to Identify Alloimmune Risk in Patients Pre-transplantation
- Session 3 - Potential Early Post-Transplant Biomarkers of Alloimmunity or Risk for Graft Loss
- Session 4 - Potential Late Post-Transplant Biomarkers to Identify Patients at Low Immunologic Risk
- Session 5 - The Challenge of Developing Data across Transplant Centers

Open Public Comment

Day 2: Patient Focused Drug Development (PFDD)– Patient Reported Outcome Measures, Tolerability, Adherence

- Session 6 – Patient-Focused Drug Development Through Patient Reported Outcome Measures and Adherence Measures
- Session 7 - Patient Focused Adherence Strategies

At the end of the meeting, a summary will be considered including potential areas of further research, information gaps, and possible next steps.

Day 1 – September 27, 2018	
7:00 am	Registration – Time to preorder lunch outside Great Room.
INTRODUCTION (8:00 am – 9:00 am) Why are we holding this workshop, the goals and how is this workshop intended to address unmet medical needs in transplantation	
15 minutes	**Welcome, Topics and Goals** Speaker: *Renata Albrecht, MD, FDA and Inish O'Doherty, PhD, C-Path*
15 minutes	A Call to Action –Unmet Needs in Transplantation. Working together as a community, the genesis of the Transplant Therapeutics Consortium (TTC) a Public Private Partnership Speaker*: Roslyn B. Mannon, MD, University of Alabama at Birmingham, Birmingham, AL*
15 minutes	The Transplant Therapeutics Consortium (TTC) current workgroups and undertakings/efforts of the Public Private Partnership Speaker: *Mark D. Stegall, MD, Mayo Clinic, Rochester, MN*
15 minutes	The Role of Public–Private Partnerships in Catalyzing the Critical Path Speaker: *Ameeta Parekh, PhD, FDA*
Session 1 (9:00 am – 10:30 am) **The Difference Between Biomarker Implementation in Clinical Practice and Biomarker Qualification for use in Drug Development** Moderators: *Katherine A. Hollinger, D.V.M., M.P.H., (DACVPM CAPT, USPHS), FDA and Inish O'Doherty, PhD, C-Path*	
15 minutes	What Evidence Is Required to Qualify A Biomarker? Speaker: *John Michael Sauer, PhD, C-Path*
15 minutes	Biomarker Qualification - Kidney Safety Project. Predictive Safety Testing Consortium (PSTC) Speaker: *Gary Steven Friedman, MD, Pfizer*
15 minutes	GFR Decline as an Endpoint in Clinical Trials of CKD Speaker: *Josef Coresh, MD, Johns Hopkins University*
15 minutes	Clinical Biomarkers vs. Qualified Biomarkers for use as Endpoints in Clinical Trials of Therapeutics Speaker: *Ulf Meier-Kriesche, MD, FAST, Veloxis Pharmaceuticals - TTC Workgroup co-chair*
30 minutes	Questions for Discussion 1. How do we know when a biomarker is ready to start the qualification process? What is needed? 2. How does one determine an appropriate Context of Use for a biomarker? How does this relate to unmet need? 3. What sources of data/evidence can be used to qualify a biomarker for a specific Context of Use? 4. What are the other benefits of the qualification process?

