Impact of PK/PD, Disease Models and Personalized Medicine to Influence FDA Decisions

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Declining Morbidity and Mortality among Patients with Advanced HIV Infection

The NEW ENGLAND JOURNAL of MEDICINE
Viral load suppression is predictive of mortality benefit

HIV Treatment: Controlling concentrations yields superior benefit than fixed dose

![Graph showing the percentage of patients with HIV RNA <500 copies/mL over weeks for concentration-controlled and fixed-dose treatments. The concentration-controlled treatment shows a higher percentage of patients achieving this criterion from the start and maintaining it over time, compared to the fixed-dose treatment.](image-url)
Predictor of Virologic Response to Ritonavir-Amprenavir in HIV Protease Inhibitor Experienced Patients
Case 1. Tipranavir
Debate at Advisory Committee & Beyond

Jenny J. Zheng, Joga Gobburu, Kellie Reynolds

Sponsor: 500 mg twice daily for everyone

Vs

Individualize dosing based on trough drug concentration & IC$_{50}$ (IQ)
$C_{\text{min}}$ in Phase 2 and Phase 3 at Different Doses
TPV $C_{min}$, IC$_{50}$, T20 co-administration significantly influence viral response

For IQ $\geq$ 100, 54% responded to TPV and 73% responded to TPV+T20
For IQ $<$ 100, 21% responded to TPV and 52% responded to TPV+T20
Possible Therapeutic Drug Monitoring Strategy

Measure IC\textsubscript{50} at baseline

Determine C\textsubscript{min} at wk 1, 2 or 3

Is IQ>100? Is tolerable?

Yes/Yes 
Continue 500/200 mg

Yes/No 
Dose ↓

No/Yes 
Dose ↑

No/No 
Alternative treatment
Reasons given for not changing

• Commercial drug assay not available
• IC$_{50}$ phenotype too expensive (~$700)
• Reimbursement
• Prospective trial needed to test hypothesis: HIV protease resistant patients benefit from IQ testing
• Implementation variation in clinical practice
• *Hidden elephant*: marketing
Dilemma

• Inside FDA Clinical Pharmacology was proposing changes. Clinical Division (OND) did not agree in this instance, but has agreed to study the issue
• Company did not agree
• How will the issue be resolved?
• How can FDA and clinicians bridge the regulatory……clinical gap to treat (e.g., dose) individual patients, not populations?
What do we really want?

- Patients/Health Professionals
  - Health
  - Effective drugs @ affordable cost

- Drug Companies
  - \( \uparrow \) Profits \( \rightarrow \) better drugs & \( \uparrow \) #
  - One dosage regimen for all

- FDA
  - Promote public health
  - \( \uparrow \) Productivity (process & very effective drugs) & \( \downarrow \) toxicity
  - Personalized medicine
Outline

• How FDA makes decisions
• High attrition, high cost, low productivity
• Model based drug development
  – Disease models
  – Modeling & simulation
• People development
• IND- application to give drug to humans based upon
  • Toxicology
  • PK/DM
  • Chemistry/Formulation
  • 1st Human protocol

Key question: is this drug safe to administer at doses, rates, routes in 1st protocol?

• Pre-IND meeting option
  • Approval endpoints
  • Development strategy
  • Target product profile strategy
  • Dose finding

• NDA-application to market new drug, dosage form, indication
  • IND information + gene tox + carcinogenicity
  • Clinical trial evidence of efficacy & safety
NDA (new drug application) Review Process

3 NDA Types

• Standard-10 month clock
• Priority-6 month
• Accelerated-<10 month, oncology/HIV unmet medical needs

Sponsor files NDA
- Filing Decision 60 days
- Key questions alignment within

Time 0

Clinical Pharmacology Review
6 weeks before action date or 2 weeks before AC

Advisory Committee Decision (NMEs)
12 months before action date

Action Date, Approval Decision
- Approve
- Approvable
- Not Approve
**NDA Decision Process**

Regulatory Briefing option (CDER senior staff)

Office Director (MD) (NCEs)

Therapeutic Division Director (MD) (e.g., Cardiorenal)

OND Team Leader (MD)

NDA Review Team

- Physician
- Clinical Pharmacologist
- Statistician
- Pharm/Tox
- Chemist
- Project manager

Advisory recommendations
Reasons for Poor Decisions

(Definition: an outcome which should/could have been anticipated)

- Conspiracy of optimism
- Framing the problem too narrowly to bring it inside my own comfort zone
- Not involving the right people
- Avoiding uncertainty
- Ignoring information I do not understand
- Being attached to ‘sunk costs’ – high spent development costs
- Ignoring risks
- Assuming no uncertainty in potential outcomes
- Making decision alone

10 Big PhRMA Companies

1 Driver for Clinical Trial M&S
Declining Success Across Clinical Phases

Science 309:726, 2005
50% Clinical Trial Failure Rate: Is it true? What to do?

