EVIDENTIARY CONSIDERATIONS
FOR INTEGRATION OF BIOMARKERS
IN DRUG DEVELOPMENT

A Symposium Co-Sponsored by FDA, M-CERSI and C-Path
Pharmacy Hall, The University of Maryland
Baltimore, Maryland
August 21, 2015
WELCOME & OPENING

Biomarkers are CRITICAL—How can we better evaluate them?

What should we do now?

What can we do now?

We still need the existing evidence.

What should the standards be for accelerated approvals?

The FDA has a process—but its consensus, timelines, and conditionality needs to be worked out by the community.

TFA’s process is different.

Consensus is critical.

This will be harder than we thought.

WHAT ARE THE GOALPOSTS?

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REVIEW: biomarker use... How did we get here?

It depends on the context of use.

What’s the level of risk?

SIGH is the highest level.

How much evidence do we need?

FRA

We didn’t know enough.

Consortia

Critical Pathways Initiative

There wasn’t a pathway in any other sector to move things forward.

And we lacked a common vocabulary.

Context of Use HELPS—but isn’t clear enough.

As a surrogate endpoint... HARD regulatory adoption...

Lack of funding for qualification...

Sluggish progress in any other sector to move things forward.

Need for baseline.

We had different probes, different images—needed a common vocabulary.
**OVERVIEW**

**FDA'S EFFORTS**

- Biomarkers have been used for a long time throughout drug development.
- Single program vs. multiple programs.
- Biomarker Qualification
  - Level of Evidence
  - Qualification
  - Why does it take so long?
- Collaborations & Workshops
- Survey

**STANDARD EFFORTS**

- Biomarker Qualification
  - Level of Evidence
- Qualification
- Why does it take so long?
- Biomarker Workshop
- Biomarker Standards

**STUDY CONSIDERATIONS**

- Design
  - Identification
  - Multiple predictors
  - Levels
  - What is the definition of a biomarker?
- Endpoints
  - Enrollment
  - Protocol
  - Randomization

**IMPLEMENTATION**

- Implementation
- Early engagement
- Planning
- Endpoints
- Analysis
  - Cross validation
  - Intermediate analyses
  - Analysis plan

**CONCLUSION**

- Streamline process
- Collaboration is important
EVIDENTIARY CONSIDERATIONS FOR CLINICAL SAFETY BIOMARKERS

MECHANISMS OF DRUG TOXICITY

Evidentiary Considerations - Safety

CLINICAL SAFETY BIOMARKERS

Sometimes we still animal studies lie to us —
• With animals we can learn at histopathology,
  • We look for biomarkers —
  • We need predictive accuracy,

EVIDENCE: SUBSTRATES

Qualification is not drug development...
It's an evolving process —-
Developing standards is up to us —-

STATISTICAL CONSIDERATIONS

Coo1
• We need clear statistical hypotheses —
  • How do we know the signal is real and what is HI-predicting?
  • How good are the tools?

Coo2
• It's hard to define universal standards —
  • It depends on Coo1 —
  • But they still rest on core statistical principles —

BIODATA:
• CoQ1:
  • Qualification is not drug development...
  • It's an evolving process —-
  • Developing standards is up to us —-

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EVIDENTIARY CONSIDERATIONS FOR CLINICAL SAFETY BIOMARKERS

Q&A - EVIDENTIARY CONSIDERATIONS

1. The challenges of keeping what we've learned.
2. When do biomarkers in protein biomarkers become relevant?
3. How do we handle the ever-expanding data (e.g., AD) combining omics' data?
4. More concisely, how do we know the data is meaningful?
5. Letter of support is not sufficient databases.
6. Any type of patients to get companies to contribute their data.
7. "Safety biomarkers - the highest standard?"
8. The FDA doesn't always act like that; is it driven by the FDA or other agency?
9. It's difficult to quantify and we also have public opinion/presence.
10. And when we are stringent, we are keeping relatively benign drugs off the market.
11. Why should we have a biomarker that relates to a biomarker to an area of interest to separate tracks whether it fits for use.

1. We have quantified a lot of data, but we must consider:
   - What do the patients get? U - preclinical work
   - We are working on an essay based on a mechanistic understanding.
   - And the risk is both the drug and the patient profile.
   - We hope to change the usual approach.
   - The point of interest is whether the organization made it take some reduction of severity.

1. What are the challenges to get the data in the future?
   - We try to make the best of the data we can as we can.
   - We can do the best that we can collaborate.

