Biomarker Qualification Evidentiary Considerations: Clinical and analytical validation of safety biomarkers

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Evidentiary Considerations for Safety Biomarker Qualification

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
Fluid-Based Safety Biomarkers: Can be used to accurately predict drug-induced tissue injury, similar to a routine clinical pathology measure.
Translational Safety Biomarkers

Nonclinical studies are conducted to demonstrate that the novel biomarkers are:
1. Responsive to histological injury of the target organ of interest
2. Not responsive to injury in other target organs
3. Not dependent upon the mechanism of toxicity

Histopathological assessment of major tissues
Assessment of standard biomarkers
Assessment of novel biomarkers

Across prototypical toxicants
Translational Safety Biomarkers

Compare response of the Novel Biomarker to histopathological response and response of the current standard biomarker

Histopathological Response (TRUTH)

Novel Biomarker Response

Current Standard Biomarker Response
Translational Safety Biomarkers

Compare response of the Novel Biomarker to histopathological response and response of the current standard biomarker

Histopathological Response (The TRUTH)

Novel Biomarker Response

Current Standard Biomarker Response
Clinical studies are conducted to demonstrate that the novel biomarkers:

1. Respond appropriately with regard to the standard biomarkers
   • Sensitivity and false positives
   • Specificity and false negatives
2. Respond appropriately with regard to medical adjudication of target organ injury

Prospective studies in patients being treated with therapeutics with known safety liabilities – for example, the use of cisplatin for the treatment of head and neck cancer vs.

Samples collected from patients with known diseases and drug overdoses
Translational Safety Biomarkers

Adverse Outcomes in Humans

Compare response of the novel biomarker to medical adjudication and response of the current standard biomarker

Medical adjudication of target organ injury

Novel Biomarker Response

Current Standard Biomarker Response
Evidentiary Considerations for Biomarker Qualification

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Study Design Acceptability
Clinical Meaningfulness/Decision Points
Benefit/Risk Assessment
General Evidentiary Criteria Framework Components

• **Assay performance**: Analytically validated method and understanding of potential sources of variability in the measurement.

• **Characterize the relationships** among the biomarker, the clinical outcomes, and the treatment required for the proposed COU.

• **Biological rationale** for use of the biomarker.

• **Type of data** and study design needed to assess the strength of association of the biomarker with its proposed clinical outcome: retrospective or prospective, registry data, and/or randomized controlled trial (RCT) data.

• **Reproducibility of data**: Need for test dataset and confirmatory dataset.

• **Comparison to current standards**.

• **Pre-specified statistical methods** must be used to demonstrate the hypothesized relationships for the COU.

• **Strength of evidence**: The level of evidence needed depends on the type of biomarker and its COU.
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Considerations for Biomarker 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
Assay Validation for Biomarkers:

*Qualification truly embraces the fit-for-purpose concept of assay validation*

Every assay for every qualification will have unique performance expectations
Evidentiary Considerations for Biomarker Qualification

Assay performance:
Analytically validated method and understanding of potential sources of variability in the measurement.

Assay Design and Technology Selection for Biomarker Assays
- Defining pre-analytical conditions
- Setting analytical performance requirements for assay
- Characterizing and documenting assay performance
- Establishing assay validation acceptance criteria
Assay performance:
Analytically validated method and understanding of potential sources of variability in the measurement.

Assay Validation Acceptance Criteria
- Accuracy (Relative)
- Analytical Measurement Range
- Parallelism
- Precision
- Selectivity
- Specificity
- Stability (sample)

PK Assay Validation

vs.

Biomarker Assay Validation
Evidentiary Considerations for Biomarker Qualification

Context of Use (COU)
How you are using the biomarker

Fit-for-Purpose use of Assay

Assay Validation Performance Expectations
Points to Consider Document:
Scientific and Regulatory
Considerations for the Analytical
Validation of Assays Used in the
Qualification of Biomarkers in
Biological Matrices

Biomarker Assay Collaborative Evidentiary Considerations
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https://healthpolicy.duke.edu/events/public-workshop-scientific-and-regulatory-considerations-analytical-validation-assays-used
Analytical Validation Considerations for Biomarker Qualification

The Points to Consider Document:
- Provides scientific insight into how to address common bioanalytical obstacles encountered during the validation of biomarker assays to be used in biomarker qualification
- Is designed to cover all biomarker classes from diagnostic biomarkers to surrogate endpoints
- Presents an approach that is customizable based on the biomarker and it’s drug development application

The Points to Consider Document is NOT:
- A checklist that can be followed without considering your biomarker and it’s drug development application
Considerations for Biomarker Qualification

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
Clinical Validation for Biomarkers:

*Demonstration that the biomarker behaves as proposed, and is correlated with the clinical outcomes*

Every biomarker will have a unique pathway to Clinical Validation
Clinical Validation for Biomarkers:

Characterize the relationships among the biomarker and clinical outcomes with respect to the proposed COU

1. Define the biological rationale for use of the biomarker
2. Demonstrate reproducibility of the behavior of the biomarker (exploratory dataset and confirmatory dataset)
3. Understand the novel biomarker’s behavior to that of the current standard biomarker
4. Apply a pre-specified statistical method to demonstrate the biomarker’s relationships to clinical outcomes and the current standard biomarker
Qualification of Glutamate Dehydrogenase

