Quantitative Risk Analysis:

IMPROVING DECISION MAKING BY QUANTIFYING UNCERTAINTY

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Given the myriad uncertainties throughout the entire drug development and commercialization process, quantitative risk analysis can provide great value when used as an integral part of decision making.

Decisions made throughout the entire drug development and commercialization process are fraught with uncertainties. Quantitative risk analysis (QRA)—also called stochastic modeling, risk modeling, or quantitative risk assessment—aims to improve decision making by taking into account variability and uncertainty and providing insight into probabilities related to decisions.

QRA has application in many areas within the pharmaceutical industry, from (early) drug development and trial design to manufacturing, finance, marketing, and business development. The objective of this article is to discuss the principles and benefits of QRA, why and how it improves decision making, and describe three pharmaceutical applications. To contrast the QRA approach and illustrate the shortcomings of the status quo approach, case study one also describes an example of more common, traditional decision making.

QUANTITATIVE RISK ANALYSIS

QRA has wide applications throughout the drug development and commercialization process. It relies on probability theory to represent a situation with variability (randomness) and uncertainty (lack of knowledge) with a mathematical model and provide outcomes and answers in probabilistic terms.

Four key benefits of QRA are that it (1) takes into account information in many shapes and forms; (2) explicitly takes into account uncertainty and variability; (3) may be used as a decision-supporting tool; and (4) is quick, user-friendly, and relatively inexpensive. Let's look at these benefits more closely.

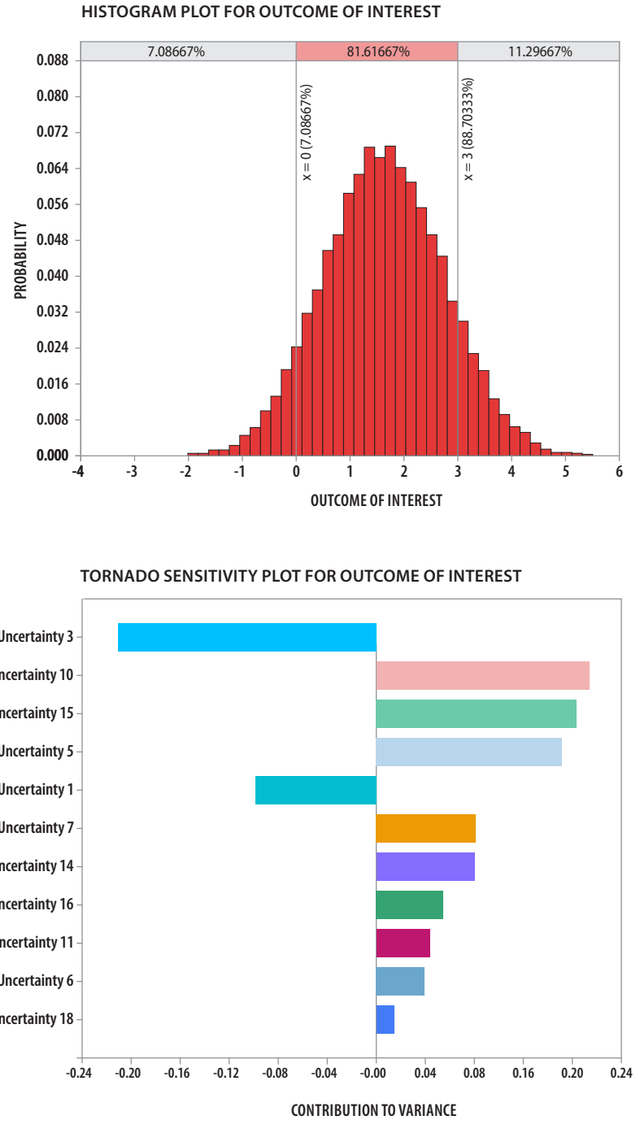

FIGURE 1. *Two example graphical results from QRA: The histogram of an example outcome shows its total amount of uncertainty and/or variability (which can be separated but is not shown here) and shows there is a ~7 percent likelihood the outcome will be negative and ~11 percent likelihood it will be above 3; the tornado plot has a rank of the key variables (e.g., risk drivers) that contribute to the uncertainty and/or variability in a particular outcome.*

Benefit 1

QRA techniques are extremely flexible in capturing and combining dissimilar information, including empirical data, expert opinion, and other mixed sources of information. QRA uses different statistical methods to make the best use of the current information and support the decision makers.

