



FDA

**U.S. FOOD & DRUG
ADMINISTRATION**

CENTER FOR DRUG EVALUATION & RESEARCH



BIOMARKERS AND DRUG DEVELOPMENT: REGULATORY PERSPECTIVE

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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



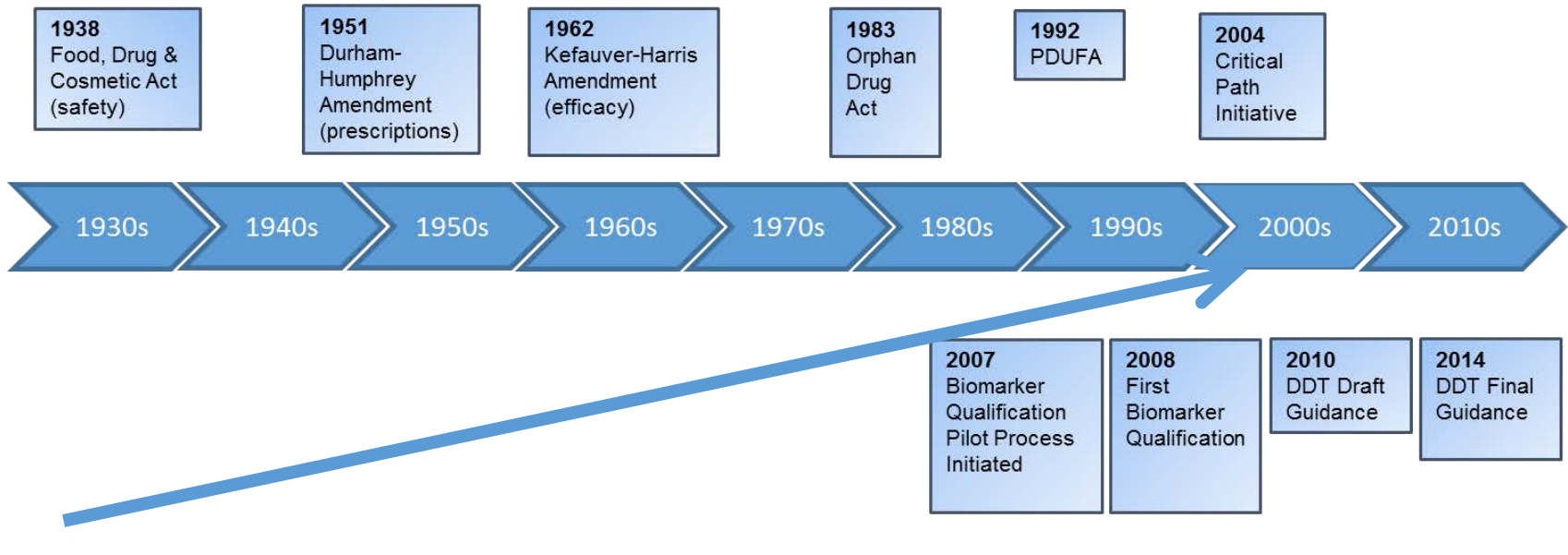
OVERVIEW

- **Communicating from a common understanding: BEST resource**
- **Biomarker Integration into Drug Development**
- **Biomarker Development**
- **21st Century Cures Qualification**
- **BQ Program Highlights**
- **Other biomarker-related resources**



