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

REGULATORY PERSPECTIVE OF NASH BIOMARKER DEVELOPMENT AND QUALIFICATION

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LIVER FORUM 12
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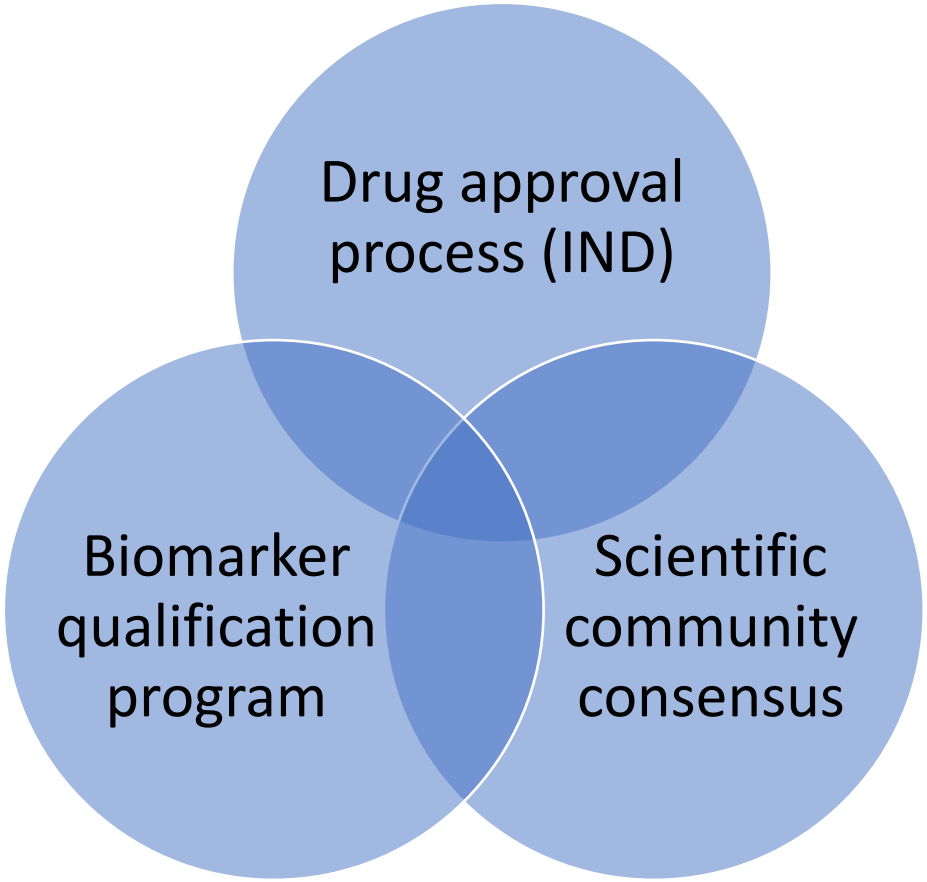
Disclaimers