For example, when making a decision on dose and delivery for a first-in-human (FIH) study, a QRA would integrate a number of data sources (e.g., in vitro studies, animal data, literature) as well as expert opinion (surveys, panels, individual experts) to estimate relevant parameters (e.g., IC50 and k) into one assessment of the overall benefit-risk.

Benefit 2

The use of QRA allows analysts to take into account the uncertainty and variability related to inputs or parameters in their models in a more flexible way than traditional statistical methods. While often used interchangeably, it is useful to distinguish both terms.

Uncertainty arises from a lack of knowledge about a parameter in the model, about the best statistical method or technique to use, or even about the overall model. Thus, uncertainty can be reduced (not eliminated) by collecting more evidence. For example, if an individual wants an estimate of the average weight of a target patient population, collecting data from 400 patients will reduce the uncertainty compared to collecting data from 20 patients.

In contrast, variability is part of the system and cannot be reduced by additional studies. No matter how many patients are observed, weights will vary. Variability can only be changed if the system is changed; for example, if a more uniform group of patients is selected.

Benefit 3

While QRA is often described from the analytical perspective, its sole aim is to support decisions. Depending on the question asked by decision-makers, QRA can provide a range of outcomes.

However, a key characteristic is that the results of a QRA are graphical summaries that are insightful and understandable for technical audiences (e.g., an early drug development team) as well as for managers and executives (e.g., evaluating a business development opportunity). Figure 1 shows two common graphical outputs.

The histogram depicts the amount of uncertainty and/or variability of an output; for example, a clinical parameter or a commercial milestone. It shows a 7 percent likelihood that the outcome will be below zero and a 11 percent likelihood it will be above 3. Also, the 90 percent-confidence interval (and any percentile) can be shown.

The tornado charts show what factors mostly contribute to the total uncertainty and/or variability. Figure 1b shows that uncertainties 3, 10, 15, 5, and 1 are the main risk drivers.

Reducing the variance of the main risk drivers would mostly reduce the overall variance in the outcome. Uncertainties 3 and 1 have a negative contribution to variance, indicating that if their values are higher, the outcome tends to be lower (and vice versa).

While the types of results from a QRA can be diverse, the outcomes are always expressed in probabilistic terms, allowing decision makers to ask their questions, such as "What is the confidence that our new drug has fewer side-effects than the gold standard?" instead of "Does our new drug have fewer side-effects than the gold standard?"

Benefit 4

User-friendly software that provides the user the ability to perform Monte Carlo simulations and probability analysis in ubiquitous platforms such as Excel® is readily available. The nature of the software allows quick analyses and model building, typically through an intuitive and graphical user interface without the need to explicitly write differential equations or formulae of probability density functions.

Well-designed QRA models are easy to modify and rerun, allowing them to be used in a team setting in which alternative scenarios can be run on the fly. Software packages typically range from $1,000 to $2,500 per user for a single-user perpetual license, limiting the upfront costs.

THREE CASE STUDIES

The following three case studies illustrate how QRA can greatly aid the decision-making process in diverse situations.

Case Study 1: Probability of Success

An understanding of the factors contributing to a molecule's probability of success (PoS)—overall program success—allows teams to make informed decisions on progression or termination of clinical assets, thus increasing the likelihood that beneficial therapies reach patients and that resources are used efficiently.

MFT2010 is an (hypothetical) investigational drug for the treatment of hypertension. Data from phase I and IIa studies suggest the potential for significant clinical benefit.

The project team has established criteria for progression into phase III based on upcoming phase IIb results. Key risks include the magnitude of efficacy and the overall safety and tolerability profile.

MFT2010 also faces risks associated with a positive hERG signal (potential for QT prolongation) and adverse effects in short-term toxicology studies. Feedback from regulatory agencies suggests that

