The Business Case for Model Informed Drug Development

Patrick F. Smith
Research and Development Productivity

Productivity \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}

Model-Informed Drug Development: A Rational Approach to Efficiently Accelerate Drug Development

Clinical Pharmacology & Therapeutics
Volume 93, Issue 6, pages 502-514, 14 MAR 2013 DOI: 10.1038/clpt.2013.54
http://onlinelibrary.wiley.com/doi/10.1038/clpt.2013.54/full#cptclpt201354-fig-0001
Regulators Affirm Importance of MIDD

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D.

We’re at a point in science where new medical technologies hold out the promise of better treatments for a widening number of vexing conditions. Over the last few decades, science has enabled fundamental advances in our understanding of the genetic and protein bases of human disease. These developments are already being translated into new medicines. In more cases, these treatments target the underlying mechanisms that drive different diseases. These advances hold out the promise of arresting and even curing a growing number of diseases.

To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don’t want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don’t add to our understanding of the product’s safety and benefits.

“I want to highlight one example of these steps, which we’re investing in, and will be expanding on, as part of our broader Innovation Initiative. It’s the use of in silico tools in clinical trials for improving drug development and making regulation more efficient.

FDA’s Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms.”
50% of FDA Scientific Priority Areas include MIDD

1. Modernize toxicology to enhance product safety

2. Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcome

5. Harness diverse data through information sciences to improve health outcomes

7. Facilitate development of MCM to protect against threats to health

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology – March 2012

- Should modeling and simulation methods be considered in **all** pediatric drug development programs? – (VOTE) YES: 13; NO: 0; ABSTAIN: 0
- Can dose(s) for the adolescent (>12 years) population be derived using adult data without the need for a dedicated PK study? – (VOTE) YES: 12; NO: 1
- Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time? – (VOTE) YES: 7; NO: 6

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm
Research and Development Productivity

Productivity ~ Pipeline \times p(\text{Technical Success}) \times \text{Value} \over \text{Cycle Time} \times \text{Cost}

M&S Impacts 4 of the 5 Key Drivers of Productivity
Reducing Development Costs and Cycle Time

Productivity \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}

Reducing Development Cost

Reducing Cycle Time
# Financial Impact of Earlier Market Entry

## Table 2: Increase in NPV of a new drug from an earlier approval and launch

<table>
<thead>
<tr>
<th>Expected Market Uptake</th>
<th>Percent Increase</th>
<th>Dollar Value ($mil) of NPV Improvement for $500 million Peak Annual Sales Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calendar Quarters Saved</td>
<td></td>
</tr>
<tr>
<td>Most Rapid</td>
<td>1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>4.0% 8.2% 12.4% 16.7%</td>
<td>$88 $178 $270 $364</td>
<td></td>
</tr>
<tr>
<td>Rapid</td>
<td>4.3% 8.7% 13.2% 17.8%</td>
<td>$82 $167 $253 $341</td>
</tr>
<tr>
<td>Average</td>
<td>4.9% 10.0% 15.1% 20.3%</td>
<td>$74 $150 $228 $307</td>
</tr>
<tr>
<td>Slower</td>
<td>6.1% 12.5% 19.1% 26.0%</td>
<td>$64 $130 $198 $267</td>
</tr>
<tr>
<td>Slowest</td>
<td>6.3% 12.7% 19.2% 25.9%</td>
<td>$14 $30 $46 $62</td>
</tr>
</tbody>
</table>
## Published Examples of Financial Impact

<table>
<thead>
<tr>
<th>Company</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERCK</td>
<td>&gt;$500M in costs avoided over 3-yr period</td>
</tr>
<tr>
<td></td>
<td>Enables ~10 critical development decisions annually</td>
</tr>
<tr>
<td>VERTEX</td>
<td>$30-40M saved in the development of HCV PI telaprevir using MIDD due to shorter trial durations</td>
</tr>
<tr>
<td>PFIZER</td>
<td>$100M reduction in annual clinical trial budgets</td>
</tr>
<tr>
<td>TUFTS</td>
<td>Adaptive Designs could save companies $100 - 200M annually</td>
</tr>
</tbody>
</table>

