Review Article

Theme: Quantitative Pharmacology, a Roadmap for Rational, Model-Based Drug Development
Guest Editor: Bernd Meibohm

The Use of Clinical Utility Assessments in Early Clinical Development

Anis A. Khan,¹ Itay Perlstein,¹ and Rajesh Krishna^{1,2}

Received 27 August 2008; accepted 8 December 2008; published online 16 January 2009

Abstract. A quickly realizable benefit of model-based drug development is in reducing uncertainty in risk/benefit, comprising individually of safety and effectiveness, two key attributes of a product evaluated for regulatory approval, marketing, and use. In this review, we investigate gaps and opportunities in using fundamental decision analytic principles in drug development and present a quantitative clinical pharmacology framework for the application of such aids for early clinical development decision making. We anticipate that implementation of such emerging tools will enable sufficient scientific understanding of the two attributes to facilitate the early termination of compounds with less than desirable risk/benefit profiles and continuance of compounds with acceptable risk/benefit profiles.

KEY WORDS: clinical utility index; modeling and simulation; therapeutic index.

INTRODUCTION

The past decade has witnessed an unprecedented number of novel targets being investigated by the pharmaceutical industry and academic laboratories. This is evident by the rise in intellectual property applications as well as scientific publications and NIH grant funding statistics (1). In addition to these changes, key regulatory initiatives such as the *Critical Path to New Medicines* in the US and *Innovative Medicines Initiative* in Europe have been developed to help promote innovation, increase efficiency in drug development cycle by enhanced biomarker use in early decision making, reduce late-stage attrition by increasing probability of success by better proof of concept studies; all a testament to the recognition that drug development has become more complex and novel strategic thinking will be needed for success (2).

An important benefit arising from these key regulatory initiatives is in understanding better and reducing the uncertainty in a given attribute, whether that is efficacy or safety or importantly both. This new type of strategic thinking is direct result of the model-based thinking at the back of Sheiner's seminal hypothesis on learn-confirm cycle (3) as well as the interpretations of the FDAMA confirmatory evidence of effectiveness has been the cornerstone of the pharmaceutical industry's emergent efforts in delineating the effectiveness of new drug candidates.

One particular aspect that has the potential to be improved on is the manner in which selection and go/no-go

decisions for new molecular entities (NMEs) are made relative to the target product profile during various phases of drug development. It is in the common interest of patients with unmet medical needs and pharmaceutical industries in search of innovative medicines to bring successful products to market quickly. Thus, the decision making at various stages of clinical development is critical. However, prior to the hypothesis of model-based drug development, this has largely been based on the individual or the organization's gestalt, a conventional decision-making process that is multidimensional, subjective, nonquantitative, and sometimes inconsistent, thus, leading to uncertainty in the effectiveness of the decisions made. Some prevalent practical challenges in decision making in a conventional paradigm continue today and include "Champion syndrome" or exuberant advocacy, inefficient consensus decision making, differential subjectivity, and lack of clarity on underlying assumptions in decisions made. Tools such as clinical utility analyses as a special case of multi-attribute analysis are useful in simplifying multi-attribute data in a single quantitative metric for consistent decision making that can assimilate both subjective and objective data and provide a framework for open debate on assumptions.

In this review, we provide a brief overview of the early origins of clinical decisions and present a quantitative clinical pharmacology framework on the use of clinical multi-attribute utility (MAU) analysis as a decision aid during early to late stage clinical development.

CLINICAL DECISION ANALYSIS

Decision analysis in its most unadulterated form has long been in use in the delivery of medical care to patients, in determining the types of treatment, or when surgical choices are made (4–7). The more complex or challenging the

¹ Quantitative Clinical Pharmacology, Department of Clinical Pharmacology, Merck Research Laboratories, Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

² To whom correspondence should be addressed. (e-mail: rajesh_krishna@merck.com)

disease, the more risk the physician takes in delivering health care choices. Naturally, when such choices are made, a balance or weight of data (related to patient's disease state, health condition, and the impact on quality of life), understanding of the evidence of risk and the element of uncertainty (probability of success or failure of a given treatment choice based on prior outcomes) and probability of making the correct choice all come into play that a physician has to make for rendering an individual patient care. The riskier a treatment choice, likely reflective of the complexity of the underlying medical condition, the larger is the uncertainty associated with that treatment choice. Thus, it is not surprising that the most basic forms of decision making are still being practiced in surgical oncology and in certain incurable forms of infectious diseases. In recent times, however, we have seen increasing use of decision analysis by health care maintenance organizations that are primarily geared to assessment of cost-benefit and cost-effectiveness analysis (32).