1. What about emergency biomarkers?
   - Covington can't be able to act quickly.
   - Disease detection was very engaged...

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   - We are working on an essay based on a mechanistic understanding.
   - And the risk is both the drug and the patient profile.
   - We hope to change the usual approach.
   - It has been shown that the organization made it take some reduction of severity.

1. With the good data, first examples can we list the standards that we would need, based on our experience?
   - Needs to be on the action team. N/A
   - Look at where we want to go.
   - We need to analyze.
   - We need all going it easier to do (uniform standards).
EVIDENTIARY CONSIDERATIONS FOR BIOMARKER-BASED ENRICHMENT OF CLINICAL STUDY POPULATIONS TO INCREASE EFFICACY OR SAFETY OF DRUGS

Biomarker-Based Enrichment

- The relationship between biomarker and efficacy
- How much evidence is there of clinical benefit?
- Defining populations: How will the biomarker be applied?

- When a biomarker is being tested with multiple drugs, it may be qualified.
- The biomarker must be validated.

- Functional/Pathophysiologic analytes without directed qualifications: Concept limitations are a barrier.
- Conduct of use is critical.
- Parameterization of the biomarker.

- Prospective risk factor:
- Reference test control:
- Biomarker:

- Biomarker validation:

- Biomarker-driven enrichment:
- Data from the clinical trial is analyzed and compared:
- Patient profiles:
- Biomarker status:
- Biomarker variability:
- Biomarker enrichment:

- Neuroimaging enrichment biomarkers:

- Hippocampal volume in AD:

- Hypocaudal density (HCD) in AD:

- Mild Cognitive Impairment (MCI) is a model of pre-AD:

- Neuroimaging:

- Kidney disease:

- Polycystic:

- Kidney disease:

- Imaging to predict progression:

- Imaging patients:

- 1. Imaging pattern:

- 2. Study:

- 3. Correlation:

- Determining the predictive value of HCD

- Allowing us to reduce the number of patients needed.

We think this is a promising direction that has the potential to improve outcomes in these trials.

Evidentiary Considerations for Integration of Biomarkers in Drug Development • August 21, 2015
EVIDENTIARY CONSIDERATIONS FOR BIOMARKER-BASED ENRICHMENT OF CLINICAL STUDY POPULATIONS TO INCREASE EFFICACY OF SAFETY OF DRUGS

ENRICHMENT - STATISTICAL CONSIDERATIONS IN BRA

PANEL

- Understanding the progression of a disease -
  we want to understand when events in variability -
  being able to define subtypes -
- Quantitative descriptions of disease progression -
  needed to take a learning sample -
  a validation sample -
  were not validating the model -
  rather the biomarker -

- COO vs. clinical COO -
  Prognostic Biomarkers mostly hold a clear COO -
  There is (1) Biomarker does what it's supposed to do -
  (2) Shows the utility -
  (3) Implications for how many treatments -

- What if we use a biomarker -
  if patient has it -
  if we know we use a biomarker -
  we have to get an exclusion -
  for the device it's well -
  for the drug we shouldn't do biomarker enrichment -
  is a false fear -

- Needing prospective data -
  in addition to retrospective -
  retrospective will be key -
  including samples from the course of the trial -
  not just baseline -

- There can be issues -
  is it truly a random sample -
  are you shrinking from negative trials -

- Observational studies -
  can use -
  one cohort -
  depends on the intended use of the biomarker -

If I can't see it I'm not interested -

P.400 Enrichment can result in misclassification -

The misclassification rate depends on disease prevalence -
  and the ratio of biomarker to clinical patient ratio -
  Sensitivity Specificity Predictive Value -
  Effect of slow progression resistant faster treatment -
**ROUNDTABLE DISCUSSION**

**STEPS TO QUALIFICATION**
- **Proposal for (limited or expanded)**
- **Data Repositories**
  - **Data Sharing**
  - **Common Taxonomy**
  - **Common Lexicon**
- **Qualification Determination**
- **Eligibility Criteria**
- **Risk of Sharing What? How?**
- **Data Standards**
  - **Data quality**
  - **Data reproducibility**
- **Enablers**
  - **Data standards**
  - **Statistical considerations**
  - **Assay/Imaging considerations**
  - **Establishing cut points**

**MOVING FORWARD**
- **Biomarker Taxonomy**
- **Common Lexicon**
- **Biospecimens**
- **Data Repositories**
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