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*Allerheiligen, CPT 2014


Lamberti and Getz Tufts CSDD Whitepaper, May 2015

Milligan et al, CPT 2013*
Case: RSV - MIDD

- Tools
  - PBPK, POPPK, PK/PD

- Application
  - Early development
    - MIDD embedded in Development Plans
    - Clinical Trial Optimization
    - Informing regulatory pathway
Respiratory Syncytial Virus (RSV) Background

• Most children have been infected while an infant

• Majority of severe infections occur in children < 2 years of age
  • 40% develop lower RTI; 2-5% require mechanical ventilation
  • Mortality 1-3% in hospitalized patients

• No approved drugs for treatment of infection (supportive care)

• ALS-8176: Novel, potent nucleoside analogue prodrug being developed as a potential treatment for RSV in children
ALS-8176 Early Development Plan

- Adult HV SAD/MAD
- Hospitalized Infants with RSV PK Study
- Adult RSV Challenge
- Adult ADME

N Engl J Med 2015; 373:2048-2058
https://clinicaltrials.gov/ct2/show/NCT02202356?term=ALS-008176&rank=4
McClure M, et al. ID Week 2015
Quantitative Pharmacology Approach to Support Early Entry into Infants

- Adult PK Data (SAD/MAD)
- Adult PK/PD (HCM) + Preclinical Data (EC50, Lung NTP PK)
- Predict Peds PK
- PK Model
- Estimate Efficacious Doses
- VK-PKPD Model
- Peds Phase 1
- Therapeutic Trials

Prediction & Refinement

Prediction & Refinement
RSV Human Challenge Model Adaptive Design

- Traditional HCM designs: few doses, pairwise comparison of dose vs. placebo
- Study Objectives
  - Demonstrate POC that ALS-8176 has antiviral activity
  - Characterize exposure-response relationship to guide further studies in pediatrics
- PK and PD data examined between each cohort to determine dose levels for subsequent quarantine
  - Could utilize any mix of placebos and doses (N=22 per group, 70% infection rate)
Defining PK/PD Targets for Antiviral Efficacy from the HCM

K Patel, et al.  ID Week 2015

Impact of RSV Model Informed Development Program

• Model based approach provided justification to move rapidly into the target patient population

• Adaptive HCM provided significant savings over traditional studies
  • Fewer subjects required, more informative dataset for exposure-response modeling
  • ~6 months and >$5 million saved in trial costs compared to competitors using more traditional approach

• Alios acquired for $1.75B based on results of the HCM
Avoiding Clinical Trials

Productivity \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}

- Reducing Development Cost
- Reducing Cycle Time
Figure 16: Simulated and Observed Ibrutinib Cmax Ratios and AUC Ratios with 95% Confidence Intervals of Weak, Moderate and Strong Inhibitors and Moderate and Strong Inducers of CYP3A4
## Impact of PBPK Modeling: Trials Not Conducted

