Evidentiary Considerations for Integration of Biomarkers In Drug Development: Safety Biomarkers

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Fluid Based Safety Biomarkers - similar to routine clinical pathology measures that can be used to **accurately predict** drug induced tissue injury in humans.
Translational Safety Biomarkers

**Nonclinical Studies:**
Anchor the novel biomarker’s performance to histopathological changes (gold standard biomarker in nonclinical toxicology studies), as well as to standard biomarker performance.

**Clinical Studies:**
Demonstrate that the novel biomarker outperforms the standard biomarker (gold standard for safety in clinical studies).
The objective of translational safety biomarker qualification is to demonstrate the **predictive accuracy** of the biomarker to detect tissue injury in humans.

This can be accomplished directly in animals by measuring biomarker concentrations and assessing histopathological changes in target organs (*The true true can be defined and measured*).

In clinical studies, demonstration of the predictive accuracy of the biomarker to tissue injury cannot be directly determined as histopathology is rarely evaluated in clinical studies.
Scientific and Regulatory Expectations for Biomarker Qualification

**Data Quality Expectations**
Well designed, conducted, and documented studies that support the use of the biomarker
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Well designed, conducted, and documented studies that support the use of the biomarker

Scientific and Regulatory Expectations for Biomarker Qualification

Qualification of a Biomarker

Extent of Context of Use

Scientific and Regulatory Expectations (Evidentiary Standards)
Scientific and Regulatory Expectations for Biomarker Qualification

Data Quality Expectations
Well designed, conducted, and documented studies that support the use of the biomarker

Risk Associated with Biomarker Failure

Scientific and Regulatory Expectations
(Evidentiary Standards)
Drug Induced Pancreatic Injury

Hypothetical Examples

Drug Induced Pancreatic Injury

Two hypothetical Context of Use examples:

1. Broad COU – based on two prospective purpose-designed clinical trials with supporting nonclinical data

2. Limited COU – based on a prospective healthy volunteer study and a study in which patients were treated with a drug known to cause pancreatic injury with supporting nonclinical data
Drug Induced Pancreatic Injury
Hypothetical Example

In search for better biomarkers of drug-induced pancreatic injury:

The clinical diagnosis of drug induced pancreatic injury remains a challenge due to the lack of specific symptoms.

Amylase and lipase are the gold standard biomarkers for pancreatic injury.
  • Amylase concentrations >3 times the upper reference limit indicates injury
  • Lipase activities parallel the increased activities

Many conditions that might present with similar clinical symptoms are also associated with increased amylase and lipase concentrations.

Amylase and lipase are among the more poorly standardized tests in laboratory medicine.
Drug Induced Pancreatic Injury
Hypothetical Example

Hypothetical biomarker panel for drug-induced pancreatic injury:

1. MiR-216a
2. MiR-375
3. Protein RA1609
4. Protein RT2864
5. Trypsinogen-1
6. Trypsinogen-2
7. Trypsinogen-3
Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 1) for drug-induced pancreatic injury:

Claim
Qualified pancreatic safety biomarkers are proposed to be used together with monitoring of conventional pancreas biomarkers (e.g., serum amylase and lipase), in early clinical drug development research to support conclusions as to whether a drug is likely or unlikely to have caused a mild injury response in the pancreas at the tested dose and duration.

Study Population
For use in healthy volunteers and patients with normal pancreatic function.
Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 1) for drug-induced pancreatic injury:

Implementation in Clinical Trial Design

1. Have *demonstrated the biomarkers responsiveness* to pancreatic injury in an animal toxicology study

2. Have shown evidence of mild pancreatic injury that is expected either not to be human relevant or to have a satisfactory safety margin over the targeted clinical therapeutic exposure

3. Have shown prior evidence in an animal toxicology study that pancreatic injury can be safely monitored
Hypothetical Context of Use (COU 1) for drug-induced pancreatic Injury:

Implementation in Clinical Trial Design

A human trial designed to evaluate safety of a drug may include qualified biomarkers (Serum RA1609, RT2864, and Trypsinogen-3):

• For research use to make decisions in real time such that an individual patient or an entire dose-cohort of subjects may be triggered to stop or to pause dose escalation of a drug when a pre-specified biomarker threshold is exceeded.

• Change in biomarker serum concentrations as defined by change from baseline will enable the conclusion that a mild pancreatic injury response to a drug candidate was likely or not likely to have occurred in response to a drug in individual subjects.

• Biomarkers are intended to complement the use of the standard biomarkers, including lipase and amylase, and should be evaluated in conjunction with standardly used safety monitoring.
Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 1) for drug-induced pancreatic injury:

Detection of preclinical pancreatic degeneration/necrosis by histopathology

Does the response of the novel biomarkers correlate with pancreatic injury?

Yes

Measure novel biomarkers in early clinical study to evaluate with standardly used safety monitoring. Do the biomarkers respond as described in COU?

No

Drug induced pancreatic injury is absent in this individual

Yes

Drug induced pancreatic injury is occurring in this individual

No

Novel biomarkers are not appropriate for use in this context
Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 1

PREDICTIVE ACCURACY

Nonclinical studies
Multiple studies (~10) with multiple pancreatic toxins (~10) primarily in the rodent with limited studies in canine and nonhuman primate

✓ Correlation of biomarker response to pathology and improved performance relative to other biomarkers
✓ Biological understanding and relevance to toxicity (mechanism of response)
✓ Consistent response across mechanistically different compounds, and similar response across sex, strain, and species
✓ Presence of dose response and temporal relationship to the magnitude of response
✓ Specificity of response to toxicity – understanding the response to toxicities in other tissues, or to pharmacologic effects without toxicity in the target organ
Drug Induced Pancreatic Injury: Proposed scientific expectation for COU 1

PREDICTIVE ACCURACY

Clinical studies

Two prospective studies in patients with currently used medications that have the potential to cause pancreatic injury.

