

Integrated Quantitative Modeling Approaches to Facilitate Drug Development Decisions

Mark Lovern PhD and Marc Pfister MD

Quantitative Solutions , NJ, USA

June 14 2011

Our New Challenge in Drug R&D

- The “4th Hurdle”: *where traditional evidence-based medicine and economic values intersect*

Hurdles 1, 2, 3 means companies require to assure

- **Efficacy**
- **Safety**
- **Manufacturing Quality**

Hurdle 4 means companies require to demonstrate

- **Cost-effectiveness***

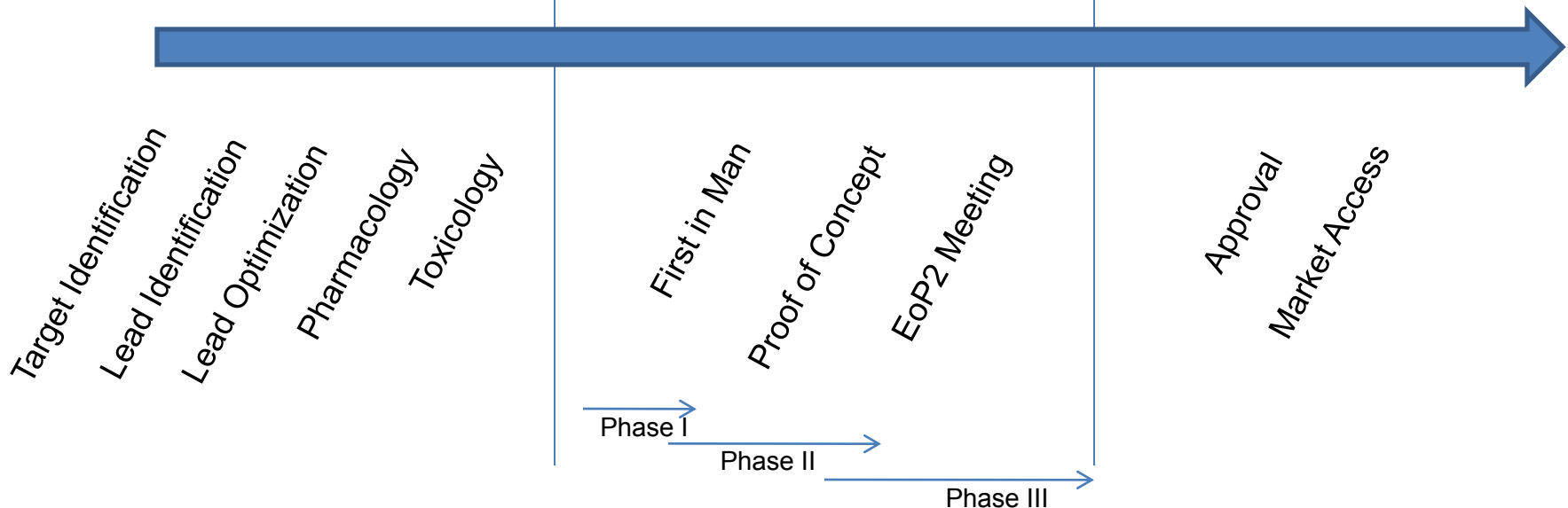
* Driven by the high cost to pay by healthcare providers (incl. government) and tax payers in countries like US and in Europe; i.e. value for money

How Do We address This? By Utilizing **Quantitative** Approaches to Optimally Inform Development Decisions

Which candidates are most likely to succeed?
What biomarkers should we capture?
What dose range is needed to compete with the leader in this drug class?

What indications are most promising?
What is the optimal dose?
What is our drug's product profile relative to competitors?

How do we differentiate our drug in the market place?
How do we facilitate market access?
What other indications is the drug likely to succeed?



