The Principles and Process of Biomarker Qualification at the FDA

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Exploratory Biomarkers
(\textit{VXDS Meetings})

Qualified Biomarkers
(\textit{Biomarker Qualification Process})

\textbf{Regulatory Applications}
Qualification

• A conclusion that within a carefully and specifically stated “context of use”, the biomarker has been demonstrated to reliably support a specified manner of interpretation and application; particularly in regulatory decision-making

• Utility in drug development, particularly regulatory decisions, is central to purpose of qualification

• Qualification can be relied upon in the absence of:
  – Serious study flaws in collecting data
  – Attempt to apply the biomarker outside the qualified context of use
  – New scientific evidence conflicting with prior conclusions

• Biomarker becomes qualified (i.e., the substance)
  – Not a device that performs the assay (CDRH as usual)
  – May need CDRH collaboration
Context of Use

• **Short-hand term for a comprehensive statement of manner and purpose of use**

• **May include:**
  – Range of clinical disorders
  – Range of drug classes
  – Range of species
  – Procedures and criteria for how samples are obtained
  – How the results are interpreted
    • Limitations on the interpretation

• **Defines boundaries of known reliability**
  – Usually not all boundaries of non-reliability

• **Biomarker may also have value outside of currently demonstrated context of use**
  – Use broadly with case-by-case consideration
  – Further work to expand qualified context of use
How do we accept biomarkers today at the FDA?

• Case-by-case. Context of use *always* drug-dependent
  – Original NDA
  – Labeling Updates

• Accepted over time.

• Codevelopment of drug and test

• **Biomarker Qualification Process**
<table>
<thead>
<tr>
<th>Task Name</th>
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<tr>
<td>1. Troponin Task Force</td>
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<td>2. ILSI/HESI Biomarker Committee</td>
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<td>3. Qualification Proposal to ILSI/HESI</td>
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<td>4. Novartis CRADA on Biomarker Qualification</td>
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<td>5. Meeting at SOT in New Orleans</td>
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<td>6. First Teleconference</td>
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<td>7. Nephrotoxicity Workshop</td>
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<td>8. Nephrotoxicity Qualification</td>
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<td>9. ILSI/HESI Nephrotoxicity Qualification</td>
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<tr>
<td>10. Circulating Tumor Cells in Metastatic Breast</td>
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<td>11. Circulating Tumor Cells in Metastatic Prostate</td>
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<tr>
<td>12. Serum Galactomannan in Aspergillosis</td>
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<td>13. Broncho-Alveolar Lavage Galactomannan in</td>
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Timeline to Development of Biomarker Qualification Process at the FDA

- **Pilot Process for Biomarker Qualification (2005-2008)**
- **Regulatory Process for Biomarker Qualification (2009- )**
From Pilot to Process

• **Formal Biomarker Qualification Process proposed in 2009**

• **Approved by the CDER Senior Management Team**

• **Legal framework to be provided by a Guidance**

• **Draft Guidance expected in Q2 2010**
Biomarker Qualification Process at CDER

1. Sponsor submits written request for biomarker qualification
2. DDT Tracking Record Created in DARRTS with status of Presubmission **
3. BQC and BQMT evaluate request
4. Proceed with qualification request? Yes
5. BQC requests BQRT Staffing
6. BQRT Assembled **
7. Sponsor sent COR-DDT-02 (Request for Briefing Document)
8. Sponsor Submits Briefing Package **

Other paths:
- Sponsor sent COR-DDT-01 (Decline Request for Qualification)
- BQC prepares Memo-to-File with Project Summary **
- Sponsor /BQRT Meeting Held
- BQ ready for Review?
- BQRT requests more information
- Sponsor /BQRT Meeting Held
- BQ PM Creates Sponsor /BQRT Meeting
- BQRT Reviews briefing document
- Sponsor completes Biomarker Qualification Data Package **
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- BQ PM Creates Sponsor /BQRT Meeting
  - BQRT Reviews briefing document
  - BQC prepares Memo-to-File with Project Summary **
  - Sponsor /BQRT Meeting Held
  - BQ ready for Review? **
    - Yes
      - BQRT requests more information
    - No
      - All information needed to complete review received? **