10:30 am--MORNING BREAK--10:45 am	
Session 2 (10:45 am - 12:00 pm) **Potential Biomarkers to Identify Alloimmune Risk in Patients Pre-transplantation** Moderators: *Ergun Velidedeoglu, MD, FDA and Ulf Meier-Kriesche, MD, FAST, Veloxis Pharmaceuticals*	
15 minutes	HLA Molecular Mismatch - A prognostic biomarker for primary alloimmunity Speaker: *Peter Nickerson, MD, FRCPC, FCAHS, University of Manitoba, Winnipeg, MB, Canada*
15 minutes	Biomarkers to assess risk of kidney allograft injury during CNI withdrawal Speaker: *Peter Heeger, MD, Icahn School of Medicine at Mount Sinai, New York, NY for the CTOT-09 Consortium*
15 minutes	Genomic SNPs – biomarkers of alloimmune risk? Speaker: *Roslyn Mannon, MD, University of Alabama*
30 minutes	Questions for Discussion 1. What are the unmet needs in drug development and clinical practice in the kidney pre-transplant setting and how do these align? 2. What biomarkers exist that could address these unmet needs, and how could these biomarkers be prioritized to enable the development of new therapies and new regimens? 3. What considerations, including biological plausibility and evidentiary criteria, would be needed to develop prioritized biomarkers for use in drug development? In clinical practice?
LUNCH (12:00 pm – 1:00 pm)	
Session 3 (1:00 pm – 2:45 pm) **Potential Early Post-Transplant Biomarkers of Alloimmunity or Risk for Graft Loss** Moderators: Moderators: *Shukal Bala, PhD, FDA and Peter Nickerson, MD, FRCPC, FCAHS, University of Manitoba, Winnipeg, MB, Canada*	
15 minutes	Noninvasive immune monitoring for subacute rejection in kidney transplantation Speaker: *Minnie M. Sarwal, MD, PhD, FRCP, DCH, University of California San Francisco, San Francisco, CA*
15 minutes	Genomic Biomarkers (CTOT-8) Speaker: *Michael M. Abecassis, MD, MBA, Northwestern Medicine, Chicago IL*
15 minutes	Genomic approach to immune stratification Speaker: *Barbara Murphy, MD, MB, BAO, BCh, FRCPI, Icahn School of Medicine at Mount Sinai, New York, NY*
15 minutes	Protein vs. gene expression as a diagnostic biomarker of alloimmunity Speaker *Roslyn Mannon, MD, University of Alabama*

15 minutes	Risk Prediction Score for Allograft loss in Kidney transplant recipients Speaker: *Alexandre Loupy, MD, PhD, CHU Necker, Paris, France*
30 minutes	Questions for Discussion: 1. What are the unmet needs in drug development and clinical practice in the early kidney post-transplant setting and how do these align? 2. What biomarkers exist that could address these unmet needs, and how could these biomarkers be prioritized to enable the development of new therapies and new regimens? 3. What considerations, including biological plausibility and evidentiary criteria, would be needed to develop prioritized biomarkers for use in drug development? In clinical practice?

Session 4 (2:45 – 4:00 pm)
Potential Late Post-Transplant Biomarkers to Identify Patients at Low Immunologic Risk
Moderators: *Yan Wang, PhD, FDA and Roslyn B. Mannon, MD, University of Alabama at Birmingham, Birmingham, AL*

15 minutes	Biomarkers of operational tolerance following kidney transplantation - The immune tolerance network studies of spontaneously tolerant kidney transplant recipients. B Cell receptor genes associated with tolerance Speaker: *Ken A. Newell, MD, PhD, Emory University, Atlanta, GA*
15 minutes	Biomarkers of Tolerance in Kidney Transplantation: Are We Predicting Tolerance or Response to Immunosuppressive Treatment? Role of steroid regulation and response in kidney transplantation. Speaker: *Maria P Hernandez-Fuentes, MD, PhD, Head of Translation Biology for Immunology, UCB Celltech*
15 minutes	Predictive Modeling of Biomarker and Clinical Outcome in Kidney Transplant Patients Speaker: *Edward Chong, MBChB, MRCP Chief Medical Officer, Vitaeris*
30 minutes	Questions for Discussion: 1. What are the unmet needs in drug development and clinical practice in the late kidney post-transplant setting and how do these align? 2. What biomarkers exist that could address these unmet needs, and how could these biomarkers be prioritized to enable the development of new therapies and new regimens? 3. What considerations, including biological plausibility and evidentiary criteria, would be needed to develop prioritized biomarkers for use in drug development? In clinical practice?

