

PHARMACEUTICALS AND MEDICAL PRODUCTS

RISK ANALYSIS TAKES A CENTRE STAGE

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The stakes for pharmaceutical companies to proactively understand and manage risk and deliver innovative and cost effective products are increasing

Introduction

The pharmaceutical industry is characterized by high risks and uncertainty throughout the business system. One estimate¹ is that pharmaceuticals can be as much as 50% riskier than the Standard & Poor's (S&P) 500. Also, research by Tufts² University suggests that only one-third of new drugs recoup their R&D investment, a sobering fact given high attrition rates, long development times and a cost of US\$0.9 - \$1.7 billion to bring a new drug to market³. In addition, the crisis in financial markets which is forcing governments to increase debt will strain industry economics further. The stakes for pharmaceutical companies to proactively understand and manage risk and deliver innovative and cost effective products are therefore increasing, and this also applies to companies developing medical devices and diagnostics.

The goal of this white paper is to illustrate how probabilistic risk analysis can provide a powerful tool to better understand and manage risks to which the pharmaceutical and medical device industry is exposed. We will first provide a brief overview of quantitative risk analysis, followed by a description of how probabilistic risk analysis can help unravel the complex interactions between risk drivers and provide insight to support better decision making. We will also offer a number of example areas where risk analysis may be particularly useful and finish the paper with conclusions and recommendations for next steps.

What is Quantitative Risk Analysis and how can it help you?

In order to understand quantitative risk analysis, it is useful to contrast it with more traditional 'deterministic' analyses. A deterministic analysis is basically a process where the analyst makes a *single-point estimate* of all the inputs into his or her analysis, which is a de facto 'base case'. For example, when analyzing the NPV⁴ of a potential new product, the analyst would estimate a single-point fixed-value assumption about the prevalence of the disease, the market share, price, competitive climate etc. Of course there is often great uncertainty about such parameters and thus the analyst may run several *scenario analyses*. The goal of such scenario analysis would be to get an understanding of the 'worse-case' as well as 'best-case'. (In a further step, the 'base case' may be supplemented with a tornado diagram to show sensitivity to key assumptions). There are, however, a number of problems with deterministic analysis. Chief among them are that deterministic analysis provides very limited⁵ understanding of the financial risks of an investment, new development project or a licensing deal, and does not provide any insights into the probabilities of achieving a certain IRR or other financial threshold or a potentially catastrophic outcome. In addition, it does not help uncover the main risk drivers that determine the risk of investment.

Quantitative risk analysis (QRA) however allows the analyst to specify and take into account how much uncertainty there may be around each and every one of the inputs in the analysis. A great advantage of QRA is therefore that we are not ignoring the risks and uncertainties, but are taking them into account. Because we are allowing for risks and uncertainties in the inputs, the outputs of the analysis better represent the risk and uncertainty of the project. For example, when performing a QRA, we are now able to determine the financial risks associated with a project and understand for example the probability of an IRR higher than the corporate cost of capital. In addition, QRA allows us to understand what risk factors cause the most risk and thus should get the most attention in any risk mitigation efforts.

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So, how does QRA actually work? While a detailed description of QRA is beyond the scope of this white paper, the most common technique used to perform quantitative risk analysis is called 'Monte Carlo Simulation' (see separate box for an explanation). This technique allows us to essentially run thousands of scenarios that provide us with an understanding of the range of possible outcomes of our analysis. A Monte Carlo model can therefore be seen as a model that takes into account likelihoods or chances that some risks and uncertainties may or may not happen. The output from a quantitative risk analysis model can answer many questions such as: "What is the probability that the IRR will exceed our corporate cost of capital?" (see box also for an example model output).

