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SUCCESSFULLY NAVIGATING THE TRANSLATIONAL TRANSITION

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DISCLAIMERS

Views expressed in this presentation are those of the speaker and do not necessarily represent an official regulatory or company position.

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

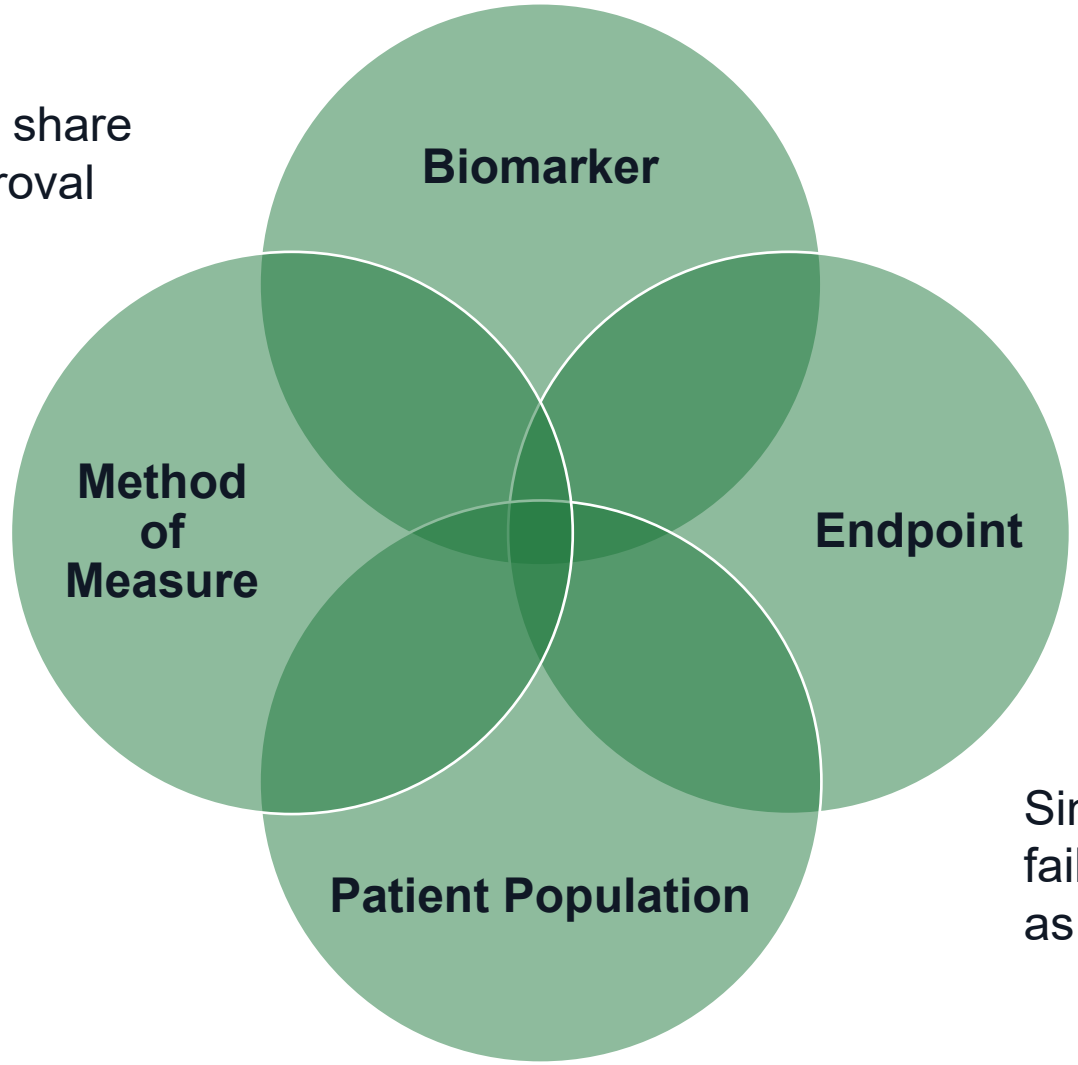
What is Unique About Regulatory Approach?

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 robust data for that context. Considerations include:

- Reproducibility of data
  e.g., high rate of discordant information in the scientific literature RE biomarker data and conclusions
- Adequacy of an analytic device's performance to support a biomarker's regulatory use
- 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

Key Considerations in Biomarker Validation

- "The evidence sufficient to qualify a biomarker depends on its context of use (COU) and the potential benefits and risks associated with its use"
- "Benefits and risks associated with a biomarker's COU drives expectations for the reliability of the biomarker to predict the outcome of interest"
- Essentials of a validation effort:
  - Specify the biomarker of interest;
  - Specify the particular test, tool or instrument that is the object for validation;
  - Clearly define the purpose, including the setting, for which the test, tool or instrument will be used;
  - Understand the potential benefits and risks associated with that use

Validation is a process that is related to a specific intended purpose. Therefore, a biomarker that has been determined to be fit-for-purpose for a given regulatory purpose, is not necessarily sufficient for another regulatory purpose

Pitfalls to Avoid

Inadequate and inappropriate planning

- If you are planning to develop a novel biomarker endpoint, you will need to engage FDA early (even preIND) to ensure that you have sufficient time to align on what data will be needed
- Reasonably match your goals to your available resources. Ultimate goals can be broken into realistic milestones to build understanding as well as identify gaps that may need to be addressed.

Ignoring the need for rigorous validation of your measurement method

- If your measurement method has not been validated, you may be making business decisions based on data that is not reliable or meaningful
- Expectation that the measurement method has been appropriately validated prior to use in Ph3
- Method will likely improve/evolve requiring pre-planning for bridging studies

Over interpretation of data from sources that have not been vetted to regulatory standards

- Peer-reviewed publications are helpful as a starting point only. The raw data is not scrutinized, results are many times not reproducible, and the conclusions are often not generalizable/overstated

Not recognizing the importance of data management

- Protocols, SOPs, and rigorous documentation are required for regulatory audits

Multimodal Biomarker Considerations

Terminology: Multimodal, composite, panel, score, etc.

- Individual components should be described, carefully chosen, and assessed for relative contribution

Strategies: Important to focus on a single COU to define the development

- Explore biomarkers and associated measurement methodologies individually and then build into a composite once value has been demonstrated
- Alternatively, define a composite of promising candidates and then refine

NOTE: do not be reluctant to make early and frequent updates based on pragmatic choices

Measurement Scenarios:

- Each member of the composite is measured with a separate platform, each of which is independently validated. The readouts are then “manually” transformed into a composite value for interpretation
  - Single score is interpreted by cut points (e.g., Mild, Moderate, Severe)
  - Group assessment schema – still have cut points for “biomarker positivity” but interpretation simplified (e.g., if any 2 of 7 are positive, composite is positive)
- Individual biomarkers of the composite are measured by a single measured by a single platform
  - Individual readouts (e.g. Chem 7) or integrated score
  - If score, then the algorithm which generates the score should be defined

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THANK YOU FOR YOUR ATTENTION