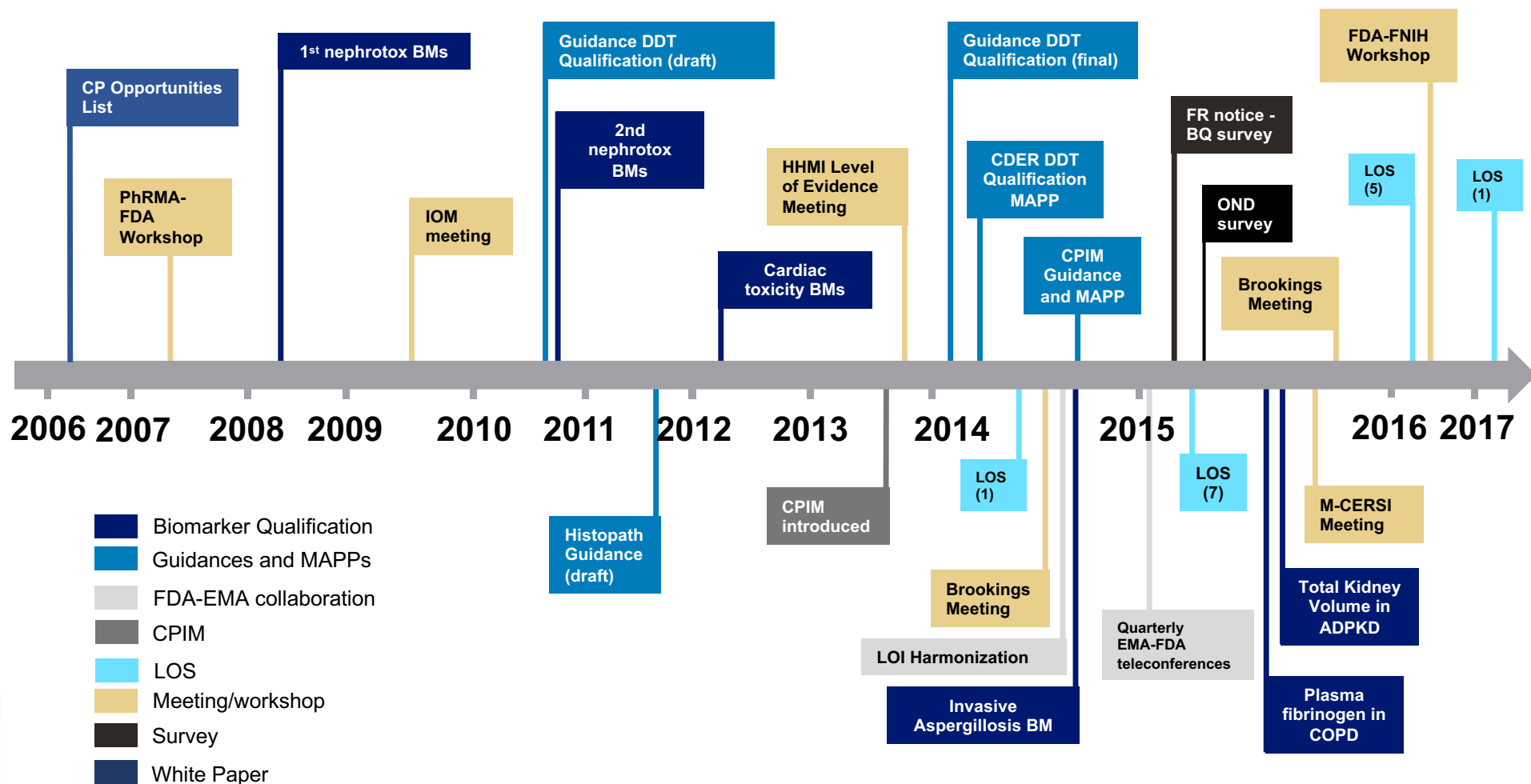
Keeping perspective... We have been developing drugs for much longer than biomarkers