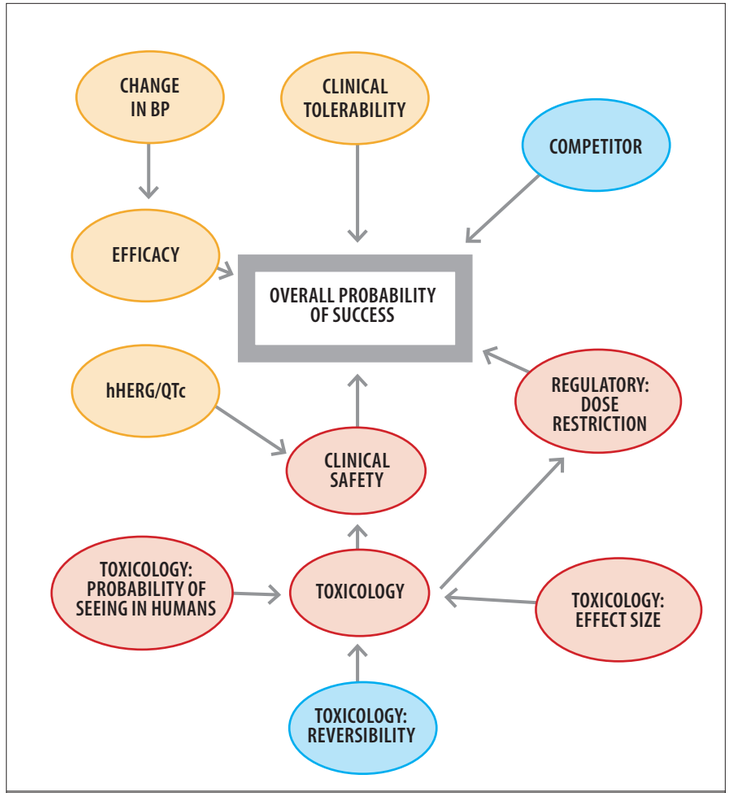

FIGURE 2. *Influence diagram of key risks in the development of MFT2010; color-coding represents the relative contribution to the overall risk for the project: orange (low risk), blue (moderate risk), red (greatest risk).*

significant dose-level restrictions may be required based on longer-term toxicology findings (effect size and reversibility) and the likelihood that these findings would be observed in humans. Finally, a key component of the PoS is its ability to provide a clinically meaningful advantage over competitor molecules in development.

Traditional Approach

The MFT2010 team decided to focus the PoS assessment on blood pressure effects and the safety/tolerability profile in the phase IIb study. The team established a point estimate cutoff for blood pressure effects, which would signal a go/no go decision.

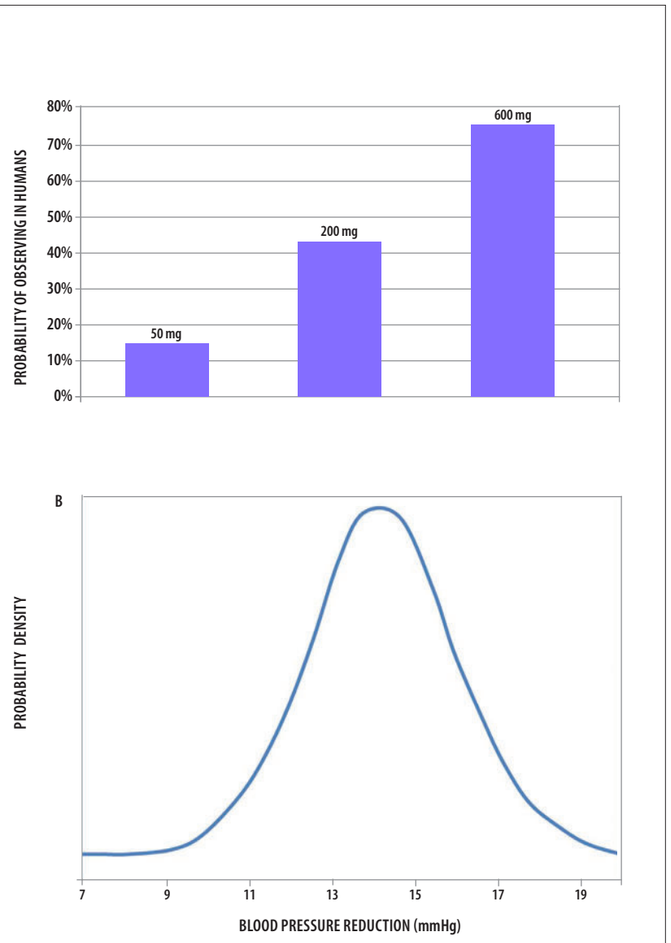

FIGURE 3. *Examples of intermediary results used to quantify the PoS of MFT2010. Panel A: Expert opinion is used to quantify probabilities that toxicology findings will translate to humans over the range of likely clinical doses. Panel B shows the probability of blood pressure reduction (mmHg) resulting from a Bayesian analysis based on results of phase IIb.*

Clinical judgment was employed to assess the relevance of any safety/tolerability signals observed in the phase IIb study. Longer-term toxicology studies will not read out until after completion of the phase IIb study.

The team agreed to await results of these toxicology studies to formally assess this aspect of the safety and regulatory risks. Risks associated with QT prolongation also awaited results of a planned clinical thorough QT study.