This approach to delivering health care has parallels in economics, defense strategies, and other unrelated fields and modern day decision analysis, while so seemingly complex, is a stochastic phenomenon that still hinges on certain common basic concepts described above. Modern day decision analysts have more advanced quantitative tools in their repertoire to analyze decision options and undertake methods to evaluate and ensure that such decisions are correctly executed.

Decision Analysis Concepts

The probability groundwork for modern day decision making originated from the work of Thomas Bayes (1763) and Pierre Simon de Laplace (1795) (8). These concepts of subjective probability played a central role in shaping the utility hypothesis of John von Neumann and Oskar Morgenstern in 1944 (8). A specific aspect of their work included concepts of preferences and weights, including a utility function, which provided an unambiguous way of making comparisons by considering probabilities. Probability-based utility functions could be added and multiplied by weighted preferences, and total utility could be calculated as a linear sum of the utility of individual attributes.

The utility concepts in the seminal work of von Neumann have particular relevance for drug development applications since his work was about a form of utility (decision) theory under uncertainty. Although, the Neumann–Morgenstern utility theories provided a theoretical framework for how the decisions can be made rationally under uncertainty, however, it does not capture the behavioral aspects of actual group decision making. Regardless of specific areas where such decisions are made, whether clinical, military, or technological decisions, they all share the common features that make the decision-making process challenging and complex (9–13). While scenarios may differ, thresholds for uncertainty may vary, choice of alternatives may have varied consequences, all decisions exhibit a characteristically similar path to implementation. The significant advantage of adaptation of such analytics is strengthening and solidifying the decision-making process that leads to consistency in approach and reduction in subjectivity. There are a number of decision analytic modeling approaches that are available for clinical

decisions. In this overview, utility concepts are specifically highlighted as the decision analytic approach.

Utility Concepts in Medicine

While the introduction of decision analysis in its earliest form can be traced to the early 1920s, the use of formal utility analysis can be traced back to the 1950s and 1960s. One of the early applications of decision analysis in its present day incarnation of the clinical utility index can be traced back to 1967 when Henschke and Flehinger (4) proposed a decision analytic framework based on utility functions for the surgical decision on prophylactic neck dissection. They argued that prophylactic neck dissection would yield benefit for patients only when the size of primary cancers exceed 2 cm. One important differentiating aspect of assessing utility in this example in particular, but oncology in general, from the other benefit/risk scenarios is the framing of preferences as “utility losses” with the goal of analyses being to minimize losses for the patient, since the patient has nothing to gain by having cancer. The authors concluded that Bayes’ strategy, which results in the smallest expected utility loss when frequency for each state of nature was known, as is the case in most decisions in cancer management, was the optimal strategy. The optimal strategy was rightfully placed in between the pessimistic strategy of minimizing the maximal loss (“minimax”) and the optimistic strategy of gambling on the most favorable possibility.

In their report, authors outline many of the common challenges they encountered in the cultural aspects of implementation that are reminiscent of modern day challenges, including but not limited to inadequacy of data to enable the decision analysis, lack of math-savvy practicing physicians to execute on the analysis, notion that common sense would arrive at the same conclusion as a complex decision analysis would, and that subjective human preferences were not suited to quantitative analysis. What is even more surprising and profoundly meaningful is that the authors proposed the simplified form of decision analysis to be included in the Physician's Desk Reference, to enable quick access for swift implementation. Although advances have been made to rationalize evidence-based medical care in recent years, it is important to note that, 40 some years later, we still have not been able to translate the value proposition of such simple but meaningful decision analysis output in the hands of clinicians practicing medicine or their corollary, to drug development scientists rationalizing the risk/benefit utility of new molecular entities.

