Disclaimer and Acknowledgments

– Disclaimer
  • Views presented herein are mine alone, and do not necessarily reflect those of Quintiles
  • All examples presented have been modified (new endpoints, new indication, etc.) to protect client confidentiality

– Acknowledgments
  • Would like to share my appreciation for my colleagues James Powers, Seth Berry and Michael O’Kelly who agreed to let me share their case studies
Talk Outline

– Traditional drug development
– Industry trends that make traditional development inadmissible
– Model-based drug development (MBDD)
  • What is it?
  • Some examples applied to specific trial design
  • Work we are doing to establish its benefit on drug development programs
– Organizational issues with moving to the MBDD paradigm
– Questions and your comments
How We Develop Drugs

Traditional approach
Statistical Models by Phase

PK Models (NCA)
Safety look in small cohort

Analysis of Variance
Lower power
Safety summarized

χ² test, CMH, t-test, or ANOVA
High power
Safety summarized
Why isn’t this good enough now?

– More financial pressure to succeed
  • Less resources (time, money, people) to work on trials
– More difficult to find novel drugs
– Standards have risen
  • tQT now required
  • Subpopulations
    – Pediatric
    – Renal or hepatic impairment
    – Safety is more of a concern
  – Regulatory requirements have gone up
    » 1996: > 50 NME approved by FDA, average cost $400 M
    » 2012: < 25 NME approved by FDA, average cost $2.5 B
Drugs Aren’t Progressing

– Phase II failure rate increasing
  • 2006: 72% failure rate
  • 2008: 82% failure rate
    – 51% failed due to efficacy
    – 17% failed due to safety
    – 29% failed due to strategic reasons
  • 2008: 18% progression

– Phase III failure rate increasing
  • 2008: 50% failure rate
    – 66% failed due to efficacy
    – 21% failed due to safety

$400 M trial for Phase III
Business Model Not Sustainable

– Payors are pressing to hold down costs
– Development costs going up
– Time pressure to get drugs to market faster
  • First mover advantage
    – Studies have not shown it to be real, but management believes it
  • Operational focus
    – Aggressive FPI, LPO timelines
    – Protocol writing: Hurry up and wait
– In a nutshell
  • Simple analyses
  • Not much integration of data (e.g., efficacy and safety)
  • Dosing regimens chosen by medical leads based on intuition
  • Phase II’s are practice for Phase III
Recap

– Traditional approach
  • Simple statistical analyses without predictive ability
  • Not much integration of data (e.g., efficacy and safety)
  • Dosing regimens chosen by medical leads based on intuition and similarity to existing products
  • Phase II’s are practice for Phase III
  • Silos among disciplines
MBDD Can Help

– Model-Based Drug Development
  • Using mathematical/statistical/computational models to represent biology and treatment practice
    – Includes PK, PD, dose-response
  • Analyses more complex
    – Nonlinear mixed-effect models (alias: population models)
  • Efficacy and safety data can be incorporated into a single, large model
  • Phase II’s are not practice for Phase III, but are to gain knowledge
  • Integrate domain knowledge from several disciplines
MBDD Across Phases

Phase I and II are learning phases
Phase I and II are learning phases, where knowledge of the drug effects improves over time.
Phase I and II are learning phases, where knowledge of the drug effects improves over time.
Model-Based Drug Development: What Is It?

MBDD is the development of integrated analyses (models) of available data (i.e., internal and external sources) and their application to inform strategy, trial design, and decision-making in drug development.

MBDD goal is to utilize internal and external data in a quantitative manner to improve drug development strategy and decision-making.

Examples of Models in MBDD
Randomized Concentration-Controlled Trial

- Mycophenolate mofetil was being developed for kidney transplant, but the drug was renally cleared
- Need to control blood concentrations to establish benefit
- Developed PK/PD model relating dose to AUC, and AUC to \( P(\text{rejection}) \)
RCCT

– $P(\text{Organ rejection}) = a + \frac{d}{1 + \exp(-b[\log \text{AUC} - c])}$
– AUC = $\gamma_1 + \gamma_2 \text{dose}, \gamma_1 \sim N(0, \nu^2)$

– Randomize to AUC levels
– Visit 1
  • Dose subject
  • Collect blood draws, get AUC
– Visit 2
  • Bayesian adjustment to dose
  • Dose subject
  • Collect blood draws, get AUC
– Visit n
RCCT

– Simulated trial parameters
  • Sample size
  • Dose adjustment limits
  • Effect of maximum dose
  • Analysis methodology for test $H_0$: Flat curve
– Other results from simulation as well
  • Number of tablets of various sizes

– Successful trial
Case Study 1: Program Simulation

– Several options for design Phase Ila and Phase IIb
– For simplicity, we will focus on sample size and doses here
– Objective was to pick doses to carry into Phase III that maximized the probability of success (P<0.05 in Phase III)
– Sample size was constrained to be 1000 in Phase IIb and 1000 in Phase III
Case Study 1: Strategy #1: Original Plan

