MODELING VARIABILITY
FOR
BIOLOGICS STRATEGIC PLANNING

By

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Submitted to the MIT Sloan School of Management and the Department of Electrical Engineering
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ABSTRACT

Making strategic decisions about resource capabilities in the uncertain business of drug development is a challenging task. Novartis, a Swiss pharmaceutical company, is expanding from its success in small molecule therapeutics into the attractive area of biologic therapeutics, both monoclonal antibody and microbial forms. While Novartis has experience developing these types of therapeutics, they have not fully-developed the quantity that the Research group expects to source the pipeline with in the next few years. Therefore the Development group needs to grow. Determining the right number and type of scientists and technicians to hire is difficult due to the variability in the portfolio. The long development timelines, low and variable success rates impact how projects progress through the pipeline. A Monte Carlo simulation model forecasts variability and displays a numerical range of projects and headcount requirements expected for several years. This data is essential for project managers, function heads, and operations leaders to develop the five-year strategic plan for biologic development. This model quantifies the uncertainty of input variables to deliver a calculated risk of output variables, which provides useful and important information for making strategic business decisions.

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GLOSSARY

Biosimilar: a generic or follow-on biologic, either mAb or microbial

EMEA: European Medicines Evaluation Agency, the European regulatory agency that approves pharmaceuticals and medical devices for commercial sale and use

FDA: Food and Drug Administration, the United States federal regulatory agency that approves pharmaceuticals and medical devices for commercial sale and use

Microbial: protein-based molecules expressed in a simpler E. Coli or yeast cell, a type of biologic therapeutic

Monoclonal antibody (mAb): complex protein-based molecules produced by B-lymphocytes that bind to and help eliminate foreign and infectious agents in the body (Reichert, 2005), a type of biologic therapeutic

Phase I/POC/IIa: first clinical trials to explore the safety and tolerability of patients to a drug, small patient population, shorter in length (Rang, 2006)

Phase IIb: clinical trial to confirm dose selection, larger patient population, longer time (Rang, 2006)

Phase III: clinical trial to confirm efficacy and safety to support registration, large patient population, long time (Rang, 2006)

Probability of success: the chance that a drug candidate has to progress from one development stage to another, based on data from clinical trials

Submission: a development phase that accounts for the time between when data is submitted to the FDA and when a drug is officially approved

INTRODUCTION

Pharmaceutical Overview

The pharmaceutical industry exists to discover, develop, produce, and market therapeutic drugs to alleviate disease states and symptoms. The industry relies heavily on scientific research to discover molecules that target specific disease pathways. This research creates the intellectual property, in the form of patents, which create value for the companies who eventually sell those drugs to patients. While blockbuster drugs can bring in billions of dollars in revenue, pharmaceutical discovery and development is a lengthy, risky and costly process. Across the industry a drug typically takes over ten years and costs over $1 billion to bring to market. This includes the fact that only twenty percent of drugs that start down the clinical development pipeline actually make it to the market. (DiMasi, 2007)

Organizationally, most pharmaceutical companies are organized into four groups; Research, Development, Operations, and Marketing. Research identifies target molecules that act to alleviate disease symptoms or address causes. Then Development determines how to scale up the process of creating the molecules into a robust manufacturing process. This occurs in conjunction with a series of clinical trials, which examine and evaluate the safety and efficacy of the drug in a selective patient population. The form and amount of material required for these trials varies by disease specifics and clinical trial designs. The purpose of clinical trials is to generate sufficient data to present to the regulatory agencies, like the FDA and EMEA, in order for them to approve the drug for commercial use. Operations is responsible for the full-scale manufacturing plants and commercial campaigns. The hand-off between Development and Operations usually occurs before Phase III clinical material is produced so that validation runs can take place in the same facility before commercial launch. Marketing ensures that drugs reach the appropriate patients once they are approved for commercial use.

The pharmaceutical industry started over a century ago and has progressed from mixing chemical compounds to growing biological proteins. Today, there are two main classes of therapeutic drugs. Small-molecule therapeutics are composed of chemical compounds formed through relatively simple manufacturing processes. Biologic therapeutics, or biologics, are composed of proteins and are manufactured inside living cells in a more complex process.