- 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

Interconnected paths to Biomarker validation



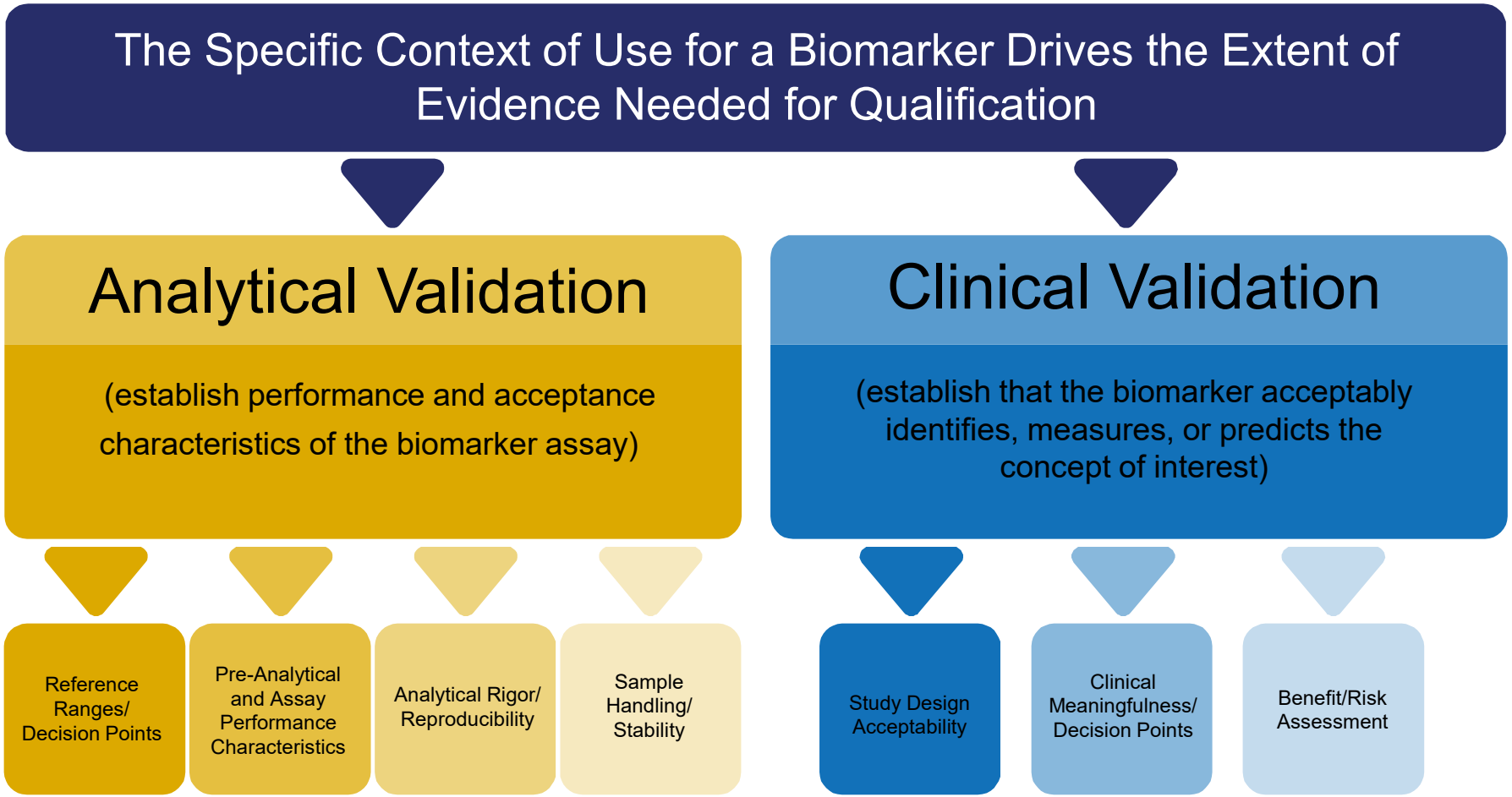
21st Century Cures (CC) 507 DDT Qualification

- 21st CC and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role
- Formalizes a three-step submission process
  - Letter of Intent
  - ***Qualification Plan***
  - Full Qualification Package
- FDA submission decision: Accept or Not Accept
- A transparent process – so all stakeholders are aware of tools in development, stage, and FDA determinations/recommendations

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

Analytical Assay and Clinical Validation Considerations in Biomarker Qualification



NASH Biomarker Considerations

Imaging biomarkers	Molecular biomarkers	Composite biomarkers	AI Biomarkers
Ultrasound	PRO-C3, PRO-C6	2 or more molecular biomarkers	Histology assessment
MRI (cT1, PDFF)	Panels of molecular biomarkers	2 or more imaging biomarkers	
MRE		Imaging and molecular biomarkers	