Model-based Drug Development (MBDD) is a Paradigm for Systematically Integrating **Quantitative** Decision Making into R&D



Biology

**Biomarkers/
outcome relationship**

Natural progression

Placebo effect



Pharmacology

Effectiveness

Safety

Preclinical/Healthy

Patient

Product Features



Patient Population

Drop-out

Adherence

Source: Gobburu & Lesko, FDA, 2009

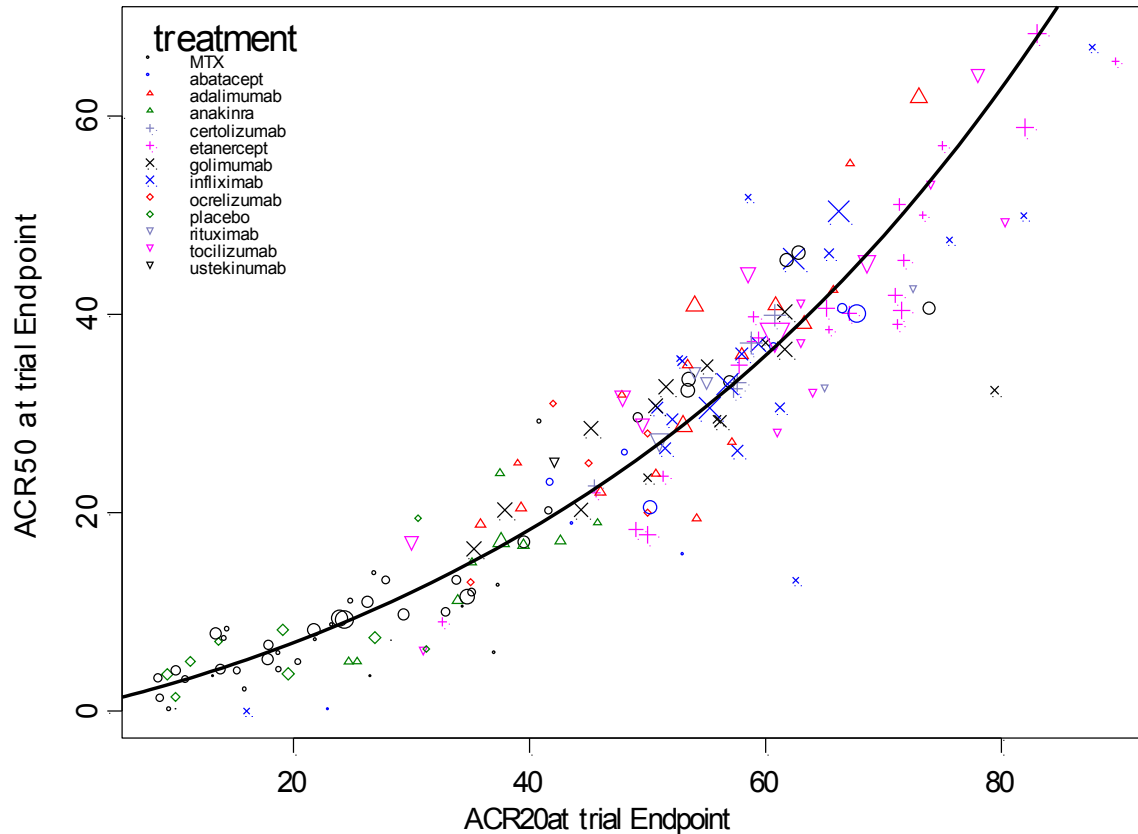
Quantitative Model-based Meta-analyses

Two Case Studies Prepared by

Mark Lovern PhD and Marc Pfister MD
Quantitative Solutions

Case Study 1 – Understanding RA Endpoints by Leveraging External Therapeutic Area Data