AFTERNOON BREAK (4:00 pm to 4:15 pm)

Session 5 (4:15 pm – 5:35 pm)
The Challenge of Developing Data across Transplant Centers
Moderators: *Marc Cavaillé-Coll, MD, PhD, FDA and Randall Morris, MD, FRCP, Stanford University School of Medicine (Emeritus), Stanford, CA*

15 minutes	Epidemiology and variation of both induction and maintenance therapy in kidney and liver transplantation. Speaker: *Krista Lentine, MD, PhD, Saint Louis University Hospital, St. Louis, MO*
15 minutes	Risk adjusted clinical and economic implications of immunosuppression selection. Speaker: *David A. Axelrod, MD, MBA, Lahey Clinic, Burlington, MA*
15 minutes	Toward Building a Network of Clinical Centers Speaker: *Mark D. Stegall, MD, Mayo Clinic, Rochester, MN*
20 minutes	Clinical Trials Networks in Oncology – A Model of Collaboration Speaker: *Margaret (Meg) Mooney, MD, Chief, Clinical Investigations Branch, CTEP, DCTD, NCI*
15 minutes	Question for Discussion 1. How do we migrate from center practices in IS treatment regimens to data-based IS selection? 2. How do center practice differences affect clinical studies testing? 3. What can be done to "harmonize" treatment selection based on underlying patient characteristics, not center pattern?
Open Public Comment (5:35 pm – 6:00 pm) Moderators: *Shanon Woodward, PharmD, OPSA, FDA, Renata Albrecht, MD, FDA and Inish O'Doherty, PhD, C-Path*	
15 minutes	Open Public Comment Opportunity for public remarks Speakers should preregister at the registration desk
10 minutes	**Summary Day 1 and Overview of Day 2**
6:00 pm	**Adjourn Day 1**
DAY 2 – September 28, 2018	
Opening Remarks for Day 2 (8:00 am – 8:10 am) *Renata Albrecht, MD, FDA and Inish O'Doherty, PhD, C-Path*	
Session 6 (8:10 am - 10:10 am) – Patient-Focused Drug Development Through Patient Reported Outcome Measures and Adherence Measures Moderators: *Renata Albrecht MD, FDA and Matthew Everly, PharmD, BCPS, FAST, Terasaki Research Institute*	
10 minutes	Patient Focused Drug Development (PFDD) in Patients who have received on organ transplant, 21St Century Cure and PDUFA VI Speaker: *Ozlem Belen, MD, MPH, FDA*
10 minutes	Patient Voice at the FDA Workshop on Antibody Mediated Rejection Speaker: *Ergun Velidedeoglu, MD, FDA*

5 x 5 (five) minutes	The Patient Perspective on their Organ, Treatment and Hopes for Future Management (changes, improvements) and how this can differ from physician perspective - *with, Shanon Woodward, PharmD, OPSA, FDA* ***NOTE: Patients will be invited to attend both days of the meeting*** Haley Newkirk Brandy Webster Alex Berrios Dean Hutto Kim Cable
15 minutes	PRO measures for symptomatic adverse events in Oncology Speaker: *Lori Minasion, MD, FACP, NCI, NIH*
15 minutes	Strategies for Adapting Existing PRO Measures: Speaker: *Sandra A. Mitchell, PhD, CRNP, AOCN, NCI, NIH*
15 minutes	PRO Measures in Transplant; The Future Speaker: *Rita R. Alloway, Pharm D, FCCP, University of Cincinnati College of Medicine, Cincinnati, OH*
30 minutes	Questions and Panel Discussion 1. What are patient priorities in transplant and immunosuppression? 2. What considerations should be taken into account for developing PRO measures focused on evaluating therapies in terms of symptomatic adverse events and tolerability, bearing in mind the different transplant stages including early post-transplant and late post-transplant? 3. How does the PRO-CTCAE relate to assessing tolerability in head to head drug trials? 4. What are lessons learned and future directions for PRO development, and how can these inform PRO development in solid organ transplantation? *Paul Kluetz, MD, OHOP, FDA, Sandra Mitchell, PhD, CRNP, FAAN, NCI, NIH, Elektra Papadopoulos, MD, MPH and Michelle Campbell, MS, PhD, COA staff, FDA*
10:10 am--MORNING BREAK--10:25 am	
Session 7 (10:25 am - 11:45 am) Patient Focused Adherence Strategies Moderators*: Ozlem Belen, MD MPH, FDA, and Rita Alloway, PharmD, FCCP University of Cincinnati College of Medicine, Cincinnati, OH*	
15 minutes	Intrapatient variability of tacrolimus levels and clinical implications Speaker: *Ruth Sapir-Pichhadze, BMedSC, MD, MSc, PhD, FRCPC, McGill University, Montreal, Quebec, Canada*
15 minutes	Tacrolimus variability in kidney transplantation, Causes, consequence and clinical management Speaker: *Teun van Gelder, MD, Erasmus Medical Centre, Rotterdam, Netherlands*
15 minutes	Patient-focused adherence strategies