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug Name</th>
<th>Indication</th>
<th>No Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson &amp; Johnson</td>
<td>Xarelto (Rivaroxaban)</td>
<td>Deep Vein Thrombosis - Pulmonary Embolism – hip/knee replacement and surgery</td>
<td>4</td>
</tr>
<tr>
<td>Actelion</td>
<td>Opsumit (Macitentan)</td>
<td>Pulmonary Arterial Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Tibotec</td>
<td>Edurant (Rilpivirine)</td>
<td>HIV infection</td>
<td>1</td>
</tr>
<tr>
<td>Janssen</td>
<td>Olysio (Simeprevir)</td>
<td>Hepatitis C</td>
<td>7</td>
</tr>
<tr>
<td>Pharmacyclics</td>
<td>Imbruvica (Ibrutinib)</td>
<td>Mantle cell lymphoma &amp; chronic lymphocytic leukemia</td>
<td>24</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Movantik (Naloxegol)</td>
<td>Opioid Induced Constipation</td>
<td>10</td>
</tr>
<tr>
<td>Genzyme A Sanofi Company</td>
<td>Cerdelga (Eliglustat)</td>
<td>Gaucher Disease</td>
<td>12</td>
</tr>
<tr>
<td>Novartis</td>
<td>Zykadia (Certinib)</td>
<td>Metastatic Non-Small Cell Lung Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Jevtana (Cabazitaxel)</td>
<td>Metastatic hormone refractory prostate cancer</td>
<td>1</td>
</tr>
<tr>
<td>Amgen</td>
<td>Blincyto (Blinatumomab)</td>
<td>Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)</td>
<td>1</td>
</tr>
<tr>
<td>Novartis</td>
<td>Farydak (Panobinostat)</td>
<td>Myeloma</td>
<td>2</td>
</tr>
<tr>
<td>Eisai</td>
<td>Lenvima (Lenvatinib)</td>
<td>Metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer</td>
<td>1</td>
</tr>
<tr>
<td>Novartis</td>
<td>Odomzos (onidegib)</td>
<td>Adult patients with locally advanced basal cell carcinoma (BCC)</td>
<td>3</td>
</tr>
<tr>
<td>Genentech</td>
<td>Alecensa (Alectinib)</td>
<td>Non Small Cell Lung Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Alkermes</td>
<td>Aristada ((Aripiprazolel)</td>
<td>Schizophrenia</td>
<td>5</td>
</tr>
<tr>
<td>Genentech</td>
<td>Cotellic (Cobimetinib)</td>
<td>Metastatic Melanoma</td>
<td>16</td>
</tr>
</tbody>
</table>
Exposure-Response Modelling Is Now Being Used to Avoid Costly Dedicated TQT Trials

A Quantitative Framework to Evaluate Proarrhythmic Risk in a First-in-Human Study to Support Waiver of a Thorough QT Study

CH Nelson¹, L Wang¹, L Fang¹, W Weng¹, F Cheng¹, M Hepner¹, J Lin¹, C Garnett² and S Ramanathan¹

Clinical Pharmacology & Therapeutics
Volume 98, Issue 6, pages 630-638, 29 SEP 2015 DOI: 10.1002/cpt.204
http://onlinelibrary.wiley.com/doi/10.1002/cpt.204/full#cpt204-fig-0004
Enhancing Probability of Success

\[
\text{Productivity} \sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}
\]
Enhancing Success Rates by Reducing Failure

Productivity $\sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}$

Enhancing Success Rates by Reducing Failure

Dose response relationship for seizure frequency

Gabapentin

Lacosamide

Lamotrigine

Levetiracetam

Oxcarbazepine

Pregabalin

New Drug

Retigabine

Tiagabine

Topiramate

Zonisamide

Dose (mg)

Seizure frequency (% change)

Courtesy J Mandema
Since all compounds have the same maximum response, their Dose Response relationship can be scaled to that for Topiramate.
In a similar way, the Dose Response for the AE drop out rate was quantified.
Comparative profile of AEDs at their (expected) marketed doses (difference from placebo)

- Seizure frequency (median % change)
- Dropouts due to AEs (%)

Gabapentin 1800 mg/day
Lacosamide 400 mg/day
Lamotrigine 400 mg/day
Levetiracetam 3000 mg/day
Oxcarbazepine 900 mg/day
Pregabalin 300 mg/day
NewDrug
Tiagabine 32 mg/day
Topiramate 400 mg/day
Zonisamide 400 mg/day
No Dose Which Will Deliver to TPP

Based on 5000 simulations at each concentration

Relative Risk to SOC

Efficacy

Safety

Doses ranging from 30 to 75 mg

Probability

Median Drug Concentrations NME Cmin (ng/mL)

