Regulatory Application of Quantitative Analysis: Impact of Biomarker Data

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA
Outline

• Critical Path Initiative
  – Model based drug development and biomarker
• Two examples
  – IND
  – NDA
• Summary
2004 FDA Critical Path Initiative

Application of New Scientific Knowledge to Drug Development:

- Model based drug development
- Pharmacogenomics in drug development
- New imaging technologies may contribute biomarkers in drug development

http://www.fda.gov/oc/initiatives/criticalpath/
2006 FDA Critical Path Update

Critical Path Opportunities Report

Critical Path Opportunities List

U.S. Department of Health and Human Services
Food and Drug Administration
March 2006
Model-Based Drug Development

“The concept of model-based drug development, in which pharmaco-statistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers an important approach to improving drug development knowledge management and development decision-making.”

Terminology

- **Model-based drug development**
  - Pharmacokinetics/Pharmacodynamics (PK/PD)
  - Modeling and simulation
  - Exposure-response
  - Quantitative clinical pharmacology
  - Quantitative disease and drug models

- **Pharmacometrics-Pharmacometricians**

- **Areas involved:** clinical pharmacology, statistics, pathophysiology, biology, bioengineering
Applications in FDA Review

- Exposure-response analysis of efficacy and safety data in IND/NDA review for the choice of dosing regimen(s) and trial design
- Dose adjustment in special populations (hepatic, renal, gender, age and drug interactions) based on intersubject variability and risk/benefit assessment
- Routine use of population PK and PD data analysis to understand variability and to provide evidence for label claims
- Issuing guidance to assist the industry in using these tools
- Case studies
Case Study 1
Drug X

- Treatment for a chronic disease
- Polymorphism in metabolic enzyme (PK biomarker)
  - a/a 20%
  - a/b 50%
  - b/b 30% Extensive metabolizers (EM’s)
  - Poor metabolizers (PM’s)
- ↓ PD Biomarker (B) & Surrogate (S) levels
- Goal: How to design a dose-ranging phase 2B trial
Genotype Caused PK Difference

- **a/a**
- **a/b**
- **b/b**

Dose Normalized AUC (ng.h/ml/1 mg)

- **EM’s**
- **PM’s**

- Genotype Caused PK Difference

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PK Difference Caused PD Difference
(Week 12, QD, 20 mg)

Surrogate Change from Baseline

EM’s
PM’s

a/a  a/b  b/b
Modeling Strategy

• Pharmacokinetics (Drug X)
  – Phase 1 data for population PK model
  – Phase 2 data for model update

• Pharmacodynamics (Biomarker and Surrogate)
  – Model established using clinical trial data available to FDA from drugs in this class & other classes
  – Simultaneous modeling biomarker and surrogate
  – Models updated with Drug X data
\[
\frac{dB}{dt} = K_{in} - K_{out} \left(1 + \frac{E_{max} \cdot C}{EC_{50} + C}\right) \cdot B
\]

\[
\frac{dS}{dt} = K'_{in} \cdot B - K'_{out} \cdot S
\]
Modeling Results for Biomarker & Surrogate
(Drug Y in 900 patients)
A Combined Dataset

Biomarker

Observed Level

Week

Surrogate

Observed Level

Week

Drug X
in 400 patients

Drug Y
in 100 patients

Combined dataset
in 500 patients
Drug X: Model Fits  
(individual patients)

Biomarker Level

- a/a, 20 mg
- a/b, 20 mg
- b/b, 20 mg

Week

Surrogate Level

5 10 15 20 25 30

0 10 20 30

0 10 20 30 40

20 40 60 80 100

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Clinical Trial Simulation

- Population PK model
  - Two-compartment model
  - Clearance dependent on genotype (a/a, a/b and b/b)
- Exposure-response model
  - Drug-Biomarker-Surrogate model
- Trial designs
  - Stratification by genotype
  - Titration by biomarker
- Inclusion criterion
  - Baseline Surrogate > 70 and < 100
- Analysis
  - Response rate at week 26 (Surrogate reduction > 10)
- 100 clinical trial replicates
Stratification by Genotype

(Genotype 1st, Parallel Dose, Placebo Control)

100 Patients = 20 a/a, 50 a/b, 30 b/b

Genotype

400 patients

Dose mg/day

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PM</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>a/a</td>
<td>40</td>
<td>120</td>
</tr>
<tr>
<td>a/b</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>b/b</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>PBO</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Time (weeks)

0  26
Titration by Biomarker
(Parallel Dose, Titration at 12 wk, Placebo Control)

Dose mg/day

All Titration by Biomarker (Biomarker ↓ <13)

- 120 (Biomarker non-responder)
- 40 (Biomarker responder)

100

- 60 (Biomarker non-responder)
- 20 (Biomarker responder)

100

- 30 (Biomarker non-responder)
- 10 (Biomarker responder)

100

- 3X (Biomarker non-responder)
- PBO (Biomarker responder)

400 patients

Time (weeks)

0 12 26

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Clear Dose-Response Relationship for Various Regimens

Response Rate at Week 26 (%)

Response Rate at Week 26 (%)

- BID_05: 39% (Genotype), 33% (Biomarker)
- BID_10: 64% (Genotype), 54% (Biomarker)
- BID_20: 84% (Genotype), 73% (Biomarker)
- QD_10: 29% (Genotype), 27% (Biomarker)
- QD_20: 53% (Genotype), 44% (Biomarker)
- QD_40: 74% (Genotype), 62% (Biomarker)
Higher Response Rate at Week 26 for Stratification by Genotype