	Speaker: *Matthew J. Everly, Pharm D, BCPS, FAST, Terasaki Research Institute*
15 minutes	Communication and Patient Labeling – What can be done to make it a useful resource Speakers: *Patient viewpoints*
20 minutes	Question for Discussion 1. How do tolerability and adherence relate to each other? 2. What influences tacrolimus levels? 3. What helps patients achieve adherence? 4. How do patients use labeling?
Summary Analysis and Next Steps (11:45 am – 12:00 pm)	
15 minutes	Biomarkers as Tools for the Development of Immunosuppressive Drugs for Organ Transplantation Speaker*: Randall E. Morris, MD, FRCP, Stanford University School of Medicine (Emeritus), Stanford, CA*
Workshop Closeout *Renata Albrecht, MD, FDA and Inish O'Doherty PhD, C-Path*	
12:30 pm	**Adjourn Day 2**

Appendix A: Biomarkers and Context of Use
Appendix B: Glossary of Terms

Appendix A

Biomarkers and Context of Use

Sept. 27-28 FDA Workshop

U.S. FOOD & DRUG ADMINISTRATION

TTC CRITICAL PATH INSTITUTE

BIOMARKERS and CONTEXT OF USE

September 27, 2018

Discuss the differences between using biomarkers in clinical practice to inform clinical decision making and using biomarkers in drug development to inform regulatory decision making

- Discuss regulatory pathways that exist at the FDA to seek the regulatory endorsement of biomarkers, focusing on biomarker qualification
- Highlight how public private partnerships may be used to enable biomarker qualification
- Discuss biomarkers under development in the developed pre, post, and late post-transplant environments

Two Major Points of Consideration for Presentations on Biomarkers

1. **Need Statement:** what is the knowledge gap or drug development need that the biomarker(s) are addressing
2. **Context of Use (COU) Statement**: A concise description of the biomarker's specified use in drug development
3. **Assessment of Benefit to the Patient:** e.g., improved sensitivity or selectivity, better mechanistic context to graft loss, enable earlier intervention or selection of certain patients that otherwise wouldn't be identifiable
4. **Assessment of Risk to the Patient**: Consequences of a false negative or positive
5. **Evidentiary Criteria:** characterizing the relationship of biomarker to the clinical outcome, biological rational, supporting patient level datasets (retrospective or proposed prospective), comparison to current standard, assay performance and statistical methods used

What evidence do we need for biomarker qualification?"- Leptak el al. Sci Transl Med. 9(417), 2017.

Considerations for Biomarker Utility are Defined by the Context of Use (COU) Statement

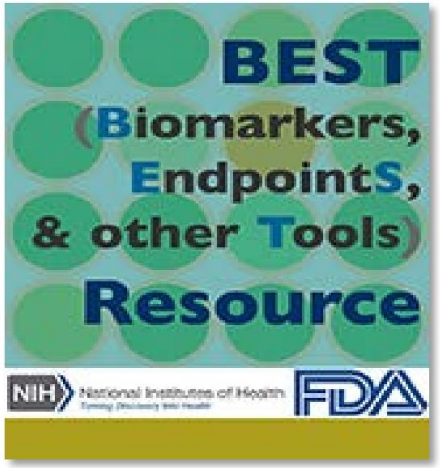
Biomarker: "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers."

A drug label is to a drug, as a COU statement is to a drug development tool:

- The COU statement will provide a concise description of how a biomarker is intended to be used in drug development
- COU simplified to only **2 elements**:
  - What **class of biomarker** is proposed and what information content would it provide?
  - What **question is the biomarker intended to address**? ("What is the biomarker's specific fit- for-purpose use?")