MULTI-ATTRIBUTE UTILITY ANALYSIS

Multi-attribute utility (MAU) analysis models are tools that assist in group decision making by helping to evaluate complex alternatives and finding the best choice under uncertainty (14,15) and have been in use in many industries. In this analysis, a utility function is constructed that helps convert a multidimensional attribute space into a single-dimensional preference scale and allows an objective selection from the alternatives available. However, in a more pharmaceutical context, at the early stages of clinical development, an assessment of risk/benefit and compound selec-

tion may depend upon the concept of “net utility,” which is comprised primarily of the sum of efficacious and toxic effects as has been described by the pioneers in the field (16) and depicted in a conceptual schematic in Fig. 1, constructed with a linear additive utility function using Eq. 1. However, in recent years, the complexity of novel targets has risen considerably, and to understand the complex longitudinal drug–biological–pathophysiological interactions, an increasing number of biomarkers are being utilized in development as early predictors for both efficacy and safety. This has led to availability of complex multidimensional quantitative data measured on multiple scales. Additionally, at the late stage in development, many other factors such as subjective clinical preferences, patient quality of life, cost of goods, and a variety of competitor information, etc., influence the decision-making process. Additionally, given the long drug development timeframe, the target product profile is often a moving target due to changing competitive environment. A clinical-utility index (CUI) analysis, which is a form of MAU analysis with a narrow focus on pharmaceutical application, helps assimilate this diverse array of information by weighing the tradeoffs appropriately and transparently (17,18).

Even though there have not been many publications regarding the internal quantitative decision-making tools from the industry, several reviews or case studies have recently been reported describing “go/no-go” or dose/regimen optimization decisions that have been made in early clinical phases of drug development on the basis of quantitative analyses. The selected examples range from dose/regimen selection (19,20), lead/backup compound prioritization in an insomnia program (21) to applications in oncology programs (19,22). In addition to application of MAU analysis in product development decisions that pharmaceutical companies make, even formulary committees have utilized such MAU decision analytics after product is marketed, to compare medication alternatives when numerous variables need to be considered in the decision-making process (23). MAU analysis has also been shown to have value when evaluating a NME for advancing

through preclinical stages through early clinical development when decisions are based on a combined analysis of the available preclinical and early clinical data (24).

Adequate model-based risk assessment is a key component in risk/benefit analysis to properly weigh tradeoffs; however, this area remains challenging due to several reasons. Occurrence of safety/tolerability events do range from very rare to frequent, and oftentimes, concurrent severity data are not available or not considered in a quantifiable manner. Additionally, due to a lack of adequate data availability, large variability and complex modeling required, there are only a few examples in literature for safety data modeling (25–27). Perhaps the most prominent safety data modeling is the PK/PD modeling of the QTc interval prolongation (28,29) due to some very high profile drug recalls from the market. Any efforts to model safety data in the early stages of development are further complicated by usually smaller sample size in a majority of phase I/II clinical trials. These limitations lead to larger uncertainty in assessing risks appropriately. Defining and quantifying a clinically relevant difference and assigning appropriate relative weights for every risk/benefit attribute is another challenging area.

Mathematically, the CUI can be expressed by the following equation:

$$CUI = \sum_{i=1}^n (W_i \cdot U_i) \quad (1)$$

where CUI is the total utility, an algebraic sum of utilities for each attribute, W is the weight, and U represents the utility function. The utility function can be elicited either as a linear scaling function as a response proportional to a clinically meaningful threshold effect or as a probability of the effect achieving a response above the same threshold. The potential advantage of the probabilistic utility function is that, in addition to the point estimate, it takes into account the precision of the estimate. Also, it provides the ability to compare candidate drugs across different indications with different efficacy and safety endpoints.

To undertake clinical utility analyses in a drug development program, the project team starts by identifying all the critical attributes important for decision making at a particular development stage, which may include, but is not limited to, biomarker responses or clinical outcomes that provide different measures of efficacy and safety, formulation feasibility, regimen selection, cost of goods, etc. CUI analysis is quite flexible to accommodate both continuous and categorical variables. A dose/exposure–response relationship is established, while considering and accounting for any dose level or baseline differences. Each attribute is then normalized by its clinically meaningful difference in order to make the drug-related changes comparable across different dynamic ranges. Depending on the stage of development and availability of data, external expert opinions and physician preferences for the product characteristics can also be incorporated in the CUI analyses. Based on all available data, the team faces the challenging task of achieving consensus on the relative importance of individual attributes and assigning the appropriate weights, which determine the relative contribution of each attribute toward the overall CUI estimation. The relative weights will also be influenced by the indication being

