Impact of Pharmacometric Analysis on Drug Approvals and Therapeutics

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The opinions expressed in this presentation do not represent official FDA policy
Today's Objectives

1. Highlight Growth of Pharmacometrics at FDA
2. Describe Scope of Pharmacometrics at FDA
3. Discuss Impact on Drug Development and Therapeutics
What is Pharmacometrics?

**Decisions**
- Go/No-go, trial design
- Approval, Label, Policy
- Personalized medicine

**Analysis**
- Quantitative disease-drug-trial modeling
- Simulations

**Information**
- Data collected in trials and studies.
- Domain expertise

Pharmacometrics is the science of quantifying disease, drug and trial characteristics with the goal to influence drug development, regulatory and
10-fold Increase in Demand

Total # IND/NDA/BLA

- <2000
- 2000-02
- 2003-04
- 2005-06
- 2007-08
- 2008-09
- 2009-10

Boceprevir
Topiramate
Scope
Guidance
P'Metrics
FDA Pharmacometrics: Return on Investment

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm167032.htm

Based on 2007-08 reviews

**Approved Dose**

- **<1 Month**
  - 30%
- **1-6 Months**
  - 45%
- **>6 Months**
  - 25%

**Evidence of Effectiveness**

- **<1 Month**
  - 40%
- **1-6 Months**
  - 45%
- **>6 Months**
  - 15%

**Safety**

- **<1 Month**
  - 18%
- **1-6 Months**
  - 64%
- **>6 Months**
  - 18%

- **<100 patients**
  - 55%
- **100-400 patients**
  - 40%
- **>400 patients**
  - 15%
Several Guidance Documents Illustrate Application of Modeling and Simulation

- Population Pharmacokinetics
- Exposure-Response
- Evidence of Effectiveness
- Combination Drugs
- Drug-Drug Interaction
- Hepatitis C Drug Dev
- Diabetes Drug Dev

320 We recommend that sponsors conduct mechanistic modeling of the concentration-viral kinetics and the concentration-safety profile from phase 1 trials to predict the most active and tolerable doses for study in phase 2. The mechanistic viral dynamics are modeled by using differential equations. The CDE is then used to develop

447 exposure-response data be obtained during the phase 2 dose-finding studies. (See the guidance for industry Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications.)
Pivotal Role in Pediatric Applications

Case Study: Topiramate
Model Based Extrapolation for All Monotherapy Approvals for Treatment of Epilepsy

Is Exposure-Response Similar in Adults?

Extrapolate Adjunct Therapy to Monotherapy
Topiramate Dosing Regimen was Derived by Matching Steady State Trough Concentrations (Cmin) for Different Age Groups

Pharmacokinetic Modeling and Simulation Based Approval

- BWT - 2 years
- BWT - 4 years
- BWT - 6 years
- BWT - 8 years
- BWT - 10 years

Median Pediatric (6-9 years) Cmin

Median Adult Cmin

Dose (mg/kg/day)

Cmin (mcg/ml)
Pivotal Role in Dosing Recommendations After Pivotal Trials Are Completed

Case Study: Boceprevir
Null Responders were Excluded from Pivotal Trials but Pharmacometrics Bridging Approach Filled the Gap

Pivotal Trials

SPRINT-2
(Untreated)

B44+P/R
B24+P/R (RGT)

B32+P/R (RGT)
B44+P/R

P/R
P/R – PegInterferon/Ribavirin

Approval

Dosing Information

Dosing For subgroups
Informed from RESPOND-2

Evidence of Effectiveness And Dosing

ALL
Previously P/R Treated
Informed from SPRINT-2

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm254073.htm
Null Responders can be identified based on Week 4 P/R response (<0.5 or <1 log decline) in untreated subjects.
Higher SVR in Subjects with <0.5 or <1 log Week 4 P/R response with Boceprevir Compared to P/R Treatment

<table>
<thead>
<tr>
<th>Week 4 Viral load decline</th>
<th>% null responders, (n/N)</th>
<th>Observed SVR in PR (Untreated Subjects)</th>
<th>Observed SVR in Boceprevir (Untreated Subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>69% (57/83)</td>
<td>4%</td>
<td>28%</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>88% (22/25)</td>
<td>0%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30%</td>
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- <1.0 log_{10} decline includes subjects who are not null responders and may over estimate SVR
- <0.5 log_{10} decline includes predominantly null responders and provides a more conservative estimate for SVR
Business and Public Health Impact

- Evidence of Effectiveness for Prior Null Responders
  - Estimated Sample Size for New Study
    200-300 patients studied over 72 weeks

- Dosing Recommendations for Untreated Late Responders
  - Impact on Healthcare Cost
    12 weeks of less therapy that costs $1100/week

These estimates are derived after regulatory review and were not considered during the review. The review focus was to scientifically justify the regulatory decision.
### Summary

**Impact on Drug Development and Therapeutics**

- Identified an exploratory subgroup potentially lacking benefit
- Asked for new study

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<tr>
<th>Herceptin®</th>
<th>trastuzumab</th>
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- Treatment of SEGA
- Pivotal Exposure-Response for evidence of effectiveness and TDM justification

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<tr>
<th>Afinitor®</th>
<th>(everolimus) tablets</th>
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- Concentration-QT analysis predicted QT effects at 40 mg/day to limit the dose

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<th>Celexa®</th>
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- Derived and recommended Pediatric Dosing Recommendations without any empirical data

| Pralidoxime Peramivir |

Summary

Impact on Drug Development and Therapeutics

- Increased Demand for Pharmacometrics at FDA
- Several Pharmacometrics Applications in Review, Research, Official Guidance and Policy
- Pharmacometrics at FDA Plays Pivotal Role in Approval and Labeling
Impact on Approval-
ER analysis provided supportive or pivotal evidence of effectiveness.

Impact on labeling-ER analysis supported D&A, Warnings, Intrinsic/Extrinsic factors sections