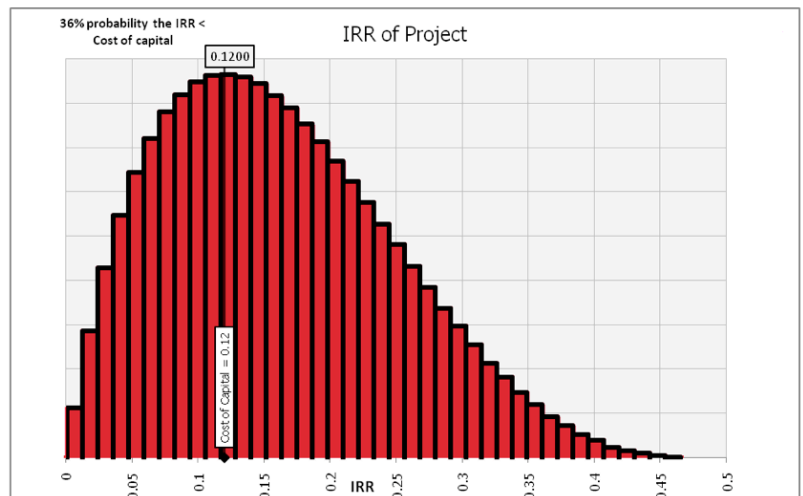
Monte Carlo Simulation – a bit more technical

Monte Carlo (MC) simulation is a quantitative risk analysis technique in which uncertain inputs in a model (for example an Excel spreadsheet) are represented by probability distributions (instead of by one value such as the most likely value). By letting your computer recalculate your model over and over again (for example 10,000 times) and each time using different randomly selected sets of values from the (input) probability distributions, the computer is using all valid combinations of possible input to simulate all possible outcomes. The results of a MC simulation are distributions of possible outcomes (rather than the one predicted outcome you get from a deterministic model); that is, the range of possible outcomes that could occur and the likelihood of any outcome occurring. This is like running hundreds or thousands of "What-if" analyses on your model, all in one go, but with the added advantage that the 'what-if' scenarios are generated with a frequency proportional to the probability of each scenario occurring.

Like the input parameters, the results of Monte Carlo Simulation models are also in the form of probability distributions that essentially take into account all uncertainties and risks. These output distributions provide a range of all possible costs AND an understanding of which outcomes are more probable. In addition, through sensitivity analysis, the model provides an understanding of which parameters or risk drivers should be focused on by management to reduce uncertainties and risks.

A number of tools exist for implementing Monte Carlo Simulation models with the most widely used being Crystal Ball, @RISK and RiskAMP.

Example Model Output



Applications of quantitative risk analysis in the pharmaceutical and medical device industry

After this quick overview of QRA we provide an overview of a number of areas in the pharmaceutical and medical device industry where quantitative risk analysis can provide real insight.

Business Strategy

The applications of quantitative risk analysis within "business strategy" ranges from business development to project and portfolio management:

1. **Business development.** As R&D productivity declines and development & marketing costs balloon, companies are turning to acquisitions and in-licensing to bolster internal development portfolios or collaborations and out-licensing to share costs & risks. In this environment, negotiations and deal structures are increasingly competitive and complex, involving equity stakes and the sharing of risk and value via co-development & co-marketing arrangements, up-front and milestone payments, stepped royalties, penalty clauses, options and even quid pro quos. Probabilistic financial models (utilizing Monte Carlo Simulation) can help you to gain insight on risks, options and value drivers in order to optimize deal structure and support negotiations and decision-making.

2. **Project management** focuses on reaching milestones on schedule and within budget whilst ensuring quality. Unfortunately, uncertainty is an inevitable aspect of projects. Understanding project risks, which can negatively impact the achievement of development targets, resources and costs, time-to-market and overall project value, represents a key challenge. A variety of modeling techniques can be applied to understand risks, opportunities and options – e.g. real options, decision tree analysis, DCF modeling and Monte-Carlo simulation - and provide the foundation for risk mitigation and contingency planning.
3. **Portfolio Management.** Maximizing portfolio value at an acceptable level of risk, given inter-correlated project risk, limited R&D investments and the need to meet financial and strategic goals requires an understanding of the drivers of value and risk at multiple levels (project, indication, therapeutic area, divisional, corporate). Techniques such as efficient frontier and value at risk (VaR), which are part of quantitative risk analysis, can help you strengthen portfolio optimization decisions and provide valuable insight into R&D productivity, confidence levels for the current portfolio's future contribution to top-line and bottom-line corporate goals and portfolio gaps.