Glutamate dehydrogenase (GLDH):
GLDH appears to be a liver specific biomarker that is not effected by muscle toxicity, unlike alanine aminotransferase, the current standard for monitoring hepatocellular injury

Context of Use (COU)
Serum glutamate dehydrogenase (GLDH) is a safety biomarker capable of detecting hepatocellular injury that can be used as a biomarker to evaluate drug-induced liver injury (DILI) in conjunction with standard hepatic injury monitoring in Phase I through Phase III clinical trials for subjects and patients with elevated serum transaminases due to muscle degeneration.
Qualification of Glutamate Dehydrogenase

Exploratory studies:

- **Study 1** Demonstrate the relationship of ALT and GLDH response to hepatocellular injury in preclinical species and humans
- **Study 2** Define normal reference range for GLHD in humans
- **Study 3** Establish relevant cut points for clinical decision making (based on ALT)
- **Study 4** Demonstrate the specificity of GLDH compared to ALT in the case of muscle injury in preclinical species and humans
Qualification of Glutamate Dehydrogenase

Clinical confirmatory studies:

Study 1  Confirmation of the linear relationship of ALT and GLDH in humans
Study 2  Confirmation that GLDH does not increase with muscle injury in humans
Study 3  Confirmation of the specificity of GLDH for liver injury (beyond muscle injury) in humans
Study 4  Further characterize the elimination kinetics of GLDH and ALT in humans
Clinical Validation of GLDH

Define the biological rationale for use of the biomarker

GLDH possess all of the biological characteristics to be a selective biomarker for the detection of hepatocellular injury.

Tissue distribution:
- Liver >> kidney, pancreas, & intestinal mucosa
- Only trace amount present in muscle, reticulocytes, lymphocyte, and other tissues

GLDH has been demonstrated in preclinical species to be a sensitive and selective biomarker for the detection of hepatocellular injury (GLDH vs. histopathology).
Qualification of Glutamate Dehydrogenase

Clinical Validation of GLDH

Demonstrate reproducibility of the behavior of the biomarker (exploratory dataset and confirmatory dataset)

Exploratory Study 1  Demonstrate the relationship of ALT and GLDH response to hepatocellular injury in preclinical species and humans

Confirmatory Study 1  Confirmation of the linear relationship of ALT and GLDH in humans
Clinical Validation of GLDH

Figure 9. GLDH thresholds corresponding to 3x and 5x ULN for ALT
Qualification of Glutamate Dehydrogenase

Clinical Validation of GLDH

Understand the novel biomarker’s behavior to that of the current standard biomarker

Glutamate Dehydrogenase (novel) vs. Alaine Aminotransferase (current standard)

Sensitivity:
Similar to ALT, GLDH is a sensitive biomarker for detecting hepatotoxicity

Specificity:
Unlike ALT, GLDH is not increased by muscle injury
Clinical Validation of GLDH

Apply a pre-specified statistical method to demonstrate the biomarker’s relationships to clinical outcomes and the current standard biomarker

Confirmatory Study 1  Confirmation of the linear relationship of ALT and GLDH in humans

3  Statistical Methods

3.1  Primary Analysis

Construct 2x2 contingency tables of the EWG definition with ALT compared to the EWG definition with GLDH. Compute measures of concordance, sensitivity, and specificity of the GLDH-based EWG definition of liver injury, defined in Section 2, to predict ALT-based EWG definition of liver injury, using proposed GLDH thresholds and computed ALT thresholds determined in the exploratory studies. The target success for each measure is ≥ 0.90, 95% Lower Confidence Bound ≥ 0.85.
Qualification of Glutamate Dehydrogenase

Clinical Validation of GLDH

Characterize the relationships among the biomarker and clinical outcomes with respect to the proposed COU

GLDH is able to accurately identify patients with adjudicated hepatocellular injury, regardless of concomitante muscle injury

<table>
<thead>
<tr>
<th>EWG w/ ALT</th>
<th>EWG w/ GLDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hepatotoxicity criteria met</td>
<td>No hepatotoxicity criteria met</td>
</tr>
<tr>
<td>≥3x ALT and ≥2x Tbil</td>
<td>≥2.5x GLDH and ≥2x Tbil</td>
</tr>
<tr>
<td>≥5x ALT</td>
<td>≥5x GLDH</td>
</tr>
<tr>
<td>≥2x ALP</td>
<td>≥2x ALP</td>
</tr>
</tbody>
</table>

Table 2. Cross-classification table for subjects (healthy and liver-injured) using the Expert Working Group definition of hepatotoxicity with ALT or GLDH.

The Expert Working Group definition of hepatotoxicity is met if one of the following statements is true: ≥3 times the upper limit of normal for ALT and ≥2 times the upper limit of normal for Tbil, OR ≥5 times the upper limit of normal ALT, OR ≥2 times the upper limit of normal for ALP.
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Thank You

Questions? Please email John-Michael Sauer, PhD, jsauer@c-path.org