Response Rate at Week 26 (%)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>BID_05</td>
<td>33%</td>
</tr>
<tr>
<td>BID_10</td>
<td>54%</td>
</tr>
<tr>
<td>BID_20</td>
<td>73%</td>
</tr>
<tr>
<td>QD_10</td>
<td>29%</td>
</tr>
<tr>
<td>QD_20</td>
<td>44%</td>
</tr>
<tr>
<td>QD_40</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>84%</td>
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</table>

Higher Response Rate at Week 26 for Stratification by Genotype.
Smaller Difference in Response Rates at Later Weeks

<table>
<thead>
<tr>
<th></th>
<th>Week 26</th>
<th></th>
<th>Week 38</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>64%</td>
<td>70%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Biomarker</td>
<td>54%</td>
<td>10%</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

Response Rate (%)

Week 26: Genotype 64%, Biomarker 54%
Week 38: Genotype 70%, Biomarker 60%
Better Response Rates at Week 26 for BID than QD

Response Rate (%) at Week 26 for different treatment regimens:

- BID_05: 39% (Genotype) 33% (Biomarker)
- BID_10: 64% (Genotype) 84% (Biomarker)
- BID_20: 84% (Genotype) 73% (Biomarker)
- QD_10: 29% (Genotype) 53% (Biomarker)
- QD_20: 44% (Genotype) 53% (Biomarker)
- QD_40: 74% (Genotype) 62% (Biomarker)
Larger Difference in Response Rates for EM Patients

Response Rate at Week 26 (%)

- PM
  - BID: 59%
  - QD: 56%

- EM
  - BID: 66%
  - QD: 53%
Some PM Patients Will Have Exposures beyond Previous Experience

Proportion of PM patients receiving high doses not studied

<table>
<thead>
<tr>
<th></th>
<th>Genotype</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID 60 mg</td>
<td>3%</td>
<td>26%</td>
</tr>
<tr>
<td>QD 120 mg</td>
<td>3%</td>
<td>32%</td>
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</table>
Conclusion

• At week 26, higher response rates were achieved in stratification by genotype design than titration by biomarker design. But the difference is getting smaller at later weeks.

• BID regimens perform better than QD regimens, especially in EM population.

• High-dose safety data in PM is needed.

• Biomarker-Surrogate relationship can be applied to other drugs with similar mechanism of action.
Case Study 2
Drug Y

• Drug Y was developed to prevent a life-threatening disease by reducing the level of a biomarker

• The sponsor was pursuing an accelerated approval based on a biomarker even though clinical endpoint analysis failed in two pivotal trials

• Question: what went wrong and how to design the next trial?
Analysis Methods

• Analysis of covariance (ANCOVA) for comparing biomarker level reduction in treatment and placebo groups

• Log-rank test for primary analysis (time-to-event between treatment and placebo groups)

• Cox-proportional model for the relationship between the biomarker level (time-dependent) and the disease event
Different Results for Biomarker and Clinical Endpoint

Biomarker Change from Baseline (%)

Study Week

Patients without An Event (%)

Study Week

P<0.001

P=0.5

Placebo

Drug

Placebo

Drug

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Reduction in Biomarker Level Led to Lower Risk of Disease

**Graph:**
- **Y-axis:** Relative risk of the disease event
- **X-axis:** Biomarker level % change relative to baseline
- **Legend:**
  - Estimated RR
  - LL of 95% CL
  - UL of 95% CL

**Key Points:**
- Hazard ratio = 10.0
- 95% CI: 2.5 - 30.0
- p < 0.001

**Legend:**
- Estimated RR
- LL of 95% CL
- UL of 95% CL
What is Wrong?

- Different statistical methods
  - Different power
  - Different variability

![Diagram](attachment:image.png)
Simulation of Biomarker Reduction Needed to Show Significant Results

- Assume optimistic values for placebo group
  - 10% increase in biomarker level
  - 15% disease event
- Calculate the relative risk (RR) between treatment and placebo groups under various degrees of biomarker reduction in the treatment group
- Calculate the predicted 95% CI for the percentage of disease event in treatment group
- Calculate the maximum percentage of disease event in treatment group to achieve p<0.05 for a response rate analysis under a given sample size
Biomarker Reduction under Current Dosing Regimen

![Graph showing relative risk of renal flare based on biomarker level changes.](graph)

- Relative risk (Drug/Placebo): 0.66
- 95%CI: (0.54, 0.8)
Biomarker Reduction Needed to Show Significant Results

![Graph showing the relationship between relative risk and biomarker level % change relative to baseline.]

**Relative risk (Drug/Placebo): 0.28**

95% CI: (0.16, 0.52)
Higher Doses Associated with Greater Biomarker Reduction
(Placebo, 1, 5, 10 mg)

Best case scenario: Emax=100%

Dose > 50 mg
Summary of Case 2

• More biomarker reduction is necessary to show the significant clinical benefit of drug Y versus placebo

• Higher doses should be studied given the safety profile under the current dose

• MTD study suggested 12 fold higher dose can be well tolerated even though the sponsor originally planned to conduct another pivotal trial with 20 mg and 10 mg arms

• The sponsor decided to include 90 mg arm
Conclusion

• Model-based drug development provides a new platform to apply quantitative methodology extensively
• Biomarker data can play important roles in model-based drug development
• Appropriate approaches should be applied to translate dose/exposure-biomarker relationship to dose/exposure-endpoint relationship
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