Using Clinical Pharmacology and Biology to Anticipate and Account for Differences in Safety and Efficacy Across a Population

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Office of Translational Sciences | CDER | US FDA

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Clinical Trials: Assessing Safety and Efficacy for a Diverse Population
In Memoriam

Dr. David Flockhart, Scientist, Teacher, Friend

Photo credit: Lauren Weghorst
Acknowledgments

- Dr. Anuradha Ramamoorthy
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- Dr. Robert Schuck
- Dr. Shiew Mei Huang
- Dr. Tom Colatsky
- Dr. Vikram Sinha
- FDA Office of Clinical Pharmacology and Partners
Themes

• Planning for Drug Response Variability
  – The Current Drug Development Paradigm
  – Reductionism and Integration

• Accounting for and Forecasting Drug Response Variability
  – Model-Informed Drug Development (MIDD)
    • Experience, Progress, and Challenges

• Beating Biology: Next-Generation Medicine
  – Precision Medicine Trends
  – Evolving Regulatory Policy

• The Complexity of Communication*

• Summary

* Not formally presented/discussed
Critical Path of Informed Decision Making

Development
- Safety
- Efficacy
- Quality

Review
- Benefit
- Risk

Action
- Access

Access
- Never
- Ever
- Yes

Use
- For Whom
- In Whom
- How
Drug Response Prediction:
From Game of Chance to Game of Skill

- Oncology: 25%
- Alzheimer's: 30%
- Incontinence: 40%
- HCV: 47%
- Osteoporosis: 48%
- Rheumatoid Arthritis: 50%
- Migraine: 51%
- Arrhythmias: 60%
- Asthma: 60%

Extrinsic
- Drug-drug interactions

Intrinsic
- Environment
  - Age
  - Race
  - Organ dysfunction
  - Disease
  - Pregnancy/lactation
  - Gender
  - Genetics
  - Others

- Medical practice
- Regulatory
- Others

Modified from Spear 2001 [PMID 11325631] | Huang and Temple 2008 [PMID 18714314] | Courtesy Dr. Michael Pacanowski [Figure 3]
Clinical Pharmacology in Drug Development and Evaluation

Pre-Clinical
- Chemical, MOA, Safety Characteristics
- Develop Bioanalytical Method
- In vitro metabolism, transporter, & DDI
- In vitro protein binding, cellular/tissue distribution
- Relevant animal/POC
- Target, mechanistic, &/or physiologic biomarker identification

Phase I
- First in human Dose-ranging studies Early PK/PD
- Early Food-Effect

Phase II
- Dose identification PK/PD in patients E-R/E-S
- Mass Balance
- In vivo DDI Extrinsic factors
- Food-Effect
- Renal/Hepatic Dx Intrinsic factors
- QTc study

Phase III
- PK/PD & E-R/E-S in target population (TP)
- Dose optimization Mitigation strategies in the TP
- BA/BE

Phase IV
- Labeling
- PMC/PMR
- Action
- Surveillance

Genomics
Pharmacostatistical Modeling & Simulation

Discovery Learn Confirm

“Dedicated” IEF Studies

Advantages
- Feasible
- Reduce noise
- Worst-case scenario
- Empirical
- Well-established
- Can be incorporated into real time development
- Decision support

Limitations
- Small, limited phenotype information
- Highly contrived
- Not systems-oriented
- Often not incorporated into real time development
- Not a nimble “lifecycle” management strategy
Labeling: PK/PD, Use, Dosing

* most gaps; † mostly popPK/more assessment needed; ‡ full complement of data
“Dedicated” IEF Studies

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Model-Informed Drug Development

- “Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making” (Lalonde)

<table>
<thead>
<tr>
<th>Indication</th>
<th>MBDD approach adopted</th>
<th>Efficiencies gained over historical designs and analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design</td>
<td>2,750 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Model-based dose–response relationship</td>
<td>1,000 Fewer patients</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Prior data supplementation, model-based dose–response relationship, sequential design</td>
<td>760 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Prior data supplementation, model-based dose–response relationship</td>
<td>120 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Model-based dose–response relationship</td>
<td>1,025 Fewer patients</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Model-based dose–response relationship</td>
<td>437 Fewer patients, increased probability of success</td>
</tr>
<tr>
<td>Global anxiety disorder</td>
<td>Omit phase IIb</td>
<td>260 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Lower urinary tract symptoms</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
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</table>

MBDD, model-based drug development.

