Drug-Diagnostic Co-development for Tuberculosis

New Tools & Pathways

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President and CEO
Critical Path Institute
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C-Path
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Marvellen deMars, PhD
A non-profit, co-founded by the FDA and Arizona for the sole purpose of serving as a neutral third party to work on the FDA’s critical path initiative.

“Neutral” Funding
Pre-competitive Focus:
Process, not products
FDA Acceptance of new methods
C-Path’s Goal

To help create the infrastructure and the **FDA-qualified** methods so that…..

(As with HIV/AIDS)

When a new, important treatment or “cure” is found, it can be developed in less than three years with a >95% chance of success…. Not 15 years with a 5% chance of success.
It is possible……
AIDS Drug Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>IND to NDA (yrs)</th>
<th>NDA to Approval (mos)</th>
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</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>1.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Didanosine (DDI)</td>
<td>2.8</td>
<td>6.3</td>
</tr>
<tr>
<td>Zalcitabine (DDC)</td>
<td>5.1</td>
<td>7.6</td>
</tr>
<tr>
<td>Stavudine (D4T)</td>
<td>5.0</td>
<td>5.9</td>
</tr>
<tr>
<td>3TC</td>
<td>4.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Indinavir</td>
<td>3.1</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>3.3 years</strong></td>
<td><strong>4.3 months</strong></td>
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</table>
New Pathways for Change

- VXDS - Voluntary “X” Data Submission
  - Genomic Data – Warfarin dosing
  - Biomarker Data – Preclinical Safety
- BQR - Biomarker Qualification Review
- Quantitative Disease Progression Models
Predictive Safety Testing Consortium (PSTC)

Planning Phase
- Coordinating Committee
- Planning 
- Writing Groups

Execution Phase
- Work Scope 
- Document
- Methods
- & Results Sharing
- Working Groups
  1. ...
  2. ...
  3. ...
  4. ...

FDA Review Phase
- FDA Submission
- VXDS
- FDA Review
- BQR
- Qualified Preclinical Safety Tests

Greater Drug Safety
PSTC Members

Advisors: FDA, EMEA
An International Sharing Endeavor

PSTC Convenes 190 Scientists Every 2 Weeks
Creatinine & BUN do not detect subtle drug injury

Twenty three new kidney biomarkers:

- Extremely Sensitive
- Seven had excellent data for submission to FDA and EMEA
April 14, 2008

RE: Review Submission of the Qualification of Seven Biomarkers of Drug-Induced Nephrotoxicity in rats.

Dear Drs. Dieterle, Mattes, and Sistare:

This letter provides the conclusions from our review of your submission supporting the qualification of seven biomarkers of drug-induced nephrotoxicity in rats. We conclude that:

The urinary kidney biomarkers (KIM-1, Albumin, Total Protein, β2-Microglobulin, Cystatin C, Clusterin and Trefoil factor-3) are acceptable biomarkers for the detection of acute drug-induced nephrotoxicity in rats and can be included along with traditional clinical chemistry markers and histopathology in toxicology studies.
EMEA Decision: “Biomarkers Qualified”

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 3 July 2008
Doc. Ref. EMEA/250885/2008 Rev. 1

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS

FINAL REPORT ON THE PILOT JOINT EMEA/FDA VXDS EXPERIENCE ON QUALIFICATION OF NEPHROTOXICITY BIOMARKERS.

<table>
<thead>
<tr>
<th>ADOPTION BY CHMP</th>
<th>April 2008</th>
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</thead>
<tbody>
<tr>
<td>FOR RELEASE FOR CONSULTATION</td>
<td>May 2008</td>
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<tr>
<td>END OF CONSULTATION (DEADLINE FOR COMMENTS)</td>
<td>Extended to July 2008</td>
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</tbody>
</table>
Biomarker Qualification

Predictive Safety Testing Consortium (PSTC)

Planning Phase
- Coordinating Committee Planning & Writing Groups
- Work Scope Document

Execution Phase
- Methods & Results Sharing
- Working Groups
  1. ...
  2. ...
  3. ...
  4. ...