The strategy summarized above, while common in drug development, has important shortcomings. There is no attempt to incorporate the multifactorial risks into a consolidated assessment and quantification of PoS. In fact, the only well-defined driver for PoS is the observed effect size in the phase IIb study.

While clinical efficacy may be robust (suggesting a clear go decision), the other risks associated with MFT2010 may overwhelm the potential efficacy benefit. Safety and regulatory risks associated with toxicology findings and hERG signals have been deferred until results of additional studies are available.

QRA-based Approach

Let's revisit the MFT2010 example using a consolidated QRA approach of all key risks and uncertainties to support decision making and ensure that critical issues affecting decisions are identified in a more transparent manner. An important first step is to qualitatively identify the key factors influencing the overall PoS and their interactions, for example using an influence diagram (Figure 2).

Upon identifying these key risks, the team progressed with a multifactorial QRA to assess overall PoS. The quantitative approaches for the various risks are summarized below.

Efficacy: Rather than using a simple point estimate approach to address the efficacy risk, the team decided to implement a Bayesian analysis of efficacy data generated during the phase IIb study (unlike classical statistics, Bayesian analysis incorporates both the current and prior knowledge of an estimate). The results of this analysis were incorporated into the QRA to quantify the probabilities of achieving various effect sizes in phase III studies (see Figure 3).

Toxicology Findings: Results from longer-term toxicology studies to assess magnitude and reversibility of toxicology findings were not available at the end of phase IIb study. However, rather than ignoring toxicology in the PoS assessment, the team leveraged the knowledge and expertise of clinical and toxicology experts.

These subjective inputs were expressed as probability distributions (see Figure 3) that were incorporated into the overall PoS. Including subjective inputs quantitatively also ensured that the impacts of the subjective inputs were transparent, reviewable, and comparable with other risks.

Regulatory Risk: Based on Figure 3, there was a clear link between the key regulatory risk (dose restriction) and the outcomes of longer-term toxicology studies. Regulatory experts were interviewed to provide quantitative, subjective input on potential dose restrictions by regulators.

Positive hERG Signal (QT risk): Although a thorough QT study will not be completed by the end of the phase IIb study, the probability of clinically significant QT prolongation was incorporated into the QRA based on pharmacokinetic (PK) and electrocardiogram data from phase I and phase IIa studies. A PK/QT model was developed and used to predict the probability of significant QT prolongation at various systemic exposures of MFT2010.

Competitor Profile: A literature search was performed to assess risks related to competitor molecules. The quantified probabilities for MFT2010 around key risks were compared to the best available competitor data. The probability that MFT2010 will be inferior/superior to a competitor was incorporated into the overall QRA.

In contrast to the team's initial piecemeal approach, the QRA approach was used to assess PoS based on all identified risks. PoS thresholds can be set based on clinical and commercial drug characteristics (and uncertainties), instead of using standard thresholds.

QRA tools can also be used to inform other aspects of development, including identifying the risks that are most influential, understanding the most uncertain risks, and implementing a value of information analysis, an approach to guide cost-effective strategies for additional studies.

Learn more about the AAPS Pharmacokinetics, Pharmacodynamics & Drug Metabolism section; visit the section's Web page via the *AAPS Newsmagazine* digital edition.

EXAMPLE APPLICATIONS OF QRA

- Efficacy
- Safety
- Regulatory
- Trial design
- Drug portfolio evaluations
- Finance
- Marketing
- Sales
- Manufacturing
- Supply Chain
- Business development
- Outcome research
- Litigation
- And many more

Case Study 2: Clinical Trial Design & Value of Information

"How do we optimize our next clinical trial?" This question is frequently asked in drug development team meetings as members ponder clinical trial design.

Asked less frequently is "What is my next clinical trial worth?" If teams seek to answer this question, they are better enabled to truly optimize their trials.

Example Problem

The following example will illustrate the trade-offs that must be weighed to design an optimal trial. In the treatment of outcomes diseases, such as Alzheimer's, companies focus on patient disease progression.

Some drugs only affect symptoms. Much more valuable drugs would mitigate or even reverse the progression. However, measuring whether a drug is disease modifying is very difficult because the clinical endpoints are extremely noisy, and the disease progression rate is sufficiently slow so that differences may not be apparent for months or years.

Ambiguous Trade-offs

Determining the optimal trial can cause ambiguous trade-offs. First it has large consequences for value to the marketplace. The difference can be between the drug being labeled disease modifying (blockbuster) or not (me-too).

Should the trial include many patients and be slower or have fewer patients and be quicker, especially in light of the uncertain timing of competitors? What are the trial costs and impact on commercial value?