Fig. 1. A schematic of the utility curve with upper and lower confidence bounds when safety and toxicity are weighted and analyzed together.

targeted, e.g., some side effects may be more acceptable and thus have relatively lower weights in oncology programs, whereas they may be considered serious in another indication and get larger negative weights. In some cases, the weighting scheme may need to be more complex, such as, nonlinear or a step function over the entire pharmacodynamic range. This can help accommodate a variety of scenarios including but not limited to exaggerated pharmacology, minimum threshold pharmacology, and baseline-dependant weighting of the response. Finally, the sum of normalized, weighted factors as a function of dose (or concentration) provides the calculated CUI estimates assuming individual contributions are additive. In addition to estimating mean CUI values, a bootstrap analysis of the efficacy and safety data can provide a large set of parameters that can be used to estimate a distribution of CUI and thus enable us to estimate confidence intervals. These estimates with confidence intervals also allow the team to create probability distributions of CUI from two competing molecules, e.g., a lead and a backup in a program or a lead candidate against a marketed drug for quantitative product differentiation. Since a certain amount of subjectivity is involved in deciding on weights and clinically meaningful differences for each attribute, as an additional step to test assumptions, a sensitivity analysis can help determine attributes that have the most influence on CUI and need to be assigned with much careful consideration and may require refinement if more information becomes available. An advantage of the CUI analysis is that it lends itself to a seamless progressive assessment during the clinical development stages from early to late phases as more knowledge accumulates and endpoints or relative weights are readjusted.

In addition to the above-mentioned approach, the Bayesian approaches have also been used with Markov chain Monte Carlo methods to obtain credible intervals using posterior probabilities in drug development settings. These methodologies have been used to solve dose regimen optimization (33) or dose escalation decisions in a clinical trial using a Bayesian adaptive design paradigm (34). Graham *et al.* utilized a Bayesian hierarchical methodology to determine optimal dosing regimen that would maximize the posterior expected utility given the prior information on the model parameters and the patient response data. The utility function in this case was defined using clinical opinion on the satisfactory levels of efficacy and toxicity and then combined by weighting the relative importance of each pharmacodynamics response (33). Yin *et al.* used the Bayesian adaptive design for dose finding in phase I/II clinical trials where they incorporated the bivariate outcomes, toxicity and efficacy, of a new treatment. This was performed without specifying any parametric functional form for the drug–response curve and jointly modeling the bivariate binary data to account for the correlations between toxicity and efficacy attributes (34).

Net clinical value concepts have been used in clinical practice for a long time in making treatment option decisions including surgical interventions; however, use of CUI in drug development decisions is relatively recent. As with any evolving area, there are currently many limitations and challenges for a broader and routine integration of such quantitative tools in common practice. These include a lack of general awareness and acceptability of these tools, challenges associated with determination and consensus on attributes, clinical meaningful

differences and the weights and tight timelines not allowing sufficient time for conducting such analyses. Additionally, there have only been a small number of peer-reviewed published examples that highlight successful use of such measures to promote broader acceptance. We recognize that it is possible that such analytics are being used to some extent for internal decision making in pharmaceutical industry, but it is not a common knowledge due to the intention of pharmaceutical companies to keep their decision process confidential, and only a handful success stories get published giving us a biased view. Availability of adequate safety data is an additional challenge that is a critical factor in CUI assessment.

Willingness to accept innovative approaches in the process of decision making may require cultural changes in a company and may take time to evolve. However, for successful application of CUI analyses, agreement on using CUI analysis outcomes for a go/no-go decision based on *a priori* specifications closely tied to the targeted product profile is important before conducting the exercise. The usefulness of CUI as an internal decision-making tool in early development is becoming more clear; however, further clarity around acceptability of sponsor-driven late stage CUI-based product differentiation analyses by regulatory agencies will add value to integration of such analyses in drug development programs and would provide encouragement for routine usage from early to late stages. The recent trend toward a more model-based development environment and implementation of adequate pharmacometrics-enabling infrastructure (30) and a decision-making behavior shift (31) will likely support a broader incorporation of such decision analytic tools for routine use.