FDA Review Phase
- FDA Submission
  - VXDS
- FDA Review
  - BQR
- Qualified Preclinical Safety Tests

Greater Drug Safety
Model-based Development

1. **Identify Key Question(s)**
   - Build Disease & Drug Model
   - MECHANISM-SYMPOTMS-OUTCOMES
   - TIME

2. **Extract Clinical Trial Information**
   - PATIENT DEMOGRAPHICS
   - DESIGN
   - PLACEBO/DRUG EFFECTS
   - DROP OUT PATTERN

3. **Simulate Scenarios**
   - TRIAL DESIGN
   - SAMPLE SIZE
   - SAMPLING TIMES
   - ENDPOINTS, ANALYSIS

4. **Plug Sponsor Data, Play & Decide**
   - (Go/No Go, trial design)

*Variety of model validation approaches were employed*
Applications in 2008

End of Phase 2A meetings

Labeling Claims

Pediatric approvals (Trileptal)
Sub-group approvals (Zoledronate)
REMS (Busulfan, peds)

Approval – Calcium channel blocker

Larry Lesko, PhD, CDER, 2008
FDA’s Disease Models

Non-small cell Lung Cancer
Alzheimer’s Disease
Parkinson’s Disease

Based on NDA data - Not current

Limited Value
Critical First Step: Data Stds

Clinical Data Interchange Standards Consortium (CDISC)

CDISC Standard Data Elements for Tuberculosis

http://cdisc.org/standards/cardio/index.html
Global consensus

FDA’s Critical Path & IMI recommendations:
- Support of collaborations with transparency
- Sharing placebo data
- Establishing disease models
- Focus on a major disease with unmet need
- Include regulatory agencies in design
- Share failures

Larry Lesko, PhD, CDER, 2008
Drug Development - 2008

Drug Development Path

- Candidate Drug
- Proof of Concept
- Proof of Clinical Utility (Clinical Trials)
- FDA Approved Drug

Drug

Biomarker

Assay

Diagnostic Development “Path”
Drug Development Path

Drug Development - 2008

- Candidate Drug
- Proof of Concept
- Proof of Clinical Utility (Clinical Trials)
- FDA Approved Drug

Drug Development "Path"

Where do we use these new tools?

Diagnostic Development "Path"
Drug – Diagnostic Co-development

Drug Development Path

Candidate Drug → Proof of Concept → Proof of Clinical Utility (Clinical Trials) → FDA Approved Drug

DATA SHARING

Disease Progression Model (In Silico)

Assay → biomarker → Drug

Companion Diagnostic Development “Path”
Drug – Diagnostic Co-development

Drug Development Path

Candidate Drug → Proof of Concept → Proof of Clinical Utility (Clinical Trials) → FDA Approved Drug

DATA SHARING

Disease Progression Model (In Silico)

Drug

Biomarker

Assay

Companion Diagnostic Development “Path”
Drug – Diagnostic Co-development

**Drug Development Path**

- Candidate Drug
- Proof of Concept
- Proof of Clinical Utility (Clinical Trials)

**ASSAY STANDARDS**

- Sensitivity
- Specificity
- Performance

**USDS Performance Certification (Laboratory)**

**DATA SHARING**

- Disease Progression Model (In Silico)

**Companion Diagnostic Development “Path”**

**Drug**

**Biomarker**

**Assay**
Drug – Diagnostic Co-development

Drug Development Path

Candidate Drug → Proof of Concept → Proof of Clinical Utility (Clinical Trials)

DATA SHARING

Disease Progression Model (In Silico)

ASSAY STANDARDS

Sensitivity, Specificity, Performance

USDS Performance Certification (Laboratory)

Indication of Clinical Utility (Based on M&S)

Drug – Diagnostic Co-development

Drug

Biomarker

Assay

Companion Diagnostic Development “Path”
Drug – Diagnostic Co-development

Drug Development Path

Candidate Drug → Proof of Concept → Proof of Clinical Utility (Clinical Trials)

Drug Biomarker

Drug Assay

ASSAY STANDARDS
- Indication of Clinical Utility (Based on M&S)
- USDS Performance Certification (Laboratory)

Disease Progression Model (In Silico)

DATA SHARING

Drug – Diagnostic Co-development "Path"
Drug – Diagnostic Co-development

Drug Development Path

Candidate Drug → Proof of Concept → Proof of Clinical Utility (Clinical Trials)

Disease Progression Model (In Silico)

DATA SHARING

FDA Approved “STRATEGY”

Drug

Biomarker

Assay

ASSAY STANDARDS

Sensitivity
Specificity
Performance

USDS Performance Certification (Laboratory)

Indication of Clinical Utility (Based on M&S)

Companion Diagnostic Development “Path”