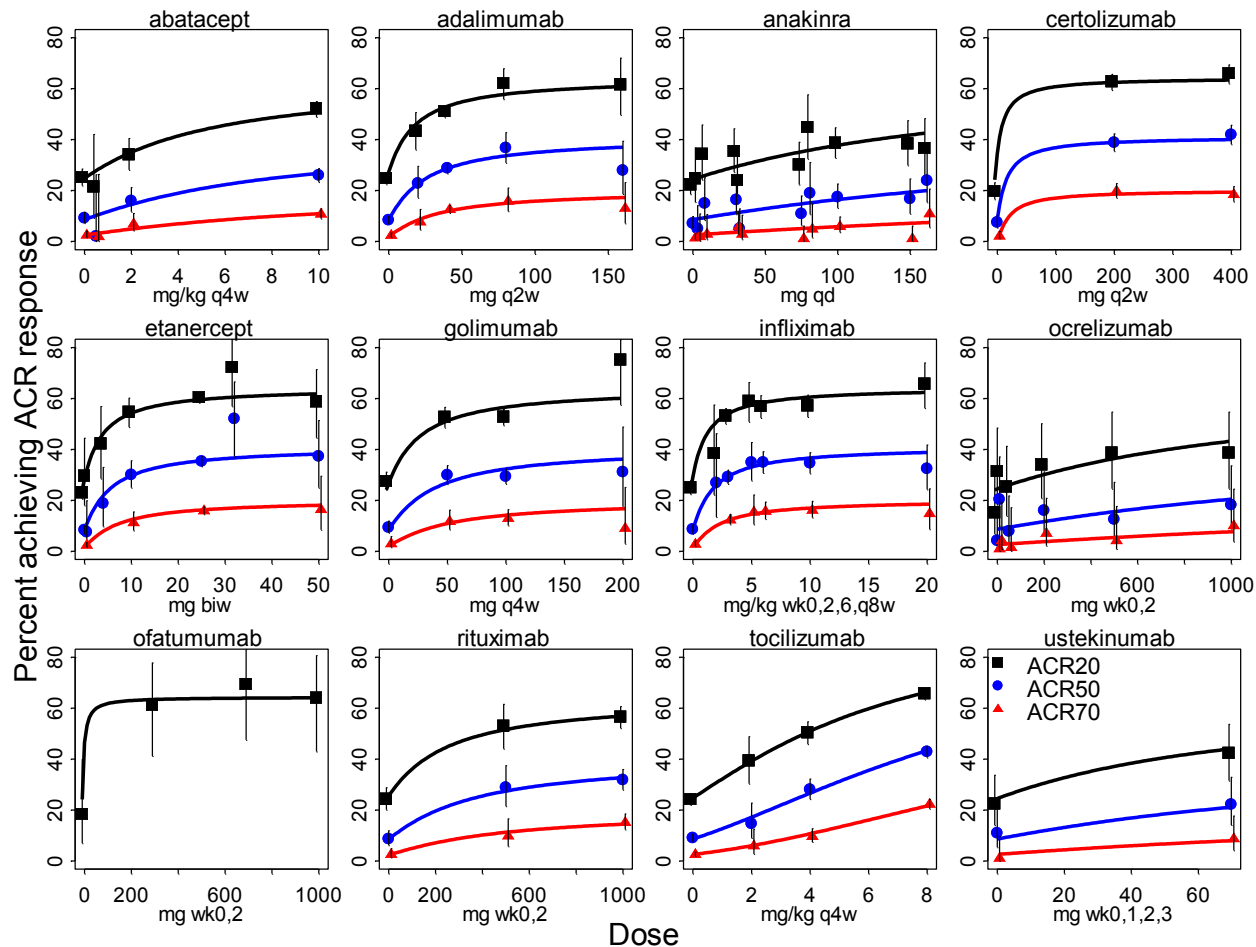
Question: Is there a consistent difference in the dose response relationship for ACR20 and ACR50 across drugs or drug classes?



Approach: Use the ACR time course (or other trial outcome data) to jointly analyze the dose response relationships for ACR20 and ACR50 and quantify the difference in placebo response, ED50 and Emax by drug and drug class

Case Study 1 – Understanding RA Endpoints by Leveraging External Therapeutic Area Data

Results: Dose response relationships were identified and best described by an E_{max} model. The relationship between ACR20, 50, and 70 was similar for all evaluated compounds.



