Evidentiary Considerations for Integration of Biomarkers In Drug Development

Session 4
Session 4: Round Table Discussion (CERSI/ FDA)

Discussion Leads:

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Steps to Qualification

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

Aggregation of Additional Data

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?
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?
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
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

<table>
<thead>
<tr>
<th>Evidence type</th>
<th>Grade D</th>
<th>Grade D+/C-</th>
<th>Grade C</th>
<th>Grade C+/B-</th>
<th>Grade B</th>
<th>Grade B+/A-</th>
<th>Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theory on biological plausibility</td>
<td>Observed association only</td>
<td>Theory, indirect evidence of relevance of the biomarker from animals</td>
<td>As for lower grade but evidence is direct</td>
<td>Theory, indirect evidence of relevance in humans</td>
<td>Human evidence in humans, non-causal pathway possible</td>
<td>As for lower grade, but biomarker on causal pathway</td>
<td>Human evidence based mathematical model of biology showing biomarker is on causal pathway</td>
</tr>
<tr>
<td>Interaction with pharmacologic target</td>
<td>Biomarker identifies target in <em>in vitro</em> binding</td>
<td><em>In vitro</em> evidence that multiple members of this drug class affects the biomarker</td>
<td><em>In vitro</em> evidence that this drug affects biomarker in animals</td>
<td><em>In vitro</em> evidence that this drug affects biomarker OR animal evidence of specificity</td>
<td>Human evidence across this mechanistic drug class</td>
<td>Human evidence that multiple members of this drug class affect the biomarker and the effect is specific to this class/mechanism</td>
<td></td>
</tr>
<tr>
<td>Pharmacologic mechanism response</td>
<td><em>In vitro</em> evidence that the drug affects the biomarker</td>
<td><em>In vitro</em> evidence that multiple members of this drug class affects the biomarker</td>
<td><em>In vitro</em> evidence that this drug affects biomarker in animals</td>
<td><em>In vitro</em> evidence that this drug affects biomarker or animal evidence of specificity</td>
<td>Human evidence across this mechanistic drug class</td>
<td>Human evidence that multiple members of this drug class affect the biomarker and the effect is specific to this class/mechanism</td>
<td></td>
</tr>
<tr>
<td>Linkage to clinical outcome of a disease or toxicity</td>
<td>Biomarker epidemiologically associated with outcome without any intervention</td>
<td>Biomarker associated with change in outcome from intervention in another drug class</td>
<td>As for lower grade but in this drug class</td>
<td>As for lower grade but multiple drug classes albeit inconsistent or a minority of disease effect</td>
<td>As for lower grade but consistent linkage and explains majority of disease effect</td>
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</tr>
<tr>
<td>Mathematics replication, confirmation</td>
<td>An algorithm is required to interpret the biomarker and was developed from this dataset</td>
<td>Algorithm was developed from a different dataset and applied here prospectively</td>
<td>Algorithm was developed from a different dataset, replicated prospectively in other sets and applied prospectively here</td>
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</tr>
<tr>
<td>Accuracy and precision (analytic validation)</td>
<td>Sources of technical variation are unknown but steps are taken to ensure consistent test application</td>
<td>Sources of technical variation are known and controlled to be less than biological signal; standardization methods applied</td>
<td>Major sources of technical imprecision are known, and controlled test/assay accuracy is defined against standards</td>
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<tr>
<td>Relative performance</td>
<td>Does not meet performance of benchmark</td>
<td>Similar performance to benchmark</td>
<td>Exceeds performance of benchmark or best alternative biomarker</td>
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</tbody>
</table>

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