Phase IIa
- Active dose
  - 1: 12
  - 2: 12
  - 3: 12
  - 4: 12
- Placebo
  - 6

Phase IIb
- Active
  - 500 subjects
- Placebo
  - 500 subjects
- 20

Phase III
- Active
  - 500 subjects
- Placebo
  - 500 subjects
Case Study 1:  
Strategy #2: Use Many Doses In IIb

Phase IIa

Active dose
1  2  3  4

12 12 12 12

6 6 6 6

Placebo

Phase IIb

Active

200 200 200 200

Phase III

Active

500

Placebo

500

Placebo
Case Study 1:
Strategy #3: Use Two Safe Doses From IIa

Phase IIa

Active dose
1 2 3 4
12 12 12 12
6 6 6 6

Placebo

Phase IIb

Active
333 333
500

Placebo

Phase III

Active
500
500

Placebo
Case Study 1: Scenario Analyses
Scenarios to cover best cases…
Case Study 1: Scenario Analyses

Scenarios to cover best cases...

... through to worst cases
Case Study 1: Scenario Analysis Results – Phase III Success

Scenarios with viable doses

Scenario 1

Scenario 2

Scenario 3

Scenario 4
Case Study 1: Scenario Analyses Results – Stopping In IIb

Scenarios with no viable doses
Case Study 1: Summary

– Seven safety+efficacy scenarios simulated to assess risks and benefits
– 3 strategies assessed, fourth ongoing
– Simulations are focussed on giving the multifunctional development team what it needs
  • e.g. Idea for strategy #3 came as a result of team discussions of simulations of strategies #1 and #2
– Simulations facilitate development team in thinking productively about new strategies
Case Study 2: Modeling Study Startup Methods for Cycle Time Distribution Estimation

Time to Site Start Up: Distribution Based on Recent Historical Data

Leverages Quintiles Historical Data
Case Study 2: Study Startup Simulation of Process

User Defined Input

HISTORICAL DATABASE

REPEAT R TIMES

HISTORICAL DATABASE

By Variable

Cumulative Curve

Target Distribution

Cumulative
Curve

Time

n

Time

n

By Variable

1

2

3

1

2

3

REPEAT R TIMES

Target Distribution

68.27%

95.46%

99.73%

Historical Distribution
Case Study 2: Study Startup Simulation of Process

– Country differences
  • Use to optimize distribution of patients among countries

– Adjust based on trial data
  • Can increase sites, plan additional or scale back recruitment, based on predictions from current data combined with historical performance

– Reduced time to LPLV substantially
Case Study 2: Example Results
Case Study 2: Study Startup Simulation of Process

– Country differences
  • Use to optimize distribution of patients

– Adjust based on trial data
  • Can increase sites, plan additional or scale back recruitment, based on predictions from current data combined with historical performance

– Reduced time to LPLV substantially
Case Study 3: Biomarker Modeling

- **Population:** Patients Infected with a Specific Type of Virus
- **Treatment:** New Molecular Entity (NME)
- **Problem:** Multiple Biomarkers Related to Efficacy of NME; Which Ones Predict Best?

  What’s the Dose-Response Curve Look Like?
  Should We Screen the Biomarkers to Enhance the Power of the Study, or is it Quicker to Include All-Comers?

- **Methodology:**
  - Model Fitting to Find Biomarkers
  - Dose-Response Modeling to Fit the Curves
  - Trial Simulation (Clinical and Operational) to Answer Questions of Inclusion / Exclusion Criteria
Case Study 3: Biomarker Modeling

- **Results**
  - Found 5 biomarkers predictive of patients most likely to respond to therapy
  - Response is function of number of biomarkers present
  - Dose-response curve was evident (statistically significant)
  - Depending on recruitment rate, could use biomarkers to enhance the probability of success in trial design
Case Study 3: Impact

- Targeting concentration of 30 (have PK model as well)
- Inclusion
  - All Comers (N=82 for 80% power)
  - Best 2 inclusion groups (N = 22)
  - Best 1 inclusion group (N = 16)
- What is the preferred I/E criteria?
  - Will approach through simulation
  - Other variables could be included, including differential drop out rates, etc.
Case Study 3:
Biomarker Modeling: Options for planned studies

All Comers (N = 82)

Top 2 Groups (N = 22)

Top Group (N = 16)
Case Study 4: Disease Progression Modeling & Simulation

- **Problem:** Need to Design Studies in Rheumatoid Arthritis (RA)
- **Constraints:** Rarely Enough Data to Support One-Off Modeling
  Preferred Endpoints Not Consistent Between US and EU
- **Methodology:** Construct Dose- and Time-Response Models in RA for Several Different Endpoints
  Model Constructed in Pharsight’s Trial Simulator for Quick Deployment to Design Trials
  Developing Models for etanercept, adalimumab, tocilizumab, anakinra, CZP, golimumab, infliximab, abatacept
  Development Used for Comparators in Simulations and Experience with Similar Compounds Applied to a Novel Compound