How to Classify Biomarkers: The BEST (Biomarkers, EndpointS, and other Tools) Glossary

- Created by the NIH-FDA Biomarker Working Group
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/



- Susceptibility / risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Monitoring biomarker
- Predictive biomarker
  Pharmacodynamic/Response biomarker – including surrogate endpoints
- Safety biomarker

Measures of disease presence and status

Measure aspects of response to treatment

FDA/NIH Biomarker Definitions

Measures of disease presence and status

- **Susceptibility/Risk Biomarker** – indicated potential for developing disease in individual
  - e.g., BRCA (1/2) and risk breast cancer; Factor V Leiden and risk DVTs; APO e predisposition to Alzheimer's; HPV subtypes and cervical cancers; CRP and coronary disease

- **Prognostic Biomarker** – used to identify likelihood of clinical event, disease recurrent or progression in persons with the disease.
  - e.g., PSA or Gleason scoring in Prostate CA, Chromosome 17p deletion and TP53 mutations to assess CLL patient's likelihood of death, total kidney volume to select PCKD at risk of declining renal function

- **Diagnostic Biomarker** – used to detect o confirm presence of disease, or subtype of disease.
  - e.g., BP for hypertension, HbA1C for DM, GFR for CKD, Ejection fraction for heart failure

- **Monitoring Biomarker** – measured serially to assess status of disease
  - e.g., HCV-RNA or HIV-RNA monitor response to antiviral treatment; PSA to monitor disease status, INR/PT warfarin

FDA/NIH Biomarker Definitions

Measure aspects of response to treatment

- **Predictive Biomarker** – used to identify individuals who are more likely to experience desired/undesired effect, compared to biomarker negative individuals
  - e.g., Breast Cancer genes 1 and 2 (BRCA1/2) mutations predictive for response to poly (ADP-ribose) polymerase; HLA B*5701 to identify patients at risk for severe skin reactions to abacavir

- **Pharmacodynamic/Response Biomarker** – used to show biological response in response to treatment
  - e.g., BP in response to antihypertensive, HbA1c in response to antihyperglycemic agent, Sweat Chloride in CF; INR evaluating response to warfarin; HCV-RNA or HIV-RNA monitor response to antiviral treatment

- **Reasonably Likely Surrogate Endpoint** – strong mechanisms and/or epidemiologic rationale that effect on surrogate is expected to correlate with clinical benefit (may be used for accelerated approval, not traditional approval)
  - e.g., 6-month culture in TB ; (very few)

- **Safety Biomarker** – measured before or after treatment to indicate likelihood or extent of toxicity
  - e.g., LFTs and hepatotoxicity; creatinine for nephrotoxicity; K+ and diuretics; urinary biomarkers

FDA: Context of Use

Examples of Biomarker Intended Use in Drug Development

- ❑ Defining inclusion/exclusion criteria
- ❑ Defining treatment allocation arms
- ❑ Cessation of a patient's participation in a clinical trial
- ❑ Establishing a drug's proof of concept in a patient population
- ❑ Supporting clinical dose selection
- ❑ Serving to enrich clinical trial for an event or population of interest
- ❑ Evaluating treatment response

Note that a drug development use may also include descriptive information such as the patient population, disease or disease stage or model system