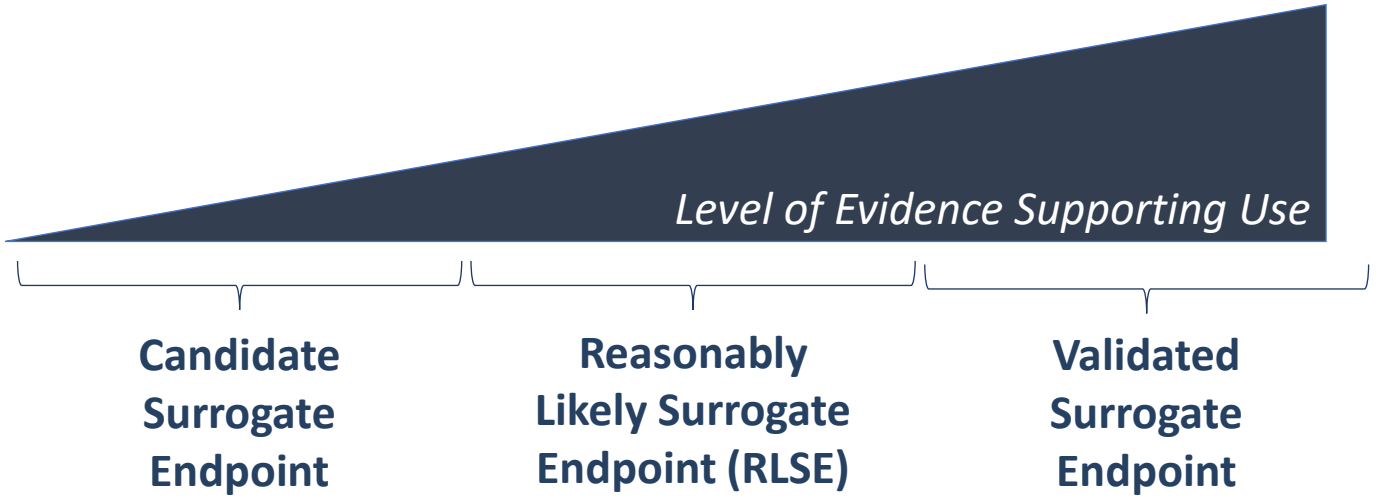
BEST (Biomarkers, EndpointS, and other Tools)
Classification: *Pharmacodynamic / Response BMs*

To support approval, FDA expects substantial evidence of effectiveness – that shows that a drug improves meaningful clinical outcomes: how a patient ***feels, functions, or survives***

- A **validated surrogate endpoint**: accepted by FDA that the effect on the biomarker *predicts* a specific clinical outcome. Validated endpoints have strong and diverse evidence supporting the relationship of the BM and the outcome. Used to support traditional approval.

- A **"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 a clinical benefit, but not yet reaching the standard for validation. Used for accelerated approval for product intended to treat a serious or life-threatening disease or condition.

Type of Surrogate Endpoints



The limitations of surrogate endpoints

- Not a direct measure of how a patient *feels, functions or survives*
- Intended to reflect and predict clinical benefit not measure the outcome
- With a surrogate endpoint, the benefit / risk assessment therefore must be based upon *assumptions / predictions of benefit*
    - Translating the extent of clinical benefit from an *indirect* measure, and also using a *limited* dataset on risk to assess harms
    - Challenging when a drug shows clear effects on a *surrogate endpoint* – but also has safety issues
- And biomarkers may *fail* to predict clinical benefit
- For a surrogate endpoint that is reasonably likely to predict a clinical benefit and is relied upon to support accelerated approval, post-marketing confirmatory trials are required to verify the clinical benefit

Supporting evidence for SE: Relationship to clinical outcome

- Rationale for use as primary endpoint
- Relationship to causal pathway
- Threshold for change required to show clinical relevance
- Consistency across different conditions
- Availability of tools to assess clinical outcome

Resources

- **Guidance documents**
  - Qualification Process for Drug Development Tools (Available)
  - Evidentiary Framework guidance (*In progress*)
  - Analytical Validation guidance (*In progress*)
  - Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (Draft)

- CDER BQP Website
  - 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)

Thank you for your attention