Case Study 2 – Guiding Phase 2b Dose Selection By Leveraging Comparator Data*

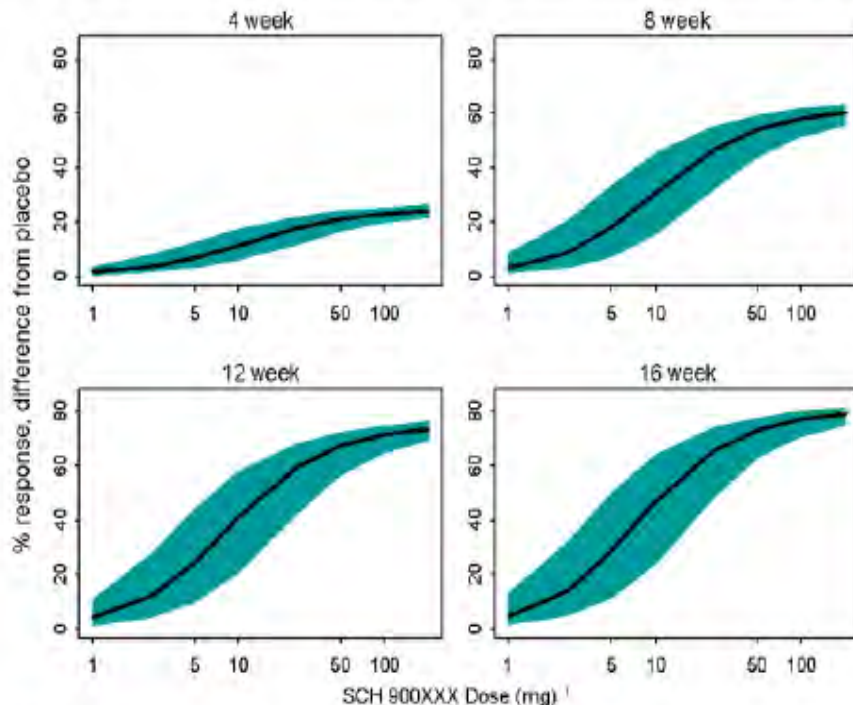
Objectives: Selection of dose levels for Phase 2b development resulting in an optimal probability to: (1) establish the plateau of the dose-response curve, (2) demonstrate a dose-response relationship, (3) determine the lowest dose resulting in maximal efficacy.

Methods: SCH 900XXX is a high affinity antibody resulting in downstream reduction of inflammatory cytokines. Phase 2b dose selection was based on a comparative efficacy analysis across 5 comparators (adalimumab, etanercept and infliximab (TNF α antagonists) and ustekinumab and briakinumab (p40 antagonists)). A dose-response model was built using data from competitors (i.e. published mean study-arm level data from > 10,000 patients) and in-house Phase 1b data of SCH 900XXX. Drug potencies were compound-specific, but other parameter estimates were assumed to be similar across all comparators or across drugs from the same class. E.g., it was assumed that SCH 900XXX shared the same onset of action as its comparators, and that drugs with a similar mechanism of action had the same maximum effect. Clinical trial simulations were conducted to evaluate various dose ranges for Phase 2b development. The selected dose range should bracket a dose resulting in maximum response and ED50.

* Kerbusch T, Wada R, Zandvliet A, et al. American Conference on Pharmacometrics 2011

Case Study 2 – Guiding Phase 2b Dose Selection By Leveraging Comparator Data*

Figure 1. Dose-response relationship of SCH 900XXX: increased response over time.

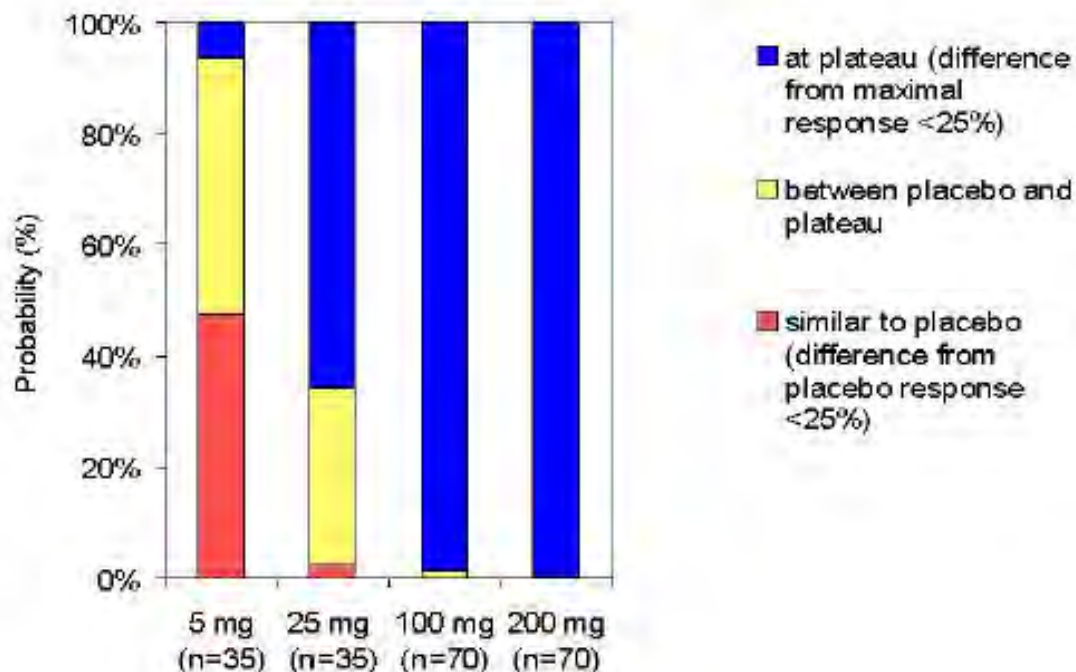


Shaded regions are 80% confidence intervals based on 2500 simulations from the variance-covariance matrix of the model parameters.