• Azathioprine in Crohn's disease patients
• Mesalazine in ulcerative colitis patients with normal pancreas function

✓ Greater diagnostic predictivity compared to amylase and lipase as defined by:

1. A formal adjudication procedure
2. A predefined statistical evaluation
Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 1

What is the RISK if the biomarker lacks predictive accuracy?

Novel Safety Biomarkers

Lack of Predictive Accuracy

Safety of Individuals in Clinical Trials
Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 1

What is the RISK if the biomarker lacks predictive accuracy?

Novel Safety Biomarkers

Gold Standard

Amylase

Lipase

Safety Net

Type I vs. Type II Error

Safety of Individuals in Clinical Trials
Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 1

Additional areas of scientific expectation:

- Nonclinical and clinical data expectation for (translational) qualification of clinical safety biomarkers

- Biomarker assay validation and performance expectations

- Expectations around clinical data generation (how much rigor in study conduct?)

- Statistical methodology expectations for confirmatory data analysis

- Is there a need for prospective sample generation and analysis or can prospective analysis occur on previously obtained samples?
Drug Induced Pancreatic Injury

Hypothetical Examples

Two hypothetical Context of Use examples:

1. **Broad COU** – based on two prospective purpose designed clinical trials with supporting nonclinical data

2. **Limited COU** – based on a prospective healthy volunteer study and a study in which patients were treated with a drug known to cause pancreatic injury with supporting nonclinical data
Hypothetical Context of Use (COU 2) for drug-induced pancreatic Injury:

Claim
A Composite Measure (CM) of serum Protein RA1609, Protein RT2864, and Trypsinogen-3 is a qualified safety biomarker of pancreatic injury response for use in normal healthy volunteer trials supporting early drug development.

Study Population
For use in healthy volunteers only.
Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 2) for drug-induced pancreatic injury:

Implementation in Clinical Trial Design

1. Have demonstrated the biomarkers responsiveness to pancreatic injury in an animal toxicology study
2. Have shown evidence of mild pancreatic injury that is expected either not to be human relevant or to have a satisfactory safety margin over the targeted clinical therapeutic exposure
3. Have shown prior evidence in an animal toxicology study that pancreatic injury can be safely monitored
Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 2) for drug-induced pancreatic Injury:

Implementation in Clinical Trial Design
A human trial designed to evaluate safety of a drug may include qualified biomarkers (Serum RA1609, RT2864, and Trypsinogen-3):

- The **CM is a measure of the fold change from baseline** of serum RA1609, RT2864, and Trypsinogen-3 expressed as fold change from baseline.

- The group average CM is qualified for study Sponsors to determine if there is an increased likelihood of a pancreatic injury response for a dose of an investigational drug in a **dose cohort** when benchmarked to results provided herein for **normal healthy volunteers**.

- The CM is **not qualified for individual subject safety monitoring**.

- Biomarkers are intended to **complement the use of the standard biomarkers**, including lipase and amylase, and should be evaluated in conjunction with **standardly used safety monitoring**.
Drug Induced Pancreatic Injury

Hypothetical Context of Use (COU 2) for drug-induced pancreatic Injury:

Detection of preclinical pancreatic degeneration/necrosis by histopathology

Does the response of the novel biomarkers correlate with pancreatic injury?

Yes

Measure 3 novel biomarker in SAD first-in-human NHV study to evaluate average composite measure (CM) for each dose group in conjunction with standardly used safety monitoring

No

Novel biomarkers are not appropriate for use in this context

> CM threshold

This dose is potentially unsafe. A decision to investigate this dose further should be considered in the context of other clinical data

< CM threshold

Continue to investigate drug doses in next NHV trial (e.g. MAD study) assuming other clinical data are reassuring, i.e. no evidence of a safety signal

Measure 3 novel BM in NHV trial to test average CM for each dose group

Novel biomarkers are not appropriate for use in this context
Drug Induced Pancreatic Injury: Proposed scientific expectation for COU 2

PREDICTIVE ACCURACY

Nonclinical studies

Multiple studies (~10) with multiple pancreatic toxins (~10) primarily in the rodent with limited studies in canine and nonhuman primate

- **Correlation of biomarker response** to pathology and improved performance relative to other biomarkers
- **Biological understanding** and relevance to toxicity (**mechanism of response**)
- **Consistent response** across mechanistically different compounds, and response similar across sex, strain, and species
- **Presence of dose response and temporal relationship** to the magnitude of response
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Drug Induced Pancreatic Injury:
Proposed scientific expectation for COU 2

PREDICTIVE ACCURACY

Clinical studies

One study in heathy subjects to define the variability associated with the biomarkers and one study with Crohn's disease patients treated with Azathioprine known to have pancreatic injury.

✓ Demonstrate that a Composite Measure of novel biomarkers can differentiate cohorts of heathy subjects experiencing drug-induced pancreatic injury from cohorts not experiencing injury.
Conclusions

We have defined two approaches to qualification of translational safety biomarkers and delineated some of the scientific expectations for these hypothetical projects.

However, we must align and codify these expectations, as well as those in other areas:

- Nonclinical and clinical data expectation for (translational) qualification of clinical safety biomarkers

- Biomarker assay validation and performance expectations

- Expectations around clinical data generation

- Statistical methodology expectations for confirmatory data analysis
Thank You

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