Comparative Efficiency

Comparable to Comp

Superior to warfarin & Inferior to Comp

Comparable to SOC

Worse than SOC and Comp

Courtesy S Allerheiligen
Research and Development Productivity

Enhancing Commercial Value of a Drug Product

Productivity $\sim \frac{\text{Pipeline} \times p(\text{Technical Success}) \times \text{Value}}{\text{Cycle Time} \times \text{Cost}}$

- Expansion of label claims
- Support Differentiation vs. Competitors
- Maximize Clinical Outcomes
The Future
Translating clinical trial patient (CTP) to real world patient (RWP) and Health Economics

Current state: focus of “translational” sciences

- **Our ultimate goal is to understand the real-world effectiveness of our therapies, which is only partially informed by clinical trial efficacy**

- **Requires robust translation between patient from the randomized clinical trial to the real world patient**
Putting it All Together
Interdisciplinary pharmacometrics linking oseltamivir pharmacology, influenza epidemiology and health economics to inform antiviral use in pandemics

Comparators
(Treatment vs. baseline)

<table>
<thead>
<tr>
<th>Costs (A) (payer)</th>
<th>Costs (B) (payer - Baseline)</th>
<th>Costs (A) (societal - Baseline)</th>
<th>Death (A)</th>
<th>Death (B)</th>
<th>Δ Death (A-B)</th>
<th>Δ LYS (A-B)</th>
<th>Δ QALYs (A-B)</th>
<th>Payer perspective</th>
<th>Societal perspective</th>
</tr>
</thead>
</table>
| **Low transmissibility and low severity**
75 mg (A) vs. no treatment (B) | 9 225 251 | 42 578 018 | 12 998 947 | 106 995 703 | 27 | 439 | 399 | 430 | Cost-saving | Cost-saving |
150 mg (A) vs. 75 mg (B) | 14 835 713 | 9 225 251 | 17 109 649 | 12 998 947 | 16 | 27 | 11 | 11 | 546 753 | 515 260 |
| **High transmissibility and high severity**
75 mg (A) vs. no treatment (B) | 94 961 869 | 144 271 547 | 171 053 550 | 272 957 742 | 974 | 1591 | 617 | 598 | 629 | Cost-saving | Cost-saving |
150 mg (A) vs. 75 mg (B) | 81 019 150 | 94 961 869 | 139 379 855 | 171 053 550 | 747 | 974 | 227 | 220 | 227 | Cost-saving | Cost-saving |
| **Low transmissibility and low severity**
75 mg (A) vs. no treatment (B) | 11 450 971 | 79 213 439 | 15 596 974 | 149 869 617 | 53 | 874 | 821 | 795 | 828 | Cost-saving | Cost-saving |
150 mg (A) vs. 75 mg (B) | 16 176 877 | 11 450 971 | 18 675 157 | 15 596 974 | 32 | 53 | 21 | 20 | 21 | 231 280 | 223 797 |
| **High transmissibility and low severity**
75 mg (A) vs. no treatment (B) | 54 113 197 | 77 547 403 | 123 371 900 | 194 871 423 | 489 | 799 | 310 | 300 | 330 | Cost-saving | Cost-saving |
150 mg (A) vs. 75 mg (B) | 49 689 085 | 54 113 197 | 102 809 041 | 123 371 900 | 375 | 489 | 114 | 110 | 117 | Cost-saving | Cost-saving |

All costs are expressed in 2013 USD.
A, the alternative intervention; B, the baseline intervention.
The Era of Model Informed Drug Development is Here

• Use of modeling approaches to develop drugs is not novel
  • Rather, it is expected
  • At least 15 FDA guidance documents include M&S as best practice

• A pediatric program that does not include M&S is suboptimal
  • Serves as a safeguard to increase likelihood that:
    • Doses utilized are more likely to be safe and effective
    • Optimal doses can be identified as rapidly as possible, exposing fewer patients to suboptimal doses
    • Reducing the number of subjects required for trials

• M&S has proven to be part of the solution to making the enterprise of drug development more financially sustainable
  • Continues to advance and its impact will continue to grow