* Kerbusch T, Wada R, Zandvliet A, et al. American Conference on Pharmacometrics 2011

Case Study 2 – Guiding Phase 2b Dose Selection By Leveraging Comparator Data*

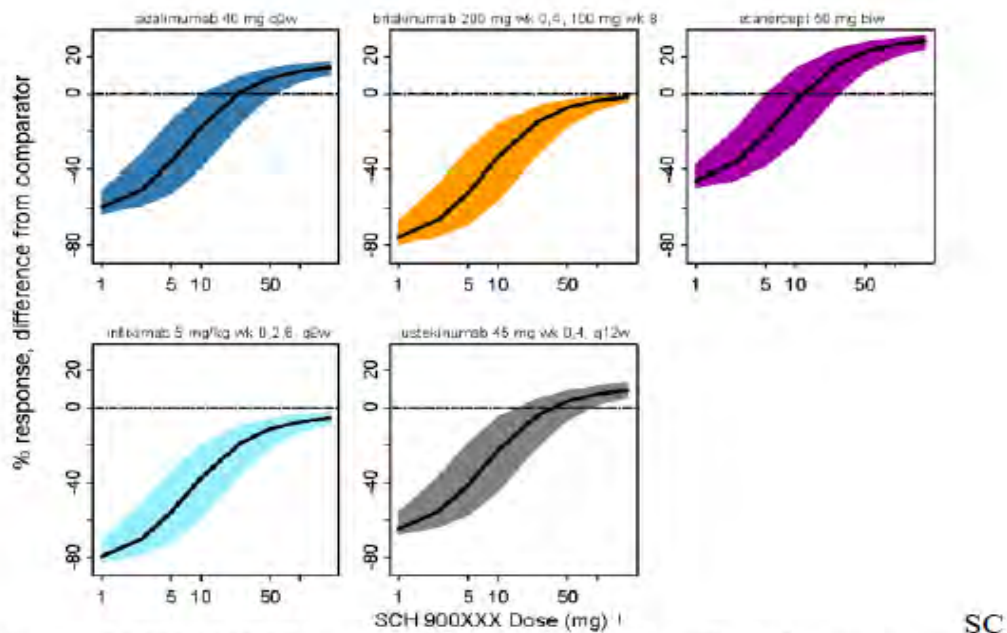
Figure 3. Results from clinical trial simulations for the selected dose range for Phase 2b development of SCH 900XXX.



* Kerbusch T, Wada R, Zandvliet A, et al. American Conference on Pharmacometrics 2011

Case Study 2 – Guiding Phase 2b Dose Selection By Leveraging Comparator Data*

Figure 2. Comparative landscaping: efficacy (y-axis) for various SC doses of SCH 900XXX (x-axis) as compared to recommended dosing regimens for adalimumab, etanercept and infliximab, ustekinumab and briakinumab.



doses of SCH 900XXX given at 0, 4, and 16 weeks. Shaded regions are 80% confidence intervals based on 2500 simulations from the variance-covariance matrix of the model parameters.