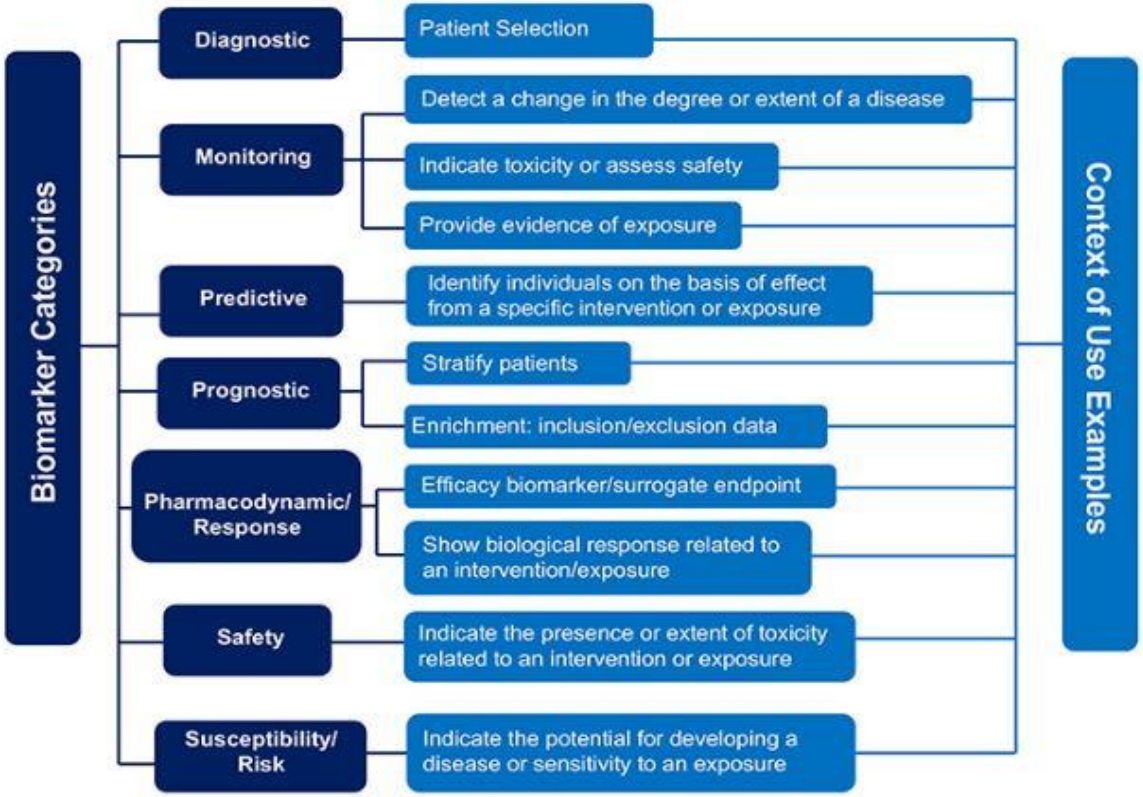
Examples of COUs

- ❑ Predictive biomarker to enrich for enrollment of a sub group of asthma patients who are more likely to respond to a novel therapeutic in Phase 2/3 clinical trials.
- ❑ Prognostic biomarker to enrich the likelihood of hospitalizations during the timeframe of a clinical trial in phase 3 asthma clinical trials.
- ❑ Safety biomarker for the detection of acute drug-induced renal tubule alterations in male rats

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535395.htm

FDA: Context of Use Construction

BEST Biomarker Category and Examples of Corresponding Drug Development Uses



A COU is generally written to be consistent with the following structure:

[BEST biomarker category] to **[drug development use].**

Biomarker Development Pathways

- **Drug-specific (IND):** based upon agreement with the division, in the context of a specific drug development program

- **Scientific community consensus:** broadly/widely used biomarker, appropriate scientific support, generally accepted by experts in the field. Examples: Banff, HbA1C,

- **Biomarker qualification program:** review and acceptance based upon appropriate submission qualification package; available for use in any development program within approved context of use

Qualification of Reasonably Likely Surrogate Endpoint

- An endpoint supported by strong mechanistic and/or epidemiologic rationale **such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials**, but without sufficient clinical data to show that it is a validated surrogate endpoint.

- Such endpoints may be used for accelerated approval for drugs and potentially also for approval or clearance of medical devices. In the case of **accelerated approval for drugs, post-marketing confirmatory trials have been required** to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit

Necessary characteristics and supporting evidence:

Prognostic

Pharmacodynamic / Response

All definitions can be found at NIH-FDA's Biomarkers, EndpointS, and other Tools (BEST) Glossary

Appendix B

Glossary of Terms

FDA WORKSHOP:
Title:
"EVIDENCE-BASED TREATMENT DECISIONS IN TRANSPLANTATION"
Subtitle:
"THE RIGHT DOSE & REGIMEN FOR THE RIGHT PATIENT/INDIVIDUALIZED TREATMENT"
September 27 and 28, 2018
White Oak Campus, Silver Spring, Maryland
Great Room

Glossary of Terms

Accelerated Approval
Regulatory approval pathway of a novel therapeutic agent based on the agent's effect on a surrogate endpoint, rather than a direct measure of clinical outcomes. Accelerated Approval necessitates the need for Phase IV confirmatory trials to ensure a surrogate endpoint actually predicts true patient outcomes.

