Evidentiary Considerations for Integration of Biomarkers In Drug Development

Session 4

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Session 4: Round Table Discussion (CERSI/ FDA)

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Steps to Qualification

Letter of Support (optional)

Aggregation of Additional Data

- What data is needed?
- How is the data aggregated?
- Data sharing
- Data quality
- Data standards
- Data reproducibility

Proposal for Limited or Expanded Context of Use

- Assays
- Sample Handling
- Statistical Considerations
- Assay Methods
- Performance characteristics
- Analyte Stability

Qualification Determination

What is at stake if we are wrong?

Beyond

Implications for clinical practice?

Implications for labeling?

How to leverage data from INDs to aid in biomarker development?

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Enablers for Biomarker Development

- Data standards
- Data quality
- Data reproducibility
- Statistical considerations
- Assay/Imaging considerations/validation
- Assay/Imaging protocols
- Establishing cut points

- How to disseminate current/best thinking? Checklists? White Papers?

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Discussions Needed (Focused Workshops)

- Biomarker Taxonomy / Common Lexicon
- Biorepositories / Data Repositories / Data Sharing
  - IRB Issues
  - Risks of sharing, what to share, how to share?
- Review Evidentiary Standards from Recent Qualifications
  - Common Successes?
  - Common Failures?
  - Should we have asked for less or more information?
- Assay / Imaging Considerations / Validation

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Table 1 Prototype "evidence map"—categorical description of different types of scientific evidence potentially relevant to biomarker qualification; subcategorical graded weight of evidence from least to most

Evidence type	Grade D	Grade D+/C–	Grade C	Grade C+/B–	Grade B	Grade B+/A–	Grade A
Theory on biological plausibility	Observed association only	Theory, indirect evidence of relevance of the biomarker from animals	As for lower grade but evidence is direct	Theory, indirect evidence of relevance in humans	Theory, direct evidence in humans, non-causal pathway possible	As for lower grade, but biomarker on causal path	Human evidence based mathematical model of biology showing biomarker is on causal pathway
Interaction with pharmacologic target	Biomarker identifies target in *in vitro* binding			Biomarker identifies target in *in vivo* binding in animals	Biomarker identifies target in *in vivo* studies or from human tissue, no truth standard		Biomarker identifies target in *in vivo* studies or from tissues in humans, with accepted truth standard
Pharmacologic mechanistic response	*In vitro* evidence that the drug affects the biomarker	*In vitro* evidence that multiple members of this drug class affects the biomarker	*In vivo* evidence that this drug affects biomarker in animals	As for lower grade but effect shown across drug class	Human evidence that this drug affects the biomarker OR animal evidence of specificity	Human evidence across this mechanistic drug class	Human evidence that multiple members of this drug class affect the biomarker and the effect is specific to this class/mechanism
Linkage to clinical outcome of a disease or toxicity		Biomarker epidemiologically associated with outcome without any intervention	Biomarker associated with change in outcome from intervention in another drug class	As for lower grade but in this drug class	As for lower grade but multiple drug classes albeit inconsistent or a minority of disease effect		As for lower grade but consistent linkage and explains majority of disease effect
Mathematics replication, confirmation		An algorithm is required to interpret the biomarker and was developed from this dataset		Algorithm was developed from a different dataset and applied here prospectively			Algorithm developed from different dataset, replicated prospectively in other sets and applied prospectively here
Accuracy and precision (analytic validation)				Sources of technical variation are unknown but steps are taken to ensure consistent test application	Major sources or variation known and controlled to be less than biological signal; standardization methods applied		All major sources of technical imprecision are known, and controlled test/assay accuracy is defined against standards
Relative performance		Does not meet performance of benchmark		Similar performance to benchmark			Exceeds performance of benchmark or best alternative biomarker

Not all types of evidence required all seven grades to be completed.