Biologics Overview

Biologics arose from scientific breakthroughs in the 1970's and grew through the emergence of biotechnology (biotech) firms. Biologics have grown in the past few decades due to their high research and development productivity in areas of unmet medical need. Most industry consultants predict that pharmaceutical sales will grow more quickly in biologics than small molecules over the next ten years. (Drews, 2003) That may be due to the saturation of small molecule therapeutics and their follow-on generics that increase competition, erode sales, and reduce margins. Historically biologics have not faced as much competition, although that is changing as more companies focus on biotechnology. The EMEA recently approved the use of follow-on biologics or biosimilars, but no company has successfully brought a biosimilar to market due to the highly-complex manufacturing processes and necessity of conducting some clinical trials. This market trend may also be driven by the reluctance of the regulatory agencies to approve new drugs that do not address an unmet medical need or show a significant improvement over patient outcomes than drugs on the market.

The higher research productivity and easier competitive landscape associated with biologics has attracted the attention of the traditionally small molecule, large pharmaceutical firms. (Drews, 2003) Therefore more pharmaceutical companies are either forming partnerships or alliances with smaller biotechnology firms or creating new biologics divisions within Research, Development, Operations, and Marketing. Strategically, the goal is to expand and diversify portfolio pipelines and increase research and development productivity.

Organizational Assessment

Novartis AG (NYSE: NVS) is a diversified healthcare company consisting of four divisions: Pharmaceuticals, Vaccines and Diagnostics, Sandoz (Generics), and Consumer Health. Novartis was legally formed in 1996 with a merger between Ciba-Geigy and Sandoz. Novartis Pharma AG (the pharmaceuticals division) generates the largest revenue, $24 billion in 2007, and contains the most resources, employing over 54,000 associates in 2007. This division is headquartered in Basel, Switzerland, but it occupies multiple sites across the globe. Currently their portfolio contains over 45 key marketed products, which diversifies their revenue into several disease areas and countries. A significant portion of annual revenue is reinvested in research and development. For Novartis, this included $5.1 billion in 2007. Novartis Pharma AG has been very successful in bringing new

products to market. It has received 17 new pharmaceutical product approvals in the US since 2000, which is the most of any pharmaceutical company. (Novartis AG Web site) However, like other pharmaceutical companies, Novartis Pharma AG also is expanding into biologics. This is consistent with the corporate diversified strategy that is a huge advantage to shareholders in terms of mitigating the riskiness of drug development.

Novartis Biologics (NBx) is a newly-reorganized unit within the Development division of Novartis Pharma AG. They are responsible for delivering scientific expertise as well as comprehensive oversight for biologic projects from protein or antibody design up through Phase II of clinical development. They also provide support for biologic projects during both early stages of research and later stages of development and commercial production. An important group within NBx is Process Sciences & Production (PSP), which is responsible for process development and production across 4 groups: Process Sciences, Clinical Manufacturing, Quality Control, and Project Management. With expertise in cell and molecular biology, fermentation, protein purification, protein characterization, bioanalytics, and bioreactor engineering, they advance laboratory-created molecules into pilot plant material for clinical trial use and then into full-scale manufacturing plant batches suitable for commercial sale. Not only is the process and analytical development technically difficult for the unique molecules, but also quality and stability of the manufacturing process must be rigorously tested. There is a comparable biologics-focused unit within the Research and Operations division of Novartis. In addition, Sandoz operates several biologics facilities that are designated for future use in developing and producing biosimilars.

Due to the projected pipeline growth and the new strategic emphasis on biologics, NBx has been asked to increase its resources to accommodate many new projects. While management is determined not to delay clinical trials by placing development activities on the critical path, they also do not want to increase headcount to a point where capacity is underutilized due to pipeline uncertainties. The organization needs to remain flexible to portfolio realizations as projects progress to later development stages. This is very difficult to predict due to timeline delays and probabilities of success. Also if the organization grows too quickly, space, training, and cohesion among groups become issues that require more attention.

While Novartis' size brings resource and investment strength, it also results in multiple approval processes. Although there are matrixed teams around projects, direct communication between divisions is weak, especially in terms of resource planning in Development and Operations.