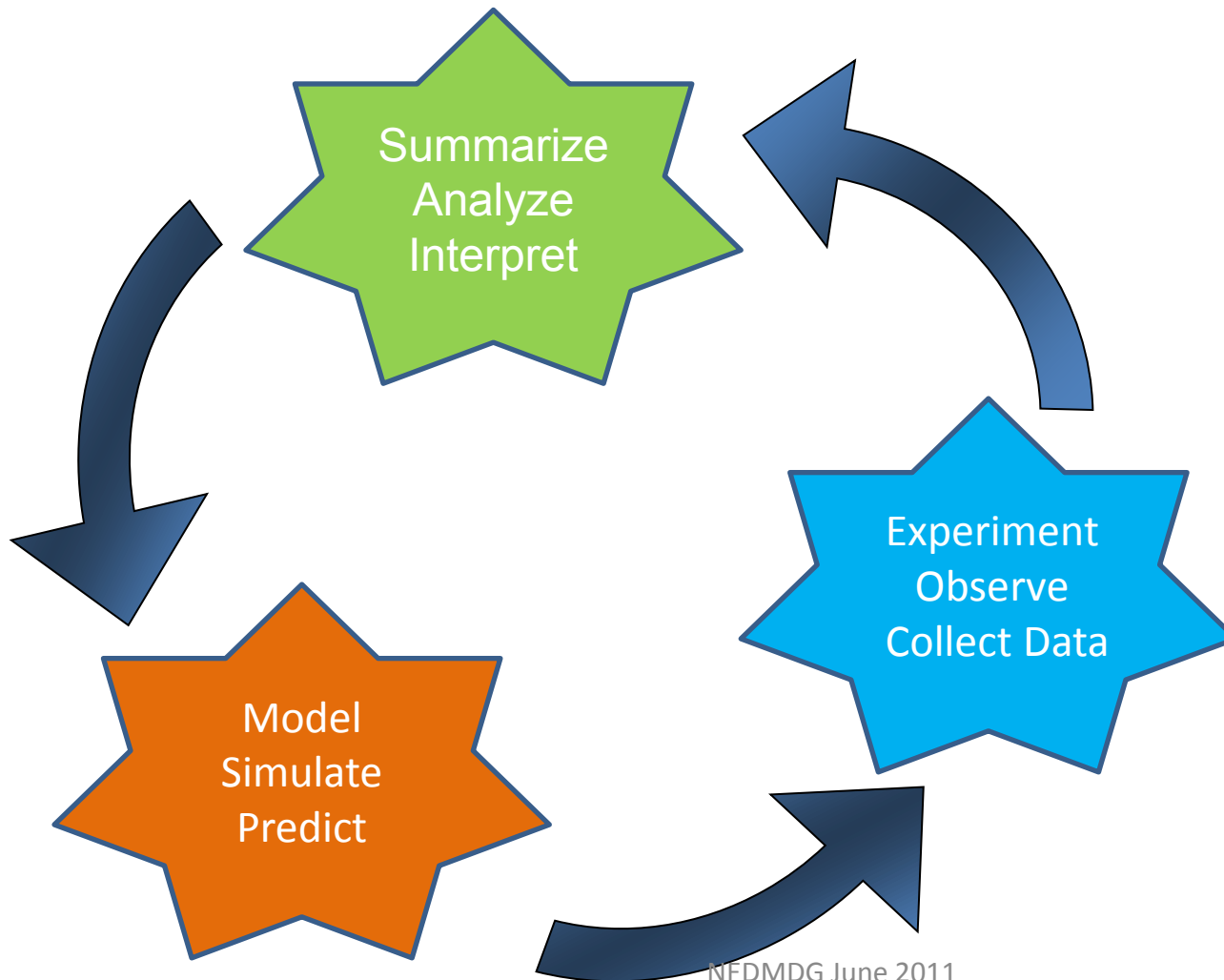
* Kerbusch T, Wada R, Zandvliet A, et al. American Conference on Pharmacometrics 2011