- FDA identified MIDD as an important pathway for lowering drug attrition and dealing with regulatory uncertainty
Most modeling in regulatory review is currently exposure-based and done using sponsor data, supplemented as needed with basic information on disease processes, drug properties, and patient populations.

Courtesy of Dr. Tom Colatsky
Physiologically-based PK Modeling

Circulation Model, Krogh 1912

PBPK Modeling, Present

## PBPK: Current Status

<table>
<thead>
<tr>
<th>Applications</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td><strong>Drug-drug Interactions</strong></td>
<td></td>
</tr>
<tr>
<td>Drug as enzyme substrate</td>
<td>- Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling</td>
</tr>
</tbody>
</table>
| Drug as enzyme perpetrator | - Use to confirm the lack of enzyme inhibition  
- Additional evidence needed to confirm predictive performance for positive interactions |
| Transporter-based | - IV/IVE extrapolation not mature  
- Complicated by transporter-enzyme interplay  
- Predictive performance yet to be demonstrated |
| **Specific populations** | |
| Organ impairments (hepatic and renal) | - Predictive performance yet to be improved  
- System component needs update |
| Pediatric | - Allometry is reasonable for PK down to 2 years old  
- Less than 2 years old ontogeny and maturation need to be considered |
| **Additional specific populations and situations** | |
| Pregnancy, race/ethnicity, geriatric, obesity, diseases  
Food effect, formulation change, pH effect  
Tissue concentration | - Limited experience to draw conclusions |
Needs/Challenges with Model-Informed Strategies

• End-users are typically not modelers
  – Don’t have the bandwidth to explore the specifics of model construction and validation
  – If I make a decision based on this readout, am I making the right/best/best informed decision?
  – These end users (including regulators), in general, lean toward a lower level of risk tolerance
  – A reality that needs to be considered in framing all aspects of the scientific and drug development/regulatory dialogue

• Transparency: identification and communication of assumptions and knowledge gaps
  – PopPK, E/R – “Industry Standard” needed
  – Unlikely that PBPK is currently fit-for-purpose for all contexts of interest
  – Articulating, as a community, where our comfort lies is critical

• Best practices for community endorsement of [mechanistic] models for a variety of uses (including regulatory)
  – Qualification or validation
  – Development of performance/sensitivity analysis metrics
  – Need for ensuring platform-independence of findings
  – Risk-based regulatory evaluation should be risk-based: plan, waive, interpret, translate studies
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Precision Medicine Trends

Guidances/White Papers in the double digits
PM strategies increasingly being used
Approvals increasing

Plenge [PMID 23868113]
Nelson [PMID 26121088]
Zineh [PMID 21923598]
Investigational Drug Landscape

Estimated volume of meeting packages and protocols with biomarker-based objectives (e.g., enrichment, stratification, endpoints) based on ~1700 electronic submissions, May 2014-Mar 2015

Courtesy Dr. Michael Pacanowski
Patient Subset Effects – Targeted Therapy Approaches

Multimodal PK

High Variability

Race Effects

Therapeutic effects

NTI

Toxic effects

Safety

Case 1

ALT/SGPT

ALT/SOT

Bili

Transaminase (U/L)

Total Bilirubin (mg/dL)
### Characteristics in Support of Targeted Drug Development

<table>
<thead>
<tr>
<th>Biomarker is the major pathophysiological driver of the disease to be studied</th>
</tr>
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<tr>
<td>Limited or adverse paradoxical activity of the drug is seen in a subgroup identified through in vitro or animal models (e.g., cell lines or animals without the biomarker)</td>
</tr>
<tr>
<td>The biomarker is the known molecular targeted of therapy</td>
</tr>
<tr>
<td>Preliminary evidence of harm from early phase clinical studies in patients without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of lack of activity from early phase clinical studies in patients without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of modest benefit in an unselected population, but the drug exhibits significant toxicity</td>
</tr>
</tbody>
</table>

Zineh and Woodcock 2013 [PMID 2357177]
A Holistic (Pharmaco-biologic) View

- Communicate
  - Quantify value
    - Empirically
    - Modeled
  - Characterize/Account for Variability
    - PK
    - PD
  - Characterize Effects
    - Systems approaches
  - Define Disease
    - Model Disease
    - Subset Pathologies
    - Subset Patients

Zineh and Woodcock 2013 [PMID 2357177]
The Role of Clinical Pharmacology in Reducing Uncertainty

“I took a test in Existentialism. I left all the answers blank and got 100.”

— Woody Allen