Timeline of U.S Drug Regulation



Timeline of U.S. Biomarker Regulation

FDA LAID THE FOUNDATION FOR QUALIFICATION OF DRUG DEVELOPMENT TOOLS





FDA Regulatory Approach to Biomarkers



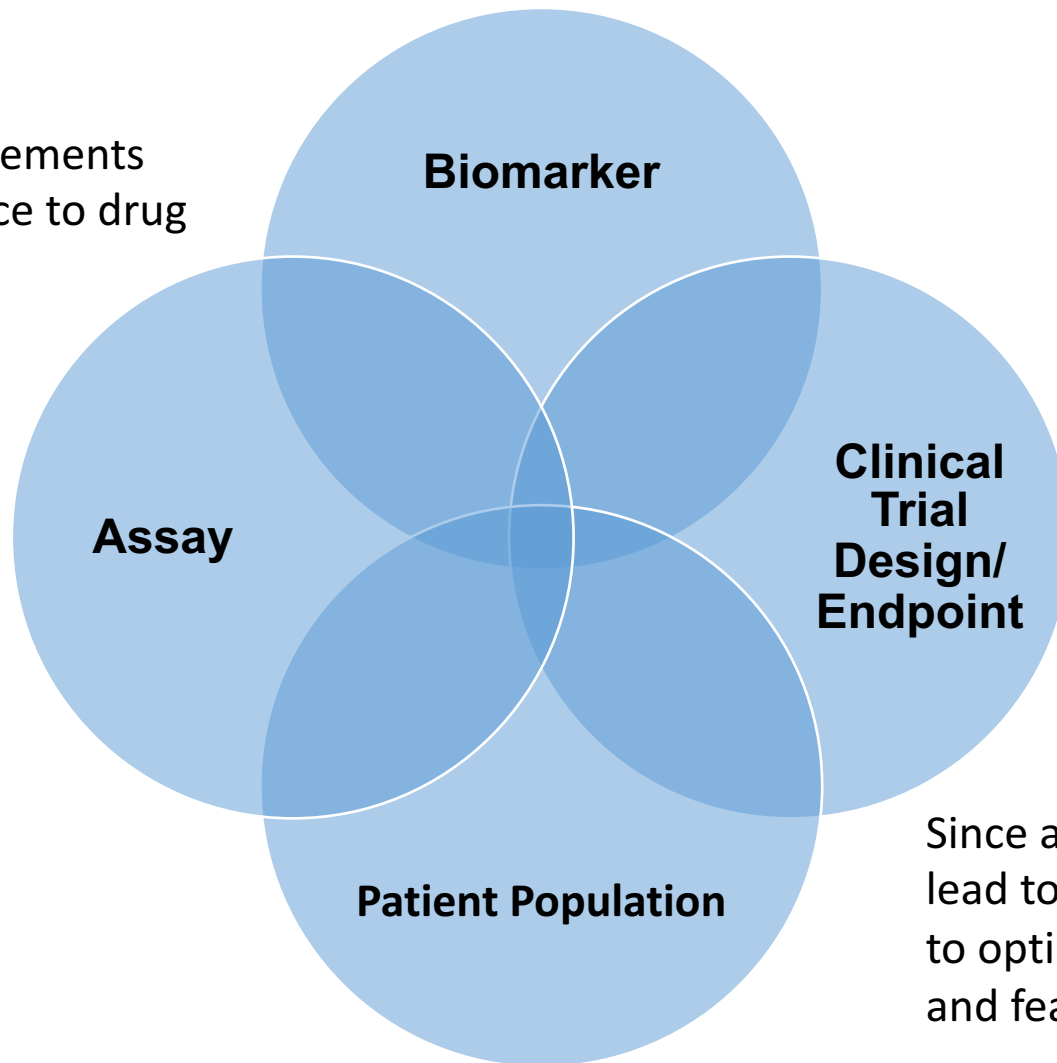
- *Definition*: a defined characteristic that is measured as an 1) indicator of normal or pathogenic biological processes or 2) response to an intervention.
- Broadly defined, with multiple biomarker types including molecular, histologic, radiographic, and physiologic. (i.e., serum protein, change in tumor size by imaging study, algorithm for QT determination on ECG)
- Characteristic is not a *clinical* assessment of how a patient feels, functions, or survives (contrasted with Clinical Outcome Assessments or COAs)
- Although a biomarker may be used by clinical or basic science research communities, regulatory acceptance focuses on a drug development context that is supported by data for that context. Considerations include:
 - Reproducibility of data (e.g., high rate of discordant conclusions RE biomarkers in the published literature)
 - Adequacy of the analytic device to assess biomarker's reliability
 - Feasibility of the biomarker should a drug be approved (e.g., will the analytic be widely available and capable of integration into clinical practice paradigms)



COMPONENTS OF DRUG DEVELOPMENT SUCCESS



Each of these elements share importance to drug approval



Since any element can lead to failure, important to optimize as appropriate and feasible



BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE



- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at <http://www.ncbi.nlm.nih.gov/books/NBK326791/>