OBJECTIVE:
Accommodate known failure sources (prior information) in clinical trial design

Root Cause
- Ø Efficacy
- ↑ Toxicity
- Placebo
- Baseline
- Dropouts
- Patient Selection
Case 2: Reducing Disease Biomarker Concentration → Lower Risk of Disease Exacerbation Irrespective of Treatment
Drug Reduces Biomarker Levels (Median)

Study X

Median Biomarker % Change

Placebo

Drug

0% - 37%
Greater Reduction in Biomarker Level Is Required for Significant Benefit

Assumptions
- Bm predicts disease exacerbation
- Largest slope
- Bm no change in placebo
- Bm↓ 37% 2° Drug
- n=150/arm
- 22% exacerbation with placebo
Higher Doses Associated with Greater Biomarker ↓

Study X

Biomarker % Reduction

Dose (mg/day)
**Duodenal Ulcer Healing Rate in Active (Cimetidine or Ranitidine) vs Placebo** (n=83 studies)

Placebo Response in Depression

JAMA 287: 1840-7, 2002

↑ trial failure risk

↑ false positive risk
Clinical Drug Development
Shifting Paradigm

Historical, Discipline-based Model (Phase)
1. Pharmacokinetics (1)
2. Pharmacodynamics (1,2)
3. Dose-Response (1,2)
4. Disease Application (2,3)

Contemporary, Therapeutics-based Model
1. Disease Model
2. Dose-Response
3. Pharmacodynamics
4. Pharmacokinetics
IMPACT OPPORTUNITIES- MODEL & SIMULATE KEY DECISIONS

COMPANY → TRIAL DESIGN (2, 3), GO/NO GO, LABELING, FORMULATION, COMBO’S, PEDS

FDA → TRIAL DESIGN (2, 3, 4), NDA APPROVAL (BENEFIT/RISK, DOSING REGIMEN), LABELING, APPROVAL CRITERIA (GUIDANCE REVISION), FORMULATION, COMBOS, QT STUDIES, PEDIATRIC WRITTEN REQUESTS
Biomarker Model
The Ultimate in Personalized Medicine

Patient Drug Response ≈ Disease Gene Marker + Biological Markers (Efficacy, Toxicity) + Drug Markers Gene Concentration + Imaging Marker

- Disease present?
- Receptor subtype present?

- Cell, protein, antibody, small MW chemical, physical measure
  - linked to endpoint outcome for efficacy or toxicity

- [Drug],
- Inhibitory concentration 90%
  - e.g., antiviral protease inhibitors

- PET, MRI,..
- Physical direct evidence for change
Modeling & Simulation Influences All Lives Today

- Weather forecasting
- Global warming scenarios
- Finance
- Engineering
  - Plant design
  - Product design
    - Airplanes
    - Cars-crash testing
    - Bridges
    - Microprocessors
    - Widgets
  - Traffic flow-roads
- Homeland Security
  - Disaster preparedness scenarios
  - Plague
- Military
- Space
- Energy
- Medical
  - Rx patients
    - Surgery
    - Diagnostics (MRI,...)
  - Education
  - Devices (hip, knee,..)
  - Drugs
    - Molecular design/receptor
    - Formulation
    - Manufacturing
    - Marketing
  - Forensic reconstruction
The Ultimate ‘Learn-Confirm’ Paradigm
Boeing JSF Modeling and Simulation Breakthroughs Reduce Program Risk, Cost

SEATTLE, Wash., Oct. 04, 2001 -- Boeing today unveiled details of a comprehensive modeling and simulation architecture that assures new levels of affordability. Demonstrated during the Joint Strike Fighter program's concept demonstration phase, these improvements will make the Department of Defense's long-standing vision of simulation-based acquisition a reality.

Combining benchmarks achieved on its 777 and Next-Generation 737 commercial aircraft, C-17 airlifter, Apache helicopter and other programs, the new Boeing JSF architecture incorporates what previously were separate, stand-alone modeling and simulation tools into an overall integrated system.

"The importance of modeling and simulation in reducing risk can't be emphasized enough." Statkus said. "We were able to eliminate the majority of bugs before we ever built or flew the X-32 aircraft. Excellent software models and revolutionary control law development made the changeover from the lab to flight test incredibly simple."
Modeling & Simulation

Why?

- Decrease bias & risk in decisions
- Overcome complexity (simultaneously thinking about many factors influencing outcome)
- Increase quality
- Decrease cost
- Decrease time
Modeling & Simulation

Modeling & Simulation Process

Collect Relevant Information

Organize into Model(s)

Simulate Outcomes or Scenarios

Predictive check

Act

Results

• Complex
• Multiple dimensions
• Raw data best

Learning

• Decision
• Prediction
• Teach
• Design
• Entertain

• ↑ Risk
• Expensive
• Important
Case 3. **Type 2 Diabetes Drug**

Jaya Vaidyanathan, Hae-Young Ahn, Dong Yim, Jenny Zheng, Yaning Wang, Joga Gobburu, Todd Sahlroot, David Orloff

