Role of Biomarker-Clinical Outcome Relationships in Clinical Drug Development: FDA Experience

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Indiana CTSI Symposium on Disease and Therapeutic Response Modeling
November 2-3, 2011
Disclaimer

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No real or apparent conflicts of interest to disclose
ACKNOWLEDGEMENTS

Yaning Wang
Kevin Krudys
Pravin Jadhav
Raj Madabushi
Ying Chen
Joga Gobburu
PM Group members

Norman Stockbridge
Robert Temple
Abraham Karkowsky
Aliza Thompson
Jialu Zhang
John Lawrence
Overview

• Regulatory Uses of Biomarkers

• Quantitative Disease, Drug and Trial Models to Explore Biomarker-Clinical Outcome Relationships

• Current Efforts

• Case Studies
Regulatory Uses for Biomarkers

It’s more than just surrogate endpoints

Surrogate Endpoints

Individualized Treatment

Pediatric Approval & Dosing

Predicting Safety

New Formulations, Indications, Populations
SURROGATE ENDPOINTS

Change in biomarker that can substitute for an observed clinically meaningful end point in evaluation of effectiveness

Examples
Blood pressure, serum creatinine, serum lipids, HIV-1 RNA, intraocular pressure, glycosylated hemoglobin
INDIVIDUALIZED TREATMENT

Biomarkers to help select responders or identify patients at increased risk of adverse event and aid in dose selection

Examples
• CCR5-tropic HIV (Maraviroc®)
• Her2 Overexpression (Herceptin®)
• CYP2C19 Variants (Plavix®)
If disease progress and treatment intervention is similar between adults and pediatrics, approvals may be based on biomarker data.

Examples
- PK/PD relationship for QTc and heart rate (Sotalol)
- PK matching (piperacillin/tazobactam injection)
Safety biomarkers can be used to predict clinical toxicity.

Examples
- Concentration-QTc Relationship
- HLA-B*5701 allele and hypersensitivity reaction to abacavir
NEW FORMULATIONS, INDICATIONS & POPULATIONS

Extensions to original approval may be based on biomarkers

Examples
• Approval of dosing regimen based on changes in bone mineral density (Risendronate)
• Approval of immediate release formulation based on $\beta_1$-blockade (Carvedilol)
Building Bridges between Biomarkers and Clinical Outcomes

• Natural history/epidemiological data and numerous outcome trials of a variety of agents (surrogate endpoints, safety biomarkers)

• Leveraging information from original approvals (pediatrics, new formulations, new indications)

• Quantitative Disease Drug and Trial Models
  – Allows integration of knowledge across trials/drugs
Disease-Drug-Trial Models

learn from prior experience, summarize knowledge and apply

- Biology
- Natural Progression
- Placebo
- Biomarker-Outcome

- Pharmacology
  - Effectiveness
  - Safety
  - Early-Late
  - Preclinical-Healthy-Patient

- Patient Population
- Drop-out
- Compliance

FDA – Pharmacometrics Efforts

• Disease databases
  – Pulmonary Hypertension
  – Multiple sclerosis
  – NSCLC
  – Alzheimer’s disease
  – Hepatitis C
  – Huntington’s disease

• Safety databases
  – QTc
  – Hepatotoxicity
Trial Database – General Structure

DM = demography, VS = Vital Signs, EX = Exposure, PC = PK Conc, CM = Co-meds

Drug ID → STUDY ID → SUB ID (DM) → LB → VS → EX → PC → CM

Endpoints: HE, CE, WE

Efficacy information

Flag for pop description

DM = demography, VS = Vital Signs, EX = Exposure, PC = PK Conc, CM = Co-meds
CE = Clinical Endpoint, WE = Worsening Endpoint, HE = Hemodynamic Endpoint
Case Study #1

What is the relationship between early tumor size reduction and patient survival in non-small-cell lung cancer (NSCLC)?
NSCLC Model: Objective

• Challenge
  – Oncology drugs have one of the lowest rates of successful drug development

• Objectives:
  – Integrate data from many clinical trials to describe quantitative relationship between tumor size related metrics and overall survival
  – Improve drug development process
Tumor size (Biomarker) – Survival (Outcome) Model

• Data:
  – 4 Trials, 8 active treatments, 1 placebo ~3500 patients, first-line and second line treatment.

• Model:
  – ECOG status (0/1/2/3),
  – Baseline tumor size (centered at 8.5 cm) as covariates
  – Percentage tumor reduction from baseline at week 8 ($PTR_{wk8}$)

$$\log(T) = \alpha_0 + \alpha_1 \cdot ECOG + \alpha_2 \cdot (Base - 8.5) + \alpha_3 \cdot PTR_{wk8} + \varepsilon$$
Model Provides Reasonable Prediction of Survival

NSCLC Model: Value to Drug Development

• Allows early assessment of the activity of an experimental regimen

• Facilitates early screening of candidate drugs for NSCLC

• Optimize trial design through modeling & simulation
Case Study #2

Use of pulmonary vascular resistance index (PVRI) as the basis of approval for a Pulmonary Arterial Hypertension therapy in pediatrics.
Pediatric pulmonary arterial hypertension

- **6-minute walk distance (6MWD)**
  - Primary endpoint for regulatory approval in adults.
  - Poor feasibility and interpretability in pediatrics.\(^1\)

- **Cardio-pulmonary hemodynamics**
  - Used for diagnosis and characterizes disease progression.
  - Represents severity and predicts survival.\(^2\)
  - Closest measure to physiological target of PAH therapies.

\(^1\)Garofano et al., Ped Card 1999, \(^2\)Benza et al., PHA 2010
ΔPVRI (Biomarker) is a significant predictor of Δ6MWD (Outcome)

**Database**
Data from 13 RCTs, 7 therapies

- PDE5 inhibitors, Prostacyclins, ERAs

- Adult patients: only WHO Group I, idiopathic/familial PAH with complete efficacy data analyzed.
  - n = 1096

- hemodynamics (MAP, mPAP, PCWP, CI, RAP, and PVRI, SVRI) and 6MWD

\[ \text{slope} = -0.032 \ (-0.039, -0.024) \]
\[ p\text{-val} < 0.0001 \]
ΔPVRI is a significant and consistent predictor of Δ6MWD across trials and mechanism.
ΔPVRI-Δ6MWD relationship can guide pediatric drug development

**Adults**: Establish a relationship between ΔPVRI and Δ6MWD to specify target for pediatrics.

**Pediatrics**: Placebo controlled, dose ranging studies to be performed to achieve different degrees of hemodynamic benefit.
Status of PVRI for Pediatric PAH

- Now a “limited surrogate” in pediatric PAH therapy development – for therapies already approved in adults.

- PHIMS – Pulmonary Hypertension Information Management System

- Sponsors required to use modeling and simulation to support pediatric PAH trial design.

Cardio-Renal Advisory Committee, July 29, 2010
Biomarker-Outcome Relationships

Next Steps

• Tools need to be developed – Disease Database
  – Data Standards
  – Analysis
• Quantitative analysis should be routinely conducted
  – Plan collection of relevant biomarkers.
  – Specify as secondary analysis in all NDAs

• Inter-disciplinary and FDA-Academia-Industry scientists need to collaborate
QUESTIONS??