Adherence
The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen

Adverse Event
Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

Adverse Reaction
A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function

Biomarker
A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. A biomarker is not an assessment of how an individual feels, functions, or survives. Categories of biomarkers include:

1. **Diagnostic Biomarker**
   A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease

2. **Monitoring Biomarker**
   A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent

3. **Pharmacodynamic/Response Biomarker**
   A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent

4. **Predictive Biomarker**
   A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product of an environmental agent

5. **Prognostic Biomarker**
   A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest

6. **Safety Biomarker**
   A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate likelihood, presence, or extent of toxicity as an adverse effect

7. **Susceptibility/Risk Biomarker**
   A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition

Context of Use (COU)
A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use. A COU is structured as follows: Development Tool is a [classification of biomarker] + [intended use in drug development]

Clinical Outcome
An outcome that describes or reflects how an individual feels, functions, or survives.

Clinical Outcomes Assessment (COA)
Measurement and assessment of a clinical outcome made through report by a clinician, patient, a non-clinician observer or through a performance-based assessment. There are four types of COAs

1. **Patient Reported Outcome (PRO) Measures**
   A type of COA measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's responses. Symptoms or other unobservable concepts known only to the patient can only be measure by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others

2. **Observer Reported Outcome (ObsRO) Measures**
   A type of COA measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health

professional. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves. An ObsRo does not include medical judgment or interpretation

3. **Clinical Reported Outcome (ClinRO) Measures**
   A type COA measurement based on a report that comes from a trained health-care professional after observation of a patient's health condition. Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient.

4. **Performance Outcome (PerfO) Measures**
   A type of COA measurement based on standardized task(s) performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed

Drug Development Tools (DDT)
A measurement or method that aids drug development. DDTs include biomarkers, clinical outcome assessments, and animal models

Endpoint
A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. The definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details as applicable

Fit-for-Purpose
A conclusion that the level of validation associated with a medical product development tool is sufficient to support its context of use

Fit-for-Purpose Initiative
A pathway for regulatory acceptance of dynamic tools for use in drug development programs that are otherwise unable to pursue formal qualification, due to the evolving nature of these types of drug development tools

Model-Informed Drug Development (MIDD)
The process of utilizing exposure-based, biological, and statistical models derived from preclinical and clinical data sources to aid in drug development. MIDD approaches can improve clinical trial efficiency, increase the probability of regulatory success, and optimate drug dosing/therapeutic individualization in the absence of dedicated trials. The MIDD pilot program was launched by the FDA in April 2018

Outcome
The measurable characteristic that is influenced or affected by an individuals' baseline state or an intervention as in a clinical trial or other exposure

Patient-Focused Drug Development
A systematic approach to help ensure that patients' experiences, perspectives, needs and priorities are captured and meaningfully incorporated into drug development and evaluation

Qualification
A conclusion, based on a formal regulatory process, that within the states context of use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review

Surrogate Endpoint
An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence

1. **Candidate Surrogate Endpoint**
   An endpoint still under evaluation for its ability to predict clinical benefit

2. **Reasonably Likely Surrogate Endpoint (RLSE)**
   An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint. RLSEs may be used for accelerated approval for drugs with a requirement for post-marketing confirmatory trials to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit

3. **Validated Surrogate Endpoint**
   An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit. A validated surrogate endpoint can be used to support marketing approval of a medical product in a defined context without the need for additional studies to demonstrate the clinical benefit directly. Validated surrogate endpoints almost always refer to a biomarker

Tolerability
The degree to which overt adverse events can be tolerated by the patient

Validation
A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose

1. **Analytical Validation**
   A process to establish that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol. This is validation of a test's, tool's or instrument's technical performance, but not its usefulness**.**

2. **Clinical Validation**
   A process to establish that a test, tool, or instrument acceptably identifies, measures, or predicts a concept of interest.