Case Study 2 – Guiding Phase 2b Dose Selection By Leveraging Comparator Data*

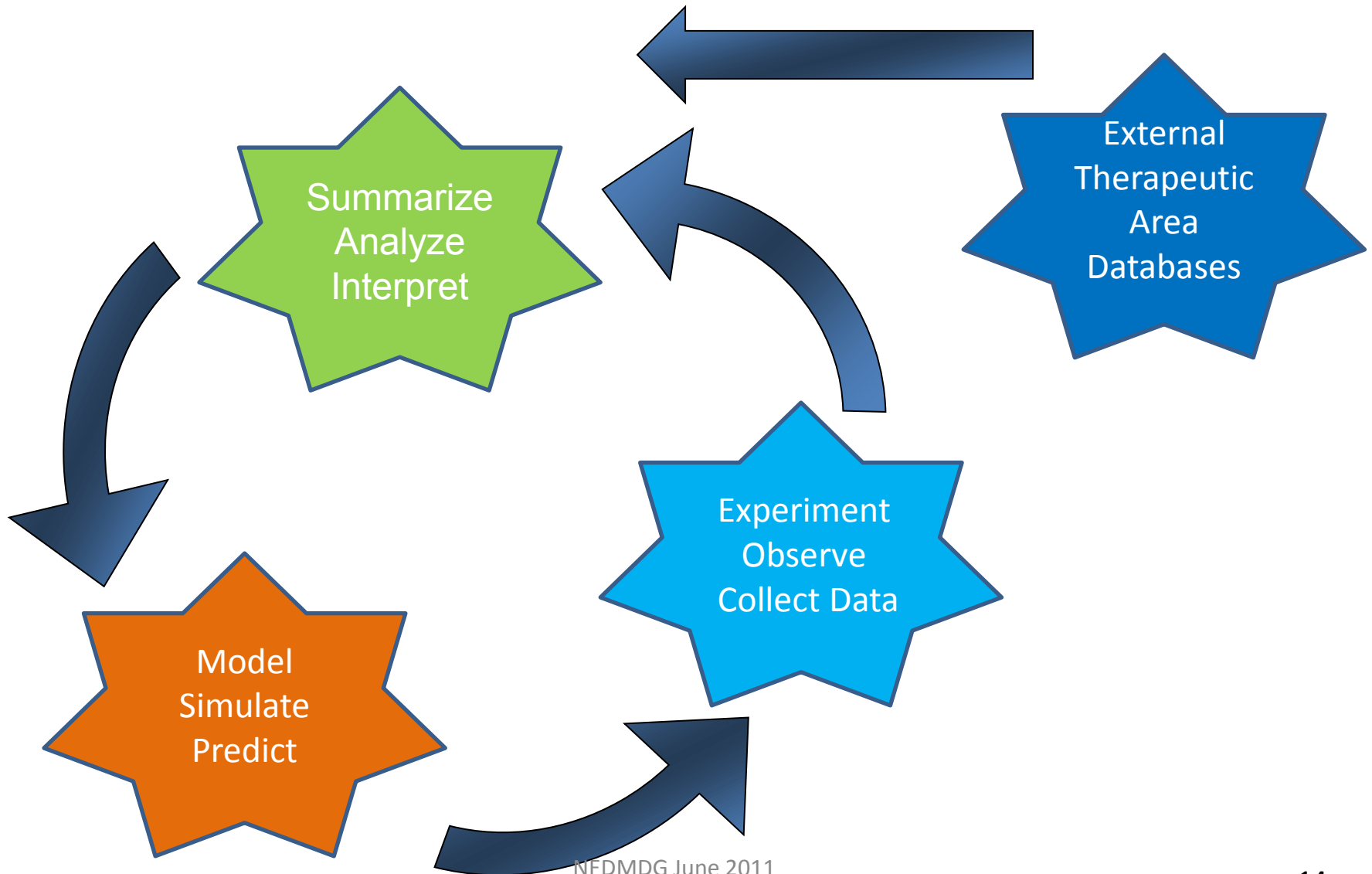
Conclusions: The recommended Phase 2 dose levels of SCH 900XXX are 5, 25, 100 and 200 mg administered at weeks 0 and 4, then every 12 weeks. The value proposal of the modeling was that a more informed and robust decision could be made by leveraging comparator data to support the limited internal data. Optimization of dose selection using an advanced modeling approach leveraging comparator data greatly enhanced the probability of success of establishing dose-response in Phase 2b development. The comparative efficacy evaluation will be refined after Phase 2b development to support decision making to go to Phase 3 and to allow for model-based dose selection for Phase 3 development of SCH 900XXX.

* Kerbusch T, Wada R, Zandvliet A, et al. American Conference on Pharmacometrics 2011

Quantitative Modeling Accelerates R&D by Iterative Knowledge Generation



Quantitative Modeling Accelerates R&D by Iterative Knowledge Generation & Integration



Quantitative Modeling Leverages Internal and External Knowledge in order to Surmount the “4th Hurdle”

- The “4th Hurdle”: *where traditional evidence-based medicine and economic values intersect*

Hurdles 1, 2, 3 means companies require to assure

- **Efficacy**
- **Safety**
- **Manufacturing Quality**

Hurdle 4 means companies require to demonstrate

- **Cost-effectiveness***

* Driven by the high cost to pay by healthcare providers (incl. government) and tax payers in countries like US and in Europe; i.e. value for money