The management of each division creates its own strategic plans which are presented to higher management teams, in this case meeting and often conflicting at the Pharmaceuticals CEO level or higher. Ideally Novartis should share resources across divisions to quickly adapt to market trends and efficiently utilize headcount and equipment capacity. There is also a push to develop third party contracts that create the option to outsource some projects. While this requires extra internal headcount to manage the collaborations and usually costs more and takes longer than developing the project internally, it increases the organization's flexibility in deploying its internal human resources.

Summary

Novartis Pharma AG is a very successful and innovative global pharmaceutical company that is fortunate to be part of a diversified healthcare company which provides adequate investment and resources for internal growth. Following industry trends and expanding its pipeline portfolio, Novartis made a strategic decision to invest in internal capabilities for biologic development. The challenge is to balance internal growth with the flexibility of third party contracts. Determining the right amount and timing of internal growth is also challenging for the Biologics management team, especially with the high uncertainty of the pipeline portfolio.

BIOLOGIC DEVELOPMENT STRATEGY

Risk and Variability in Biologic Development

Biologic discovery and development is a risky business model. Once a potential target molecule is found, a company must spend millions of dollars to test it in clinical trials which take eight years on average and typically have about a twenty percent success rate of reaching regulatory approval. (DiMasi, 2007) In addition, every molecule is different; although there are standard cell lines and process development steps, there is a high level of variability around developing good manufacturing processes supporting commercial production. In *Science Business*, Gary Pisano describes the uncertainty involved in biologic development as falling into two categories. Primary uncertainty deals with "unknown unknowns." This correlates to the uncertainty of the science behind identifying target molecules and learning how they interact with various disease mechanisms, which confronts academic and professional researchers. Even with years of research experience, it is hard to predict how a target molecule will act in human patients. Secondary uncertainty deals with the "known unknowns" that can be described by probability distributions. (Pisano, *Science Business: The Promise, the Reality, and the Future of Biotech*, 2006) This correlates to the time per phase and probabilities of success per phase that development organizations try to plan around. Historical data collected in studies like the 2007 *Cost of Biopharmaceutical R&D* study by the Tufts Center for the Study of Drug Development gives industry averages in timelines and probabilities of success. (DiMasi, 2007) This data can be used to construct probability distributions to forecast pipeline portfolio success.

Project Statement

Novartis Research predicts a drastic increase in its biologic pipeline over the next ten years, so Development needs to increase its internal resources to meet these demands. However, the resources required for the development of a biologic project are difficult to estimate due to the variability in the time and probability of success of each development phase. Aggregated across a portfolio, strategic resource planning becomes even more difficult. Additionally, Novartis is feeling pressure from the market drug pricing in hopes of curtailing the increasing cost of health care, especially in the United States. This translates into internal corporate goals to reduce development

costs and increase productivity. Therefore internal resource growth must be carefully forecasted to maintain organizational capacity and flexibility.

Project Objectives

The goal here is to develop a model to forecast for resource needs across a portfolio of biologic development projects. By defining input variables with probability distributions, the model predicts a frequency distribution for headcount requirements with an associated probability of occurrence. The model should be easy to update and delivers forecasts within a working day. The model should be usable by Development by the end of the project timeline.

Approach

First, I seek to understand the organization and context of the project objectives. This involves a literature review of the pharmaceutical and biotech industries, resource planning, and modeling. This also includes interviews with various leaders and associates within Novartis Biologics and other areas of the company, such as Portfolio Management and Information Systems. Resource planners at other companies are questioned to develop industry benchmarks. Next, internal data are collected on required capacities for development activities to build data templates for different types of biologic projects. Then a draft model addresses the requested attributes. The draft is tested with example scenarios and improvements are implemented. The final model runs the desired portfolio scenario and shows forecasts to create a strategic resource plan. Finally, this thesis documents the model assumptions, shows a scenario analysis, makes strategic recommendations from the model output, and provides instructions for users to operate the model.

Timeline

The introduction to the industry and company through interviews and literature review took two months to complete. The research on modeling techniques and data collection took one month initially, but was revised later. The draft model took two months to build and improve. The final model was ready in the fifth month of the project. The sixth month was spent presenting the model and implementing feedback as well as documenting the model and its assumptions in this thesis document. The model was in use by Development and Operations in the sixth month, which is when the project was completed.