17 December 2012 Copyright 2011 - Quintiles
Case Study 4: Disease Progression Modeling & Simulation

- **Client Uses**
  - Tocilizumab Example
    - Model for other compounds also
  - Model Incorporated into Several Trial Simulations
  - Plan Biosimilar Program
  - Utilize Adaptive Design
    - PK BE
    - Followed by Sample Size Re-estimation
  - Apply Design Changes When Changing Endpoints (ACR20 to DAS28)
Case Study 4: Disease Progression Modeling & Simulation

Drug/Dose Effects

ACR20 Response (percentage)

Time (week)

- Low Dose
- Medium Dose
- High Dose
Case Study 4: Impact

- Models used to design biosimilar trials
- Used as inputs into trial simulations
  - Design then optimized for length of trial, number of subjects, statistical analysis method, missing data handling, etc.
- Reduced proposed sample sizes
Success and Failure

Lessons Learned
Roche's RoACTEMRA monotherapy showed superior improvement in rheumatoid arthritis signs and symptoms versus adalimumab monotherapy.

Statistically significant greater improvement in signs and symptoms, as measured by mean change in DAS28 (primary endpoint), DAS28 remission and low disease activity, ACR20, 50 and 70 (secondary endpoints).
Recall Case Study 4: Focus on just adalimumab and tocilizumab

Our model uses methotrexate as background versus monotherapy in the Roche study, but we still predicted the results.
Biologic PK/PD Model (betaseron)

- Used to treat multiple sclerosis
- Broad dose-response curve
- Never could develop a model to predict behavior beyond ANOVA model
Approval of gabapentin

Gabapentin

- Originally approved for partial seizures of epilepsy in 1993
- Sponsor was seeking approval for post herpetic neuralgia
- Two trials conducted
  - Trial 1: placebo, 3600 mg/day
  - Trial 2: placebo, 1800 mg/day, 2400 mg/day

Food & Drug Administratino Modernization Act 1997 (10,11), states in Section 115: “... based on relevant science, that data from one adequate and well controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness.”

Source: Miller et al (2005)
Approval of gabapentin

Source: Miller et al (2005)
Approval of gabapentin

- **Result**
  - Additional confirmatory trial not needed
  - Modeling provided the additional evidence needed for approval
  - Drug approved for this indication

Source: Miller et al (2005)
Lessons Learned

- Models can predict clinical trial results
  - Need to spend effort to develop the models
  - Model becomes increasingly useful as it is being built
- For some compounds, not useful
  - Chiefly those with very broad dose-response curves, or binary effects
- Haste makes waste
Organizational Issues and Benefits
Expectations need to be properly set

– MBDD and adaptive trials are not faster for an individual trial

– MBDD and adaptive trials are:
  • Faster for the program
    – Bridging based on models to avoid trials
    – Better identification of “good” doses
  • Increase chances of success

– Need access to people trained in the methodology
  • Technical skills: Statisticians, kineticists, pharmacologists, clinicians
  • Organization: Project managers, senior executives
  • Affected: Monitors, data managers, outsourcing executives, regulatory
Model Based Drug Development:  The Return on Investment

- Dr. Richard Lalonde (Head of Clinical Pharmacology, Pfizer) at American Conference on Pharmacometrics, 2008

  • “Enhanced Clinical Trial Design (ECTD) initiative reduced the cost of our Phase 2 and 3 trials”
  
  - **SAVINGS of $75M in 2006 and $100M in 2007**
  - Joint Effort of Clinical Team and Pharmacometrics Group
  - Most Savings: Smaller Dose-Response Studies
    - Based on Dose-Response Models vs Pair-Wise Comparisons
  - Interim Analyses to Stopping Trials Early for Futility.
  - Time Savings to Conduct Studies with Fewer Patients

- **Overall Metric:**

\[
\text{All Phase 2/3 Trials Clinical Cost} \div \text{Number of Successful Phase 3 Trials (Aggregated Over 3 Years)}
\]
Benefits

– Improves communication across disciplines
– Helps define what we know and how certain that knowledge is
– Can utilize many data domains to improve drug development
– Better decision making
Conclusions

– When properly implemented, MBDD and adaptive trials:
  • Speed up development
  • Improve decision making
  • Improve probability of success
    – Kill assets that need to be killed
    – Develop assets fully that should be fully developed
  – Benefits accrue most when used across whole development
  – Already used for label claims
  – Has proven use in reducing the number of trials in drug development (e.g., Miller et al 2008)