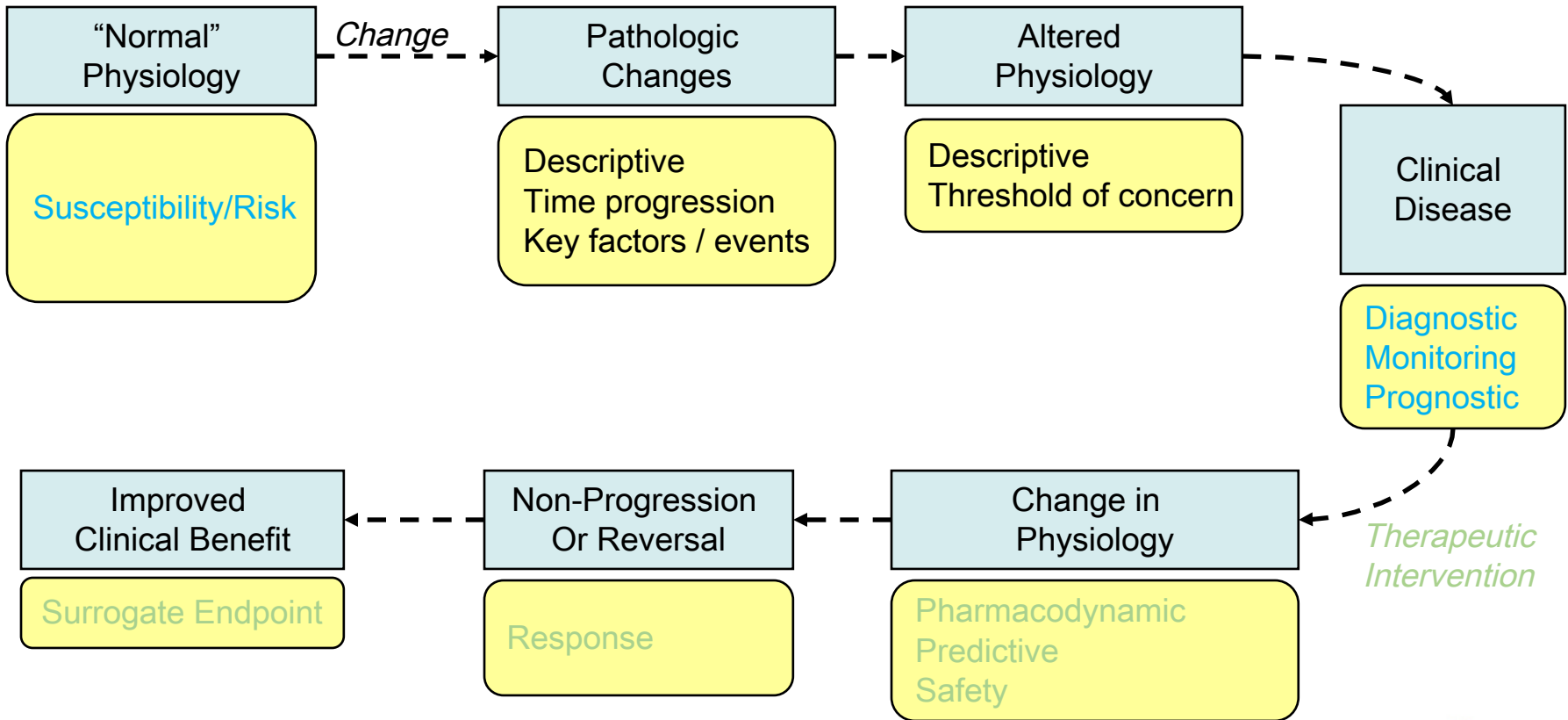
Biomarker Classes from a Drug Perspective



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- **Susceptibility/Risk**: Indicates potential for developing disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition
- **Diagnostic**: Detects or confirms the presence of a disease or condition of interest or to identify individuals with a subset of the disease
- **Monitoring**: Assesses status, through serial measurement, of a disease or medical condition including degree or extent of disease
- **Prognostic**: Identifies likelihood of a clinical event, disease recurrence or progression, in patients who have the disease or medical condition of interest in the absence of a therapeutic intervention
- **Predictive**: Identifies patients who are more likely to experience a favorable or unfavorable effect from a specific treatment
- **Pharmacodynamic/Response**: Indicates that a biological response has occurred in a patient who has received a therapeutic intervention. May become clinical trial endpoints and for a very small subset, surrogate endpoints.
- **Safety**: Indicates the likelihood, presence, or extent of toxicity to a therapeutic intervention when measured before or after that intervention

“Fit for Purpose”: BEST Biomarker Classes in Perspective





CONSIDERATIONS FOR BIOMARKER UTILITY



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?

“Total Kidney Volume, measured at baseline, is 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.”¹



BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



**Drug Approval
Process**



**Scientific
Community
Consensus**



**Biomarker
Qualification
Program**

Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.