Although, CUI can provide an integrated quantitative framework for decision making, it is critical to consider at an early stage what the key factors are and how much information is going to be available at any given stage of development for such analyses. For a successful integration of CUI in the product development decision tree, it is necessary to ensure that adequate data will be available early in the development program to help focus on the optimal target product profile and in the late stage of development for dose/regimen optimization or product differentiation. In Fig. 2, we present

Fig. 2. A schematic of the relative clinical utility assessment for decision making from early to late stages of development, incorporating expert clinical opinion with pharmaceutical development considerations

a schematic of the framework for incorporation of such analyses in clinical programs, which incorporate criteria for CUI assessment based on attributes that are important from both patient and pharmaceutical development perspective and can be incorporated in clinical decision strategy from early to late stages of development. Early in the clinical development (phase I/II), potentially efficacy and toxicity criteria play the key role in molecule advancement decisions with larger uncertainty, as not all the factors are considered; however, during the late stage development, patient net benefit, product differentiation become more important in developing marketing strategies.

SUMMARY

In this report, we have reviewed a framework for the model-based assessment of therapeutic index in the early clinical development space. This recommendation is based on key assumptions:

- Efforts are underway within pharmaceutical organizations to increase scientific objectivity in drug development by reducing the “champion” syndrome—where internal experts are vested in the success of a drug and sometimes are not objective enough or tend to minimize or overlook the possible deficiencies of a given NME. This behavior has the potential to influence the assignments of weights and tradeoff and can undermine the utility of decision tools that are based on MAU approaches.
- Identifying the reference profile and determining the clinically important difference. Development teams in early clinical space often struggle with understanding the level of significance that could be deemed clinically relevant or important. For a utility analysis to be successfully implemented, a good understanding of the clinically important change is needed.

These assumptions are dependent on cognitive aspects of decision making, with individual and organizational behaviors influencing the level of utility of these approaches. It is therefore critical that organizations be sensitive to the level of training and education that are inherent in the application of these tools to real-time decision making. We remain optimistic that such tools, if successfully leveraged as aid to decision making, will achieve the overarching benefit of reducing uncertainty in risk/benefit in the continuing learn/confirm cycle of model-based drug development. As more such methods are implemented, the industry as a whole has a lot to gain through collective learning of best practices and engaging in well-informed decision making.