- Topic: Phase 3 trial design when 3x genotypic drug clearance difference
- UGT2B15 metabolic enzyme frequency distribution (N=374)
  - *1/*1 21%  
  - *1/*2 52%  
  - *2/*2 27%  
    - Extensive metabolizers (EM’s)
    - Poor metabolizers (PM’s)
- Indication: Type 2 diabetes mellitus
- Mechanism of action: PPAR_{x,y,z} agonist
- ↓ FPG & HbA1c
- ↑ weight
Modeling Strategy

- Pharmacokinetics
  - Phase 1 data for population PK model
  - Phase 2 data for model update

- Pharmacodynamics (FPG and HbA1c)
  - Model from FDA clinical trial data
  - Simultaneous modeling FPG and HbA1c
  - Models updated with sponsor data
Diabetes

\[
\frac{dFPG}{dt} = K_{in} - K_{out} \left(1 + \frac{E_{max} \cdot C}{EC_{50} + C}\right) \cdot FPG
\]

\[
\frac{dHbA1c}{dt} = K'_{in} \cdot FPG - K'_{out} \cdot HbA1c
\]

Bill Jusko’s model
Modeling Results for FPG & HbA1C

Drug X in 1,000 patients

FPG

Observed FPG (mg/dL)

Week

-10 0 10 20 30 40

0 100 200 300 400 500

HbA1c

Observed HbA1c (%)

Week

-10 0 10 20 30 40

4 6 8 10 12 14

4 6 8 10 12 14

4 6 8 10 12 14

0 100 200 300 400 500

0 100 200 300 400 500

0 100 200 300 400 500

0 100 200 300 400 500

Observed DV

Observed DV

Observed DV

Observed DV

PRED

IPRE

PRED

IPRE

PRED

IPRE

PRED

IPRE

PRED

IPRE
We made up a Hybrid Dataset

- Drug X (Sponsor) in 72 patients
- Drug X (other) in 28 patients
- Hybrid dataset in 100 patients
Model Fits
(individual patients)

FPG, mg/dL

HbA1c, %

*1/*1, X mg

*1/*2, X mg

*2/*2, X mg

Time, weeks
Enrichment by Genotype

(Genotype 1st, Parallel Dose, Placebo Control)

100 Patients = 27 *2/*2, 52 *1/*2, 21 *1/*1

PM

EM

Dose mg/day

PM

EM

4X

12X

2X

6X

X

3X

PBO

PBO

0

26

Time (weeks)
**HbA1c Change from Baseline at Week 26**
*(naïve only, no placebo effect)*

- PM response ~ EM response @ 3X dose
- Dose-response evident
- BID better than QD
Enrichment by Response
Randomize Low Dose Non-Responders (FPG ↓ <1.5 mmol/L) to Med and High Doses

% Non-responders at week 12 (FPG ↓ <1.5 mmol/L)

<table>
<thead>
<tr>
<th>Simulation</th>
<th>2 Sponsor trials X mg QD</th>
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<tbody>
<tr>
<td>*1/*1 EM</td>
<td>70</td>
</tr>
<tr>
<td>*1/*2 EM</td>
<td>64</td>
</tr>
<tr>
<td>*2/*2 PM</td>
<td>45</td>
</tr>
</tbody>
</table>

Time (weeks)

0 12 26
Recommendations & Follow-on Thoughts

• Trial Design Strategies:
  a) Enrichment by genotype: stratify into parallel dose
    • Dose selection: X & 2X mg daily doses for PM’s are informative (naïve + experienced)
    • BID performs better than QD, more so in EM’s
    • Sustained release could help
  b) Enrichment by response
    • Further evaluation by M&S if sponsor is interested.

• FDA analysis sent to sponsor
**Drug-disease models at FDA**

- **Primary sources:** literature, scientists, prior NDA’s
- **Types**
  - Mechanistic
  - Empirical
- **Diseases over past year**
  - HIV
  - Diabetes Mellitus
  - Parkinson’s Disease
  - Vasomotor Symptoms (Hot Flashes)
  - SLE-renal flare
  - Prostate Cancer- chemical castration
  - Kidney transplant rejection
- **In Development**
  - Osteoarthritis
  - Non-small cell lung cancer
- **Considering**
  - How to share models & some data on public website. Public dialogue on growing models
People

– Attributes
  • Quantitative skills (Clin PK/PD, Biostats, Engineering)
  • Clinical Judgment
  • Teamwork
  • Communication

– Training
  • New hires
  • Fellows
  • Sabbaticals
Ideal Pharmacometrics Training Location

300+ Companies
INDs & NDAs

'Measure'
• Disease change
• Safety change
• Dose-response
• Personalize

'Short cycle time'

'expresso'

'Answers count: High Impact'
Personal Impact Triangle

Primary Skill
(e.g., PK/PD)

Application
(e.g., Epilepsy)

People Skill
(e.g., Negotiation)

Skill High Low
A-B Knowledge, Judgment Effectiveness
A-C Influence Judgment
A-B-C Wisdom, Influence, Effectiveness, Impact
Closing Thoughts

• Technology & Leadership drive opportunity
• Dose-response still important source of drug development failure & toxicity once drugs are on market
• These problems are real, not abstract & provide a great mission for a career
• Impact is education & more