More patients will provide a more reliable estimate of progression, but the cost of delaying the launch can be considerable. Similarly, the financial risk of a failed trial can be tremendous; taking a short cut might yield an ambiguous or negative trial result, even when that same drug could be proven a winner with a better design.

Further, there is considerable uncertainty in the degree of efficacy and tolerability. These trade-offs are hard to compare

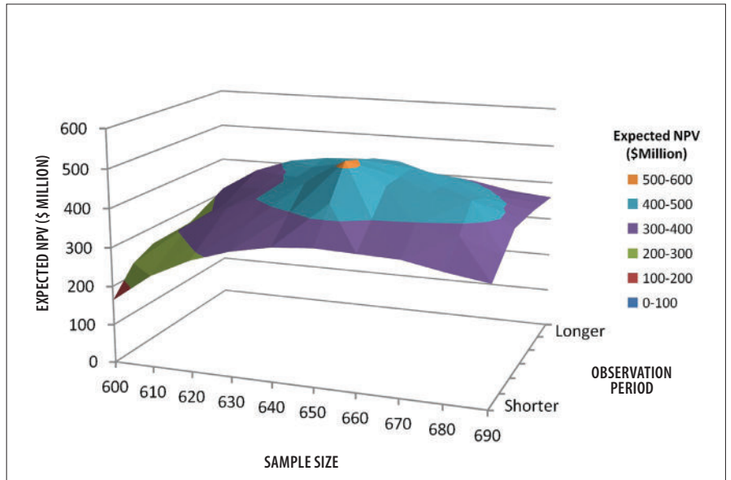

FIGURE 4. *Example graphical result from integrated QRA to inform clinical trial design. The orange peak shows the point of maximum eNPV.*

to most teams, leading to suboptimal decisions that omit critical issues and ignore relevant past clinical data.

Estimating Value

Estimating the value of each clinical trial alternative using a well-conducted QRA allows teams to cope with trade-offs systematically. The consequences of failure and value of success can be put into equal terms using financial metrics, such as expected net present value (eNPV).

The PoS can be estimated using clinical data translated into probabilities via drug and disease modeling and trial simulation, combined as appropriate with industry attrition rates and expert opinion. Further, the uncertainty around how good or bad the drug will be (product profile) can be generated using the same clinical data and clinical utility metrics. Expert opinion can also be included in the estimation.

The team can then compare trial alternatives on equal terms, finding the optimal design while considering uncertainty (see Figure 4). Notably, the same techniques can be used to measure the value of information gained from using surrogates or biomarkers in earlier clinical trials, estimating how certain one can be of their predictive value and thus informing the design of trials to more quickly kill ineffective drugs while advancing good ones.

Case Study 3: Business Development Decision

Buying or selling, in- or outlicensing, or codeveloping products involve the evaluation of numerous clinical and commercial risks. In business development (BD), those risks are typically evaluated through what-if or scenario analyses.

Although useful, such analyses only help with understanding possibilities but do not provide any insights into the probabilities associated with reaching certain financial results. Also, QRA is typically constrained to estimating the expected values (e.g., eNPV) in the few pharmaceutical firms that perform a QRA of their BD deals.

Quantifying Risks/Options

QRA models capture clinical and commercial uncertainties into one model, providing more accurate valuations and a better understanding of risks (e.g., probability of NPV > 0). Especially in the typical short time frames available to value BD opportunities, a quantification of risks can provide valuable insight for management as to why the opportunity should (or should not) be pursued and prioritize the most important factors for success.

QRA can also allow for the valuation of opportunities in which one or either party is given the flexibility to change the contract at a later point in time (i.e., evaluation of option).

CONCLUSION

Throughout the full drug development and commercialization process, QRA can considerably improve team and managerial decision making in situations of risk and uncertainties. Although using QRA to support decision making can never guarantee the best outcome, it can improve the odds of deploying research and development or financial resources more effectively. Given the high risks and large financial stakes within the pharmaceutical industry, QRA can considerably improve decisions when used as an integral part of the decision-making process.

Interested in learning more about QRA? The authors have set up a special Web site at www.epixanalytics.com/aaps that contains further information on how to get started with QRA, useful references, example models, and a forum to share your experience or pose question to the authors or other readers.

DISCUSSION POINT

We want to know your opinion! Please discuss the following question with your colleagues via AAPS' Facebook and LinkedIn pages. Go to the AAPS Newsmagazine *digital edition to link to the AAPS Facebook and LinkedIn pages directly.*

For which applications within the pharmaceutical industry do you think QRA would be most useful? Why?