REFERENCES

1. I. Kola, and J. Landis. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* **3**:711–715 (2004).
2. R. Krishna. Introduction to dose optimization In *Dose Optimization in Drug Development* vol. 161, Taylor and Francis, Oxford, UK, 2006.
3. L.B. Sheiner. Learning and confirming in clinical drug development. *Clin. Pharmacol. Ther.* **61**:275–291 (1997).
4. U. Henschke, and B.J. Flehinger. Decision theory in cancer therapy **20**:1819–1826 (1967).
5. M.H. Hsieh, and M.V. Meng. Decision analysis and Markov modeling in urology. *J. Urol.* **178**:1867–1874 (2007).
6. E.B. Elkin, A.J. Vickers, and M.W. Kattan. Primer: using decision analysis to improve clinical decision making in urology. *Nat. Clin. Pract. Urol.* **3**:439 (2006).
7. J.R. Beck, M.W. Kattan, and B.J. Miles. A critique of the decision analysis for clinically localized prostate cancer. *J. Urol.* **152**:1894 (1994).
8. H. Raiffa. *Decision Analysis*, Random House/McGraw Hill, 1968.
9. J.O. Berger. *Statistical Decision Theory and Bayesian Analysis*. Springer-Verlag, New York, 1985.
10. Z. Philips, L. Ginnelly, M. Sculpher, K. Claxton, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol. Assess.* **8**(36), (2004)
11. K. Claxton, M. Sculpher, and M. Drummond. A rational framework for decision making by the National Institute for Clinical Excellence. *Lancet.* **360**:711–715 (2002).
12. J.D. Habbema, P.M. Bossuyt, D.W. Dippel, S. Marshall, and J. Hilden. Analysing clinical decision analyses. *Stat. Med.* **9**:1229–1242 (1990).
13. M. Hunink, P. Glasziou, J. Siegel, J. Weeks, J. Pliskin, A. Elstein, and M. Weinstein. *Decision Making in Health and Medicine: Integrating Evidence and Values*, Cambridge University Press, Cambridge, 2001.
14. R.L. Keeney, and H. Raiffa. *Decisions with Multiple Objectives: Preferences and Value Tradeoffs*, Cambridge University Press, New York, New York, 1993.
15. R.T. Clemen. *Making Hard Decision: An Introduction to Decision Analysis*, 2nd edn, Duxbury Press, Pacific Grove, CA, 1996.
16. M. Rowland, and T.N. Tozer. *Clinical Pharmacokinetics: Concepts and Application*, Lea & Febiger, Philadelphia, PA, 1980.
17. B. Korsan, K. Dykstra, W. Pullman. Transparent trade-offs. *Pharmaceutical Executive* 2005.
18. B. Poland, and R. Wada. Combining drug–disease and economic modelling to inform drug development decisions. *Drug Discov. Today.* **22**(6):1166–1170 (2001).
19. A. Roy, M. Pfister. Optimizing Dose Selection with Respect to multiple Safety/Efficacy Endpoints using Clinical Utility Concepts. *PAGE* 2006.
20. G. Dai, A. Roy, X. Zhou, L. Kayitalire, L. Alland, M. Egorin, G. Giaccone, M. Pfister. Determination of optimal dose and dosing regimen for phase 2 with clinical utility index: application to an anti-tumor agent. *Clin. Pharmacol. Ther.* **81**(Supplement 1): Abstract PI-23 (2007).
21. D. Ouellet, N. Patel, J. Werth, D. Feltner, B. McCarthy, R. Stone, D. Mitchell, R. Lalonde. The use of a clinical utility index in decision making to select an insomnia compound. *Clin. Pharmacol. Ther.* **79**(2):Abstract OII-A-2 (2006).
22. J.S. Barrett, M. Gupta, and J.T. Mondick. Model-based drug development applied to oncology. *Expert Opinion in Drug Discovery.* **2**(2):185–209 (2007).
23. T.I. Bettinger, G. Shuler, D.R. Jones, and J.P. Wilson. Schizophrenia: Multi-attribute utility theory approach to selection of atypical antipsychotics. *Ann. Pharmacother.* **41**:201–207 (2007).
24. S. Eriksen, and R. Keller. A multi-utility-function approach to weighing the risks and benefits of pharmaceutical agents. *Med. Decis. Making.* **13**:118–125 (1993).
25. J.A. Passarell, A.K. Meagher, K. Liolios, T.H. Grasela, T. Babinchak, E.J. Ellis-Grosse. Pharmacokinetic/Pharmacodynamic model for the tolerability of tigecycline in healthy volunteers. EEMID Meeting 2005, Copenhagen, Denmark.
26. P.H. Zingmark, M. Kagedal, and M.O. Karlsson. Modelling a spontaneously reported side effect by use of a Markov mixed-effects model. *Journal of Pharmacokinetics and Pharmacodynamics.* **32**:261–281 (2005).
27. K. Ito, M.M. Huttmacher, J. Liu, R. Qiu, B. Frame, R. Miller. Exposure-response analysis for spontaneously reported dizziness in pregabalin-treated patient with generalized anxiety disorder. *Clinical Pharmacology and Therapeutics* 2008; epub 6 February 2008).
28. V. Piotrovsky. Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. *AAPS Journal.* **7**(3):E609 (2005).
29. I. Caverio. Using pharmacokinetic-pharmacodynamic modeling in safety pharmacology to better define safety margins: a

- regional workshop of the safety pharmacology society. *Expert Opinion in Drug Safety*. **6**(4):465–471 (2007).
30. T.H. Grasela *et al.* Pharmacometrics and the transition to model-based development. *Clin. Pharmacol. Ther.* **82**(2):137–142 (2007).
 31. E.J. Russo, P.J. Shoemaker. *Winning Decisions*. Doubleday Publishing, 2001.
 32. R.T. Anderson, R. Balkrishnan, and F. Camacho. Risk classification of medicare HMO enrollee cost levels using a decision-tree approach. *The American Journal of Managed Care*. **10**:89–98 (2004).
 33. G. Graham, S. Gupta, and L. Aarons. Determination of an optimal dosage regimen using a bayesian decision analysis of efficacy and adverse effect data. *J. Pharmacokinetics and Pharmacodynamics*. **29**:67–87 (2002).
 34. G. Yin, Y. Li, and Y. Ji. Bayesian dose-finding in Phase I/II clinical trails using toxicity and efficacy odds ratios. *Biometrics*. **62**:777–787 (2006).