Sales & Marketing Planning

Quantitative risk analysis also has applications within a variety of sales and marketing planning domains including sales forecasting and sales force deployment:

1. **Sales Forecasting** often relies on single point estimates of assumptions with a Tornado diagram to show sensitivity. This generates a naïve and flawed view of risk when a holistic view is needed. It is therefore important to incorporate probabilistic algorithms for the drivers of market share, e.g. efficacy, order of entry, sales and marketing spend. The application of Monte Carlo simulations can provide decision makers with an understanding of the distribution of sales outcomes, confidence levels and the extent to which individual assumptions contribute to overall sales variance.
2. **Sales force deployment.** The optimization of sales force territory allocation is a key challenge for sales and marketing management. An interesting and detailed case example of a modeling project in this area can be found in the case studies part of Vose Consulting's website⁶.

Epidemiology & Clinical Development

The United States Food and Drug Administration & the European Medicines Agency have established risk management guidelines emphasizing the need for risk management programs throughout the life cycle of a drug. In addition, recent high profile product withdrawals due to drug safety underscore the need for a proactive approach to manage clinical development risk and best practice in pharmacovigilance.

1. **Epidemiology.** Probabilistic models supported by historical or market data in combination with expert opinion can be used to better understand disease epidemiology and treatment. These include decision trees to map decision points for treatment algorithms as well as Bayesian and Markov chain models to analyze health states and transitions that recur and change, such as the progression, remission and relapse of chronic diseases and treatment outcomes.
2. **Clinical development.** The probability of successfully completing a clinical trial is a key element in managing development risk. Stochastic modeling and Monte Carlo Simulation can be effectively used to explore and model clinical study design and predict clinical trial outcomes. Primary and secondary end-points can be specified as Monte Carlo forecast values sampled from relevant distributions describing historical data for a control arm and feasibility data for the study arm(s). In a second step, efficacy can be optimized to minimize adverse events.
3. **Pharmacovigilance.** Rare side effects and adverse drug reactions (ADRs) are often unknown at launch. Post-marketing pharmacovigilance uses tools such as data mining to identify “signals” suggesting a potential relationship between drugs and ADRs and to establish drug event associations (DEA's). Data mining techniques draw on a wide range of statistical approaches such as disproportionality analyses, multivariate regression and Bayesian statistical analysis.

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Advantages of Quantitative Risk Analysis

In summary, using quantitative risk analysis in the pharmaceutical and medical device industry can provide a number of important advantages over traditional methods:

- Risk analysis changes the entire paradigm of how stakeholders think about and address risk and uncertainty. The process of developing a quantitative risk analysis encourages an open discussion about risks and uncertainty. This by itself is an important and often useful exercise.
- It incorporates historical data as well as expert opinion (or a combination thereof) and takes into account any relevant information and uncertainty inherent in the data rather than ‘burying’ these uncertainties⁷.
- Quantitative risk estimates are not forced into the “pigeon hole” of a single point estimate or expected value reflected by traditional methods which ignore or attempt to “average out” the risk and uncertainty. For example, a positive project eNPV of \$80m may hide the fact that 90% of all outcomes generate a loss of up to \$20m. Instead, risk analysis recognizes that most estimates and forecasts are inherently uncertain. The risk analysis process helps the stakeholders and project team to also identify risk drivers on which management should concentrate their efforts to reduce the risks and uncertainties.

In order to reap the benefits from using quantitative risk analysis, the pharmaceutical, diagnostics and medical devices industry needs the appropriate risk analysis skills to develop accurate and useful models, correctly interpret the results and properly critique risk analysis. Where outside expertise is needed, we provide a list of items to look for when hiring outside consultants.

What to Look For in a Risk Analysis Consulting Firm

Locating, choosing and hiring the best consulting firm capable of assisting with the application of QRA to the pharmaceutical and medical device industries can be very challenging. To assist in this process, we provide a few key areas that we consider critically important to the selection process:

- **Technical expertise:** Does the consulting firm have staff with the technical expertise to create a robust and functional yet transparent risk analysis? Can they demonstrate proof of such expertise?
- **Experience:** What type of experience does the firm’s staff have in the area of risk analysis within the pharmaceutical and medical device industry? What other types of projects have they worked on? An experienced consultant will produce a better outcome in a shorter period of time.
- **Broad background:** There are many statistical, probability and modeling techniques and tools available. Choose a consultancy with broad experience (experience with a particular software package is not enough), familiarity with a variety of techniques and with the ability to apply the best mix of available methods to your situation.
- **Customer focused and flexible:** It is important for a consultancy to pay careful attention to your specific requirements and provide a customized solution tailored to your needs.
- **Informative and educational:** Work with an outside firm that is truly interested in raising the level of knowledge of your entire team. Also, the solution you receive should be completely transparent and not be a “black box” that only the consultant understands. With increased expertise and a transparent model, your team should be able to modify and reuse the solution without the need for re-hiring the consultancy.
- **Personal service:** You should expect personal service, a high level of responsiveness and complete integrity and independence from a risk analysis consultancy. Be sure to ask for and check references, request a proposal outlining what services will be provided as well as complete costs and a timeline.

Next Steps

This paper has only briefly introduced the application of quantitative risk analysis to the field of pharmaceuticals and medical devices. If you need help starting, implementing or completing a risk-based analysis, or want to develop the in-house expertise, consider contacting Vose Consulting. Vose Consulting’s philosophy is to combine its demonstrable health care-specific risk expertise with its extensive risk experience from a wide range of industries. Within health care, our expertise falls into three broad areas championed by partners and consultants:

- Business strategy, including business development, project & portfolio management
- Sales & Marketing planning - sales forecasting and sales force optimization
- Epidemiology and clinical development – including clinical study design, safety and pharmacovigilance

We have also played an instrumental role in the drawing up of international risk guidelines in the World Health Organization, the United States Food and Drug Administration and other regulatory bodies.

We offer a wide range of risk analysis services and have extensive experience including:

- **Facilitating the development of a dedicated internal risk analysis function:** We have helped a number of pharmaceutical firms design, develop, train and implement an internal risk analysis department.
- **Risk analysis modeling:** We can rapidly design, develop, and validate complex risk analysis models customized to your specific application.
- **Model review:** Vose Consulting has reviewed and critiqued hundreds of models built by our clients. We can produce an assessment of your model's soundness, completeness and accuracy as well as provide recommendations for improvement. Many clients have found this to be a valuable and cost effective service.
- **Training courses and workshops:** We offer both public and custom in-house training courses in the area of quantitative risk analysis.
- **Custom software tools:** Risk analysis models are often built using standard, off-the-shelf software tools and in most cases this works very well. Sometimes however, it may be necessary or desirable to have a custom software tool or application built for specific and unique requirements. Vose Consulting has a team of highly experienced professional software engineers who have built a number of bespoke risk analysis applications for our customers.
- **Expert witness services:** Vose Consulting has provided expert witness services for legal disputes in the courts of Australia, the United States, the United Kingdom and the World Trade Organization. Dispute areas have ranged from corporate revenue insurance to antimicrobial resistance and trade restrictions.

Conclusion

We hope this paper has been useful for you. We invite you to let us know your questions, insights, suggestions and ideas at info@voseconsulting.com.

Please contact us at sales@voseconsulting.com to discuss Vose Consulting services, training or software.

Also, please visit our website www.voseconsulting.com to see our client list as well as additional whitepapers, case studies and the list of currently scheduled training courses.

You are also invited to download a FREE risk analysis training tool ModelAssist from our colleagues at Vose Software – <http://www.vosesoftware.com/modelassist.htm>

¹ V Wayne Guay, Professor of Accounting, Wharton, University of Pennsylvania (13-year period ending 2004)

² Duke University & Tufts Centre for the Study of Drug Development

³ Lower estimate Tufts (period 1995-2000), upper Bain & Co (includes 1 year of marketing and sales costs).

⁴ NPV stands for the Net Present Value

⁵ Only very limited understanding because the worse-case and best-case scenarios only provide insight into two possibilities, and not probabilities.

⁶ See www.voseconsulting.com >> Pharma, Medical Products >> Example Projects

⁷ A good risk analyst is however very critical about the data he/she uses and the assumptions underlying the data and will make sure to highlight and include any uncertainties that 'come with' the data or expert opinions

Founded in 1989, Vose Consulting is a leading international firm specializing in quantitative risk analysis. Our primary goal is to help clients make better, more informed decisions in the face of uncertainty and risk. We accomplish this goal through a combination of risk analysis consulting, training, and software. A core focus of our organization is the provision of cutting-edge risk-based consulting services to customers from industries in the private and public sectors.