Summary

While biologic development is risky, novel therapeutics are approved to meet unmet medical needs and create corporate profits which allow for further investment in research and development. Therefore pharmaceutical and biotech leaders must find tools to manage the uncertainty inherent in their business models. Specifically, Development needs a tool to forecast internal resource growth requirements that accounts for the uncertainty in the pipeline portfolio. The management team wants a model that easily shows headcount ranges based on pipeline projections, timeline variability, and probabilities of success. Through a literature review, data collection, and model drafts, a final model provides improved data for strategic resource planning.

LITERATURE REVIEW

Biologic Drug Development

The literature review of biologic drug development focuses on different strategies in timing and flow of development activities. This outlines the necessary development activities and areas for flexibility. Gary Pisano describes the key organizational challenges that confront process development groups in *The Development Factory.* Basically, process development exists to transform a complex, inefficient, and potentially unsafe process from the laboratory to a practical, efficient, robust, and safe process suitable for a commercial manufacturing plant. (Pisano, *The Development Factory: Unlocking the Potential of Process Innovation*, 1997) In biologic development this usually takes three steps, a pilot plant campaign, a medium-scale manufacturing campaign and a full-scale validation campaign. Each campaign consists of three to five batches of material. While the campaigns test process design and improvements, they are also critical to provide material to conduct clinical trials and quality control testing. Organizationally, companies split pilot plant and manufacturing plant operations and management. It is usually less expensive and faster to run a campaign in a pilot plant; however market demand usually requires a larger amount of material and therefore a larger-scale plant for commercial production. (Heinzle, 2006) Since regulatory agencies also approve manufacturing processes and specific plant operations, at least one validation campaign must occur prior to the launch campaign.

The goal of development organizations and project managers is to reduce the development and production time and costs. Although clinical trials generally determine the critical path in products being approved and launched, a biotech's competitive advantage derives from its ability to rapidly and efficiently develop processes. "The goal here is to create an overall optimal process for the production of the desired product." (Heinzle, 2006) Plus, the faster a product is launched and the less it costs to launch, the higher sales and profit margins will be due to increased time on the market with patent protection. With these goals in mind, the organizational structure and interfaces between Development and Operations are the keys to smooth development transitions. It is clear that tech transfer, when processes are scaled up and transferred between facilities, is a key competency that affects timelines and costs. Efficient tech transfers require practice and good communication between development groups, a task that larger organizations trying to emphasize

new areas find difficult. (Pisano, *The Development Factory: Unlocking the Potential of Process Innovation*, 1997)

Biologic development has not yet been standardized like other pharmaceutical and industrial processes. There is an industry push to deploy the same cell lines and create development platforms. This strategy can streamline the development process by allowing most projects to use the same techniques in the same order. However, it will be difficult to standardize biological processes in the same manner as Toyota has with auto manufacturing or Intel has with semiconductor manufacturing. Another area for improvement is the yield from the manufacturing process. The yields have increased significantly at Novartis over the past five years. Based on the new yields, the future strategy is to run more campaigns in the pilot plants since the output is similar to larger, older plants, but less expensive to produce.

Another area in which pipeline portfolio uncertainty affects key decisions is in infrastructure investments. The high cost and long timelines of building a new, FDA-approved manufacturing facility make investment decisions risky. Companies cannot afford to delay development due to lack of capacity in pilot and manufacturing plants, but they also cannot afford to let plants and operators sit idle if the pipeline portfolio fizzles out in early stages. Novartis has an advantage in this respect because it can share capacity with Sandoz, which is developing biosimilars in identical plants. Another popular option is outsourcing. Third-party contracts provide the option to pay another company to perform some or all development steps. Although this typically requires more time and internal resources to manage the contracts, the cost of building an idle plant can be higher and take longer to respond to portfolio changes. Novartis has taken advantage of this flexibility as it tests the stability of its newer pipeline prospects.

Simulation Modeling

The literature review of simulation modeling looks at how to model risk and uncertainty. It is important to keep in mind the organizational goals and limitations and well as user background. Novartis has a robust project management software program to track the progress and costs of specific projects. Development project managers apply a standard template and adjust the time, resources, and costs according to the technical differences with each project. The actual time, resources, and costs are recorded as the