- Review Team checks in Discipline Reviews **
  - BQRT Lead compiles reviews into Executive Summary Integrated Review **
  - Executive Summary reviewed by BQMT
  - BQMT approves Executive Summary? **
    - Yes
      - BQC prepares results of Review **
      - Advisory Committee (AC) Required? **
        - Yes
          - Sent to AC
        - No
          - Regulatory Briefing Scheduled
          - Executive Summary forwarded to Office Directors
    - No
      - Regulatory Briefing Held and decision made to Qualify Biomarker
          - Executive Summary Accepted? **
            - Yes
              - Results signed by CDER Director
            - No
              - Sponsor Receives one of following Communications: COR-DDT03 (Not Qualified) COR-DDT04 (Qualified)
              - Tracking Record Status set to one of following: Qualified Not Qualified Closed Withdrawn
              - Review Complete
Translational Biomarkers from the C-Path Institute Predictive Safety Testing Consortium
Summary of Regulatory Conclusions

The FDA and EMEA came to the conclusions that:

• The renal biomarkers submitted were acceptable in the context of non-clinical drug development for detection of acute drug-induced renal toxicity;

• The renal biomarkers provide additional and complementary information to the currently available standards;

• The use of renal biomarkers in clinical trials is to be considered on a case-by-case basis…

Clinical Application of Tubular Biomarkers

Histopathology detected in multiple animal models, but BUN and SCr in control range.

Kim-1 and Albumin are measured to confirm reversibility of histopathology.

Are Kim-1 and Albumin diagnostic?
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Phase I/II clinical trial decision-making: monitor Kim-1 and Albumin.

Non-monitorable toxicity: clinical trial delayed.

Clinical

Nonclinical
Process Qualification Update

• **Nonclinical qualification completed**
  – Translational Biomarkers of Nephrotoxicity of the PSTC

• **Review Stage**
  – Translational Biomarkers of Nephrotoxicity of ILSI/HESI
  – Galactomannan Test for Aspergillosis
  – Preclinical Application of Cardiac Troponins

• **Consultation and Advice Stage**
  – Toxicogenomic Analysis to Explore + Chromosome Ab
  – Circulating Tumor Cells in Metastatic Breast Cancer
  – Circulating Tumor Cells in Prostate Cancer
  – Translational Biomarkers of Hepatotoxicity of the PSTC
  – Translational Biomarkers of Skeletal Muscle Toxicity of the PSTC
Evolution of FDA Guidance and ICH Guidelines
Qualification Guidance for Drug Development Tools

- High-level document
- Biomarkers and Patient Reported Outcome Instruments
- Definitions for biomarkers, PROs and qualification
- Rationale for qualification
- Process
- Procedures for making recommendations available
- Does not discuss evidentiary standards.
- Draft published Q2 2010.
ICH E16

• ICH E16 harmonizes the content, context and format for qualification submissions across the US, Europe and Japan.

• First international harmonization document about biomarker qualification.

• Does not cover levels of evidence.
Development of a Biomarker Qualification Pipeline
Lessons in Biomarker Qualification

Definitions
Scientific and Technical Knowledge
Measurements
Standards
Process
Guidance
Collaboration
Cost
Benefit
Model for development of a biomarker qualification pipeline.

• Problem: biomarker qualification submissions require drivers and resources that may not be easily identified and organized. How do we get to a steady stream of biomarker qualification submissions?

• Goal: develop a Process for the Systematic Identification and Development of Candidate Biomarkers for Qualification

• Proposal: apply what we have learned about consortia assembly and drivers throughout the Pilot version of the Biomarker Qualification Process
Model for development of a biomarker qualification pipeline.

• Candidate Identification
  – *Internal*: canvas CDER scientists and clinicians about exploratory biomarkers considered important by them
    • Also helps “seed” BQRT recruitment
  – *External*: canvas professional organizations of scientists and clinicians about exploratory biomarkers considered important by them
    • Also helps with public input and debate about qualification-readiness
Model for development of a biomarker qualification pipeline.

- **Candidate Development**
  - *Teleconference 1*: initial consensus for qualification.
  - *Workshop*: share information about “prime time” biomarkers
  - *Consortium*
    - Legal framework for sharing information, samples and studies
    - Baseline knowledge: summary of published data.
    - First approximation for context of use
    - Sharing of proprietary data
    - Prospective studies
    - Submission of qualification request
Model for development of a biomarker qualification pipeline.