SCIENTIFIC COMMUNITY CONSENSUS APPROACH FOR BIOMARKER DEVELOPMENT



**Scientific
Community
Consensus**



Strengths

- Extensive knowledge base of exploratory biomarker data in published literature
- Opportunity for broad and multiple community inputs
- Public access and cost-sharing approach (e.g., NIH and other grant funded research)

Limitations

- Published data may not be not reproducible
- Protracted time for consensus building
- Variability of study designs, populations, and analytics
- Applicability to regulatory paradigms



DRUG APPROVAL (IND/NDA/BLA) APPROACH FOR BIOMARKER DEVELOPMENT



Strengths

- Generally, biomarker use has a well-defined purpose
- Data (clinical trial information) available to the biomarker developer
- Opportunities to bring in outside experts
- Potential business advantage

Limitations

- Biomarker may not be generalizable
- Limited opportunities for additional data sources
- Company responsible for development costs
- Limited opportunities for engagement with outside stakeholder groups
- Biomarker information in drug labels and reviews are available only upon drug approval



BIOMARKER QUALIFICATION APPROACH FOR BIOMARKER DEVELOPMENT

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**Biomarker
Qualification
Program**



Strengths

- Context of use clearly established
- Opportunity to pool resources , share costs and bring outside experts
- Leverage outside stakeholder groups
- Outcome is a public guidance with supporting reviews

Limitations

- If part of a group effort, stakeholders may have differing goals, level of commitment, and engagement
- Data (clinical trial information) may not be readily available
- Data sharing and aggregation may be challenging



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



ANALYTICAL ASSAY AND CLINICAL VALIDATION CONSIDERATIONS IN BIOMARKER DEVELOPMENT



The Specific Context of Use for a Biomarker Drives the Extent of Evidence Needed for Qualification

Analytical Validation

(establish performance and acceptance characteristics of the biomarker assay)

Reference Ranges/
Decision Points

Pre-Analytical and Assay Performance Characteristics

Analytical Rigor/
Reproducibility

Sample Handling/
Stability

Clinical Validation

(establish that the biomarker acceptably identifies, measures, or predicts the concept of interest)

Study Design Acceptability

Clinical Meaningfulness/
Decision Points

Benefit/Risk Assessment

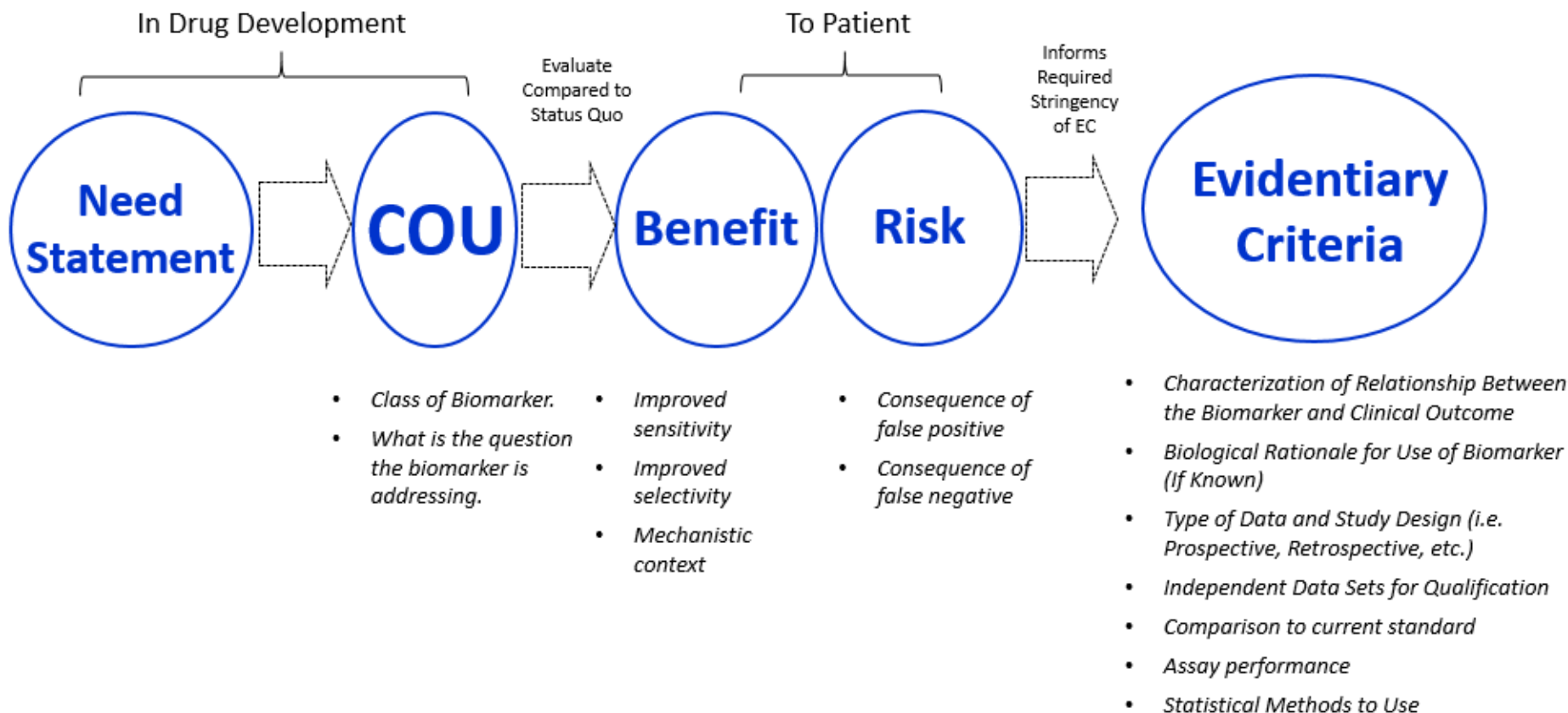


ANALYTIC CONSIDERATIONS

- Pre-analytics: Including all quality assurance (QA) and quality control (QC) measures
- Analytic Parameters:
 - Accuracy
 - Measurement Method Range
 - Sensitivity
 - Parallelism
 - Reproducibility
 - Selectivity
 - Specificity
 - Linearity
- Imaging: Image sharpness/resolution, field of view, depth of field, and distortion



CONCEPTUAL FRAMEWORK FOR BIOMARKER DEVELOPMENT FOR REGULATORY ACCEPTANCE





SOME ENABLERS FOR BIOMARKER DEVELOPMENT

- Data standards (e.g., CDISC efforts)
- Data quality
- Data reproducibility
- Data sharing
- Assay/imaging pre-analytic standardization
- Assay/imaging protocols/SOPs
- Evaluating impact on clinical trial elements (e.g., choice of cut-point on number of patients screened vs enrolled)

Overview of 21st Century Cures (21CC) Legislation and PDUFA VI: Impacts on Biomarker Qualification Activities



DRUG DEVELOPMENT TOOL (DDT) QUALIFICATION

Qualification is a conclusion that within the stated *context of use*, the DDT *can be relied* upon to have a specific interpretation and application in drug development and *regulatory review*

Potential for wide applicability to support drug development programs:



*Clinical Outcome
Assessments*



Biomarkers

*Usually in narrow context of use
(biological, radiological threats)*



*Animal Models
(Animal Rule)*



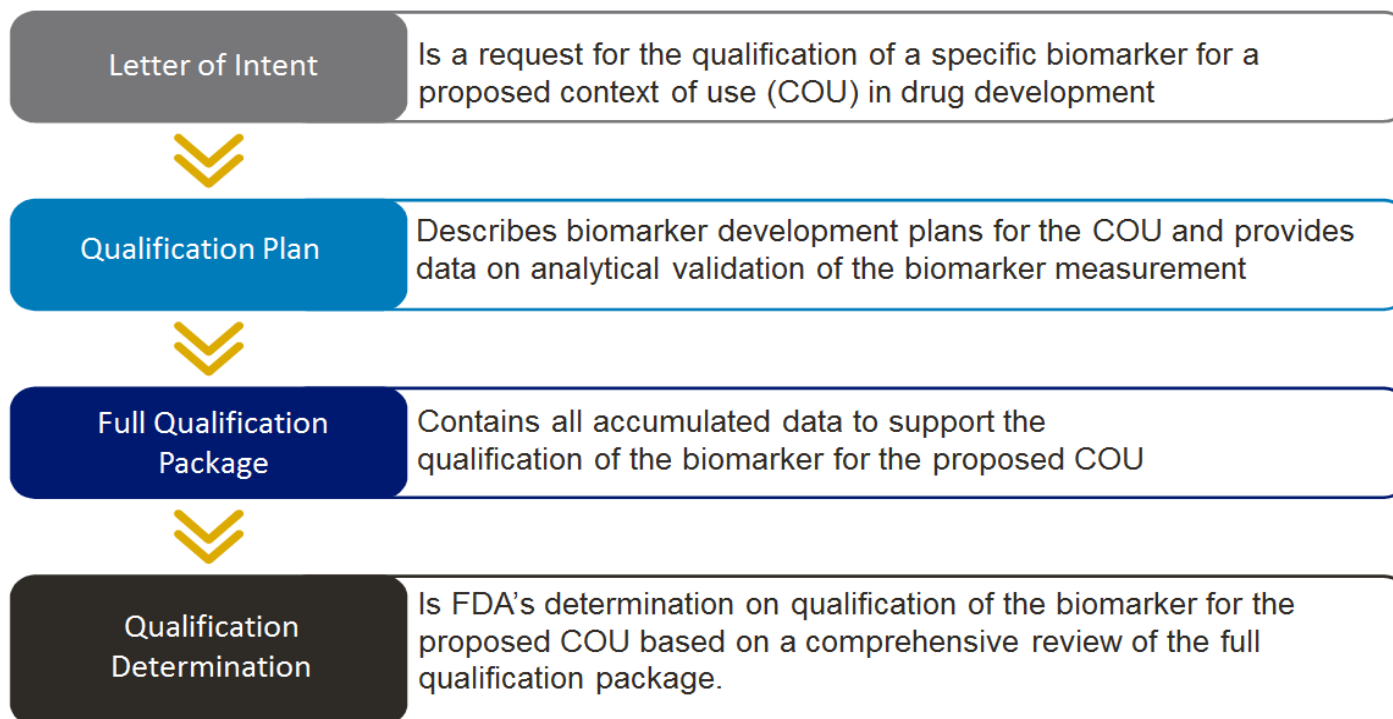
21st Century Cures legislation: Section 507 Qualification of Drug Development Tools

- 21st Century Cures and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role
- Formalizes a three-step submission process
 - Letter of Intent
 - ***Qualification Plan***
 - Full Qualification Package
- A transparent process – so all stakeholders are aware of tools in development, stage, and FDA determinations/recommendations
- Requires setting and implementing “reasonable timeframes” for submission review/decision



21CC BIOMARKER QUALIFICATION: SUBMISSIONS

Biomarker Qualification Process





CONTENT FOCUS FOR SUBMISSION TYPES

- LOI Submission:
 - Identification of drug development need
 - Information to support that the proposed biomarker and its COU would address that need
 - Feasibility assessment of proposal will include information to support that measurement of the novel DDT is, in fact, possible.
- QP Submission:
 - Define biomarker development project plan to support the COU
 - Reach agreement on the interpretation and significance of existing data
 - Identify knowledge gaps and align on mitigation plan or additional data to address those gaps
 - Important that analytical validation has been mostly completed
- FQP Submission: Data and analyses to support the clinical validation for the COU



TRANSPARENCY PROVISIONS

Under 21CC, DDT qualification becomes a transparent public process:

- All interested parties know what tools are in development, stage of development, and FDA determinations including rationale
- Information about the submission and FDA's determination including recommendations will be posted on DDT website
- For legacy projects, we plan to post only new information after transition (e.g., we will not make public information prior to legislation enactment or to agreement to transition to 507)
- De facto Letter of Support (LOS) as part of DDT engagement



THREE-TIERED INTERNAL REVIEW

- DDT Program Assessment and Recommendations
 - Work with requestor to clarify DDT, COU, and project proposal
 - Provide tool-specific recommendations based on past and ongoing projects
- Discipline-specific SME Assessment and Recommendations
 - Includes OND division management participation
 - Evaluate based on regulatory precedent, current disease-specific challenges, and level of impact on drug development programs
- CDER DDT Committee Assessment, Recommendations, and Decision
 - Opportunity for broad senior CDER input early and throughout in the process
 - Work towards greater consistency across therapeutic areas and divisions



21ST CC: ACCEPTANCE OF BIOMARKER INTO QUALIFICATION

- Acceptance decision for each submission (LOI, QP, FQP) based upon scientific merit:
 - Does the proposal address an impactful drug development need?
 - Is there enough information to suggest a likelihood of success?
 - What is the feasibility of the proposed analytical biomarker measurement approach?
- Prioritization of review of submissions based upon:
 - “the *severity, rarity, or prevalence* of the disease or condition targeted by the drug development tool and *the availability or lack of alternative treatments* for such disease or condition; and
 - the identification by the Secretary or by biomedical research consortia and other expert stakeholders, of such drug development tool and its proposed context of use *as a public health priority*” (italics added)
- Recision or modification of qualification determination
 - Based upon new information that alters conclusions that supported qualification determination



21ST CC/PDUFA VI DDT DELIVERABLES

- Establish a “*taxonomy*” of biomarkers in collaboration with biomedical research consortia and other interested parties through a public process, for use in drug development
 - See BEST (<https://www.ncbi.nlm.nih.gov/books/NBK326791/>)
- *Biomarker Public Meetings and Guidances* – Provides a conceptual framework describing the appropriate standards and scientific approaches to support the development of biomarkers delineated under the taxonomy established (within 3 years)
 - 21CC DDT Process Public Meeting (Dec 11, 2018)
 - Biomarker Panels Meeting (June 14, 2019)
 - Biomarker Qualification Guidances (507 Qualification Process, Analytics, Statistics)



BIOMARKER QUALIFICATION PROGRAM UPDATES

21CC Implementation

- Program moved to OND for better alignment with biomarkers developed under IND
- Developed transition plan for legacy projects
- Coordination with CBER for inter-Center consistency and support for their DDT programs
- Continued collaboration with EMA for alignment on process and approach
- Public posting for transparency
 - List of Qualified Biomarkers
(<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm>)
 - Biomarker Qualification Submissions
(<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm>)



BIOMARKER QUALIFICATION PROGRAM UPDATES (2)

- Program Improvements
 - Website updated to reflect 507 process and to become more user friendly
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm>
 - LOI, QP, and FQP submission content outlines have been developed
 - Developed requirements for new IT platform (submission portal, document knowledge management, business tools)
 - Working on DDT Process Guidance and other projects.
 - Establishing program SOPs
- Project Overview Metrics (Aug 2017 – Aug 2018)
 - 13 LOI submissions
 - 4 Legacy project transition summaries
 - 2 QP submission
 - 2 new qualification determinations
 - Clinical nephrotoxicity safety panel and malarial monitoring biomarker for treatment initiation
 - 4 Letters of Support issued



TABLE OF SURROGATE ENDPOINTS



21st Century Cures Act, Subtitle B—Advancing New Drug Therapies

SEC. 507. QUALIFICATION OF DRUG DEVELOPMENT TOOLS.

“Transparency

“(E) A comprehensive list of—

“(ii) all surrogate endpoints which were the basis of approval or licensure (as applicable) of a drug or biological product (including in accordance with section 506(c)) under section 505 of this Act or section 351 of the Public Health Service Act.”

- <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm>
- 101 adult and 56 pediatric disease/patient population/surrogate endpoint combinations
- 12 surrogate endpoints that may be appropriate for use in drug approval even though no successful drug program as of yet
- More disease/therapeutic areas use surrogates than commonly discussed
- Will be updated every 6 months



IND TYPE C MEETING FOR NOVEL SURROGATE ENDPOINTS



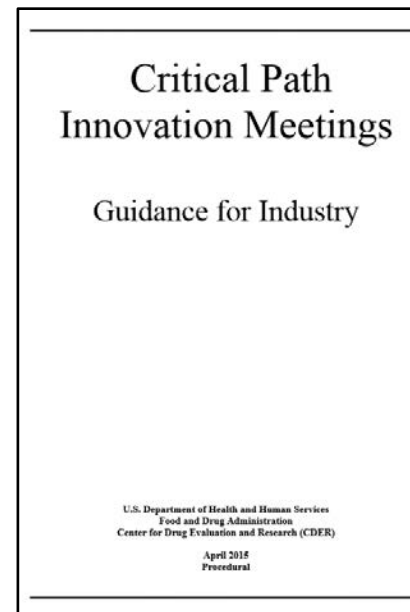
- <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm606684.htm>
- [PDUFA VI Commitment](#)
- Meeting package due at time of request that includes preliminary human data indicating drug has an impact on the SE at a dose that is “generally tolerable”
- Package content examples include:
 - Rationale for use of surrogate endpoint (SE)
 - Relationship of SE with casual pathway(s)
 - Threshold for change required to demonstrate clinical relevance
 - Consistency of SE response
 - Reliability of quantifying changes in clinical outcome before and after tx
 - Predictive value of therapeutic-induced changes in SE
 - Off-target effects of therapy
 - Reliability of measurement tool to detect SE



CRITICAL PATH INNOVATION MEETING



- Discussion of the science, medicine, and regulatory aspects of innovation in drug development
- Non-binding meeting
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers and clinical outcome assessments, natural history studies, technologies (not manufacturing), and clinical trial designs and methods



Office of Translational Sciences
**Critical Path
Innovation Meeting**

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



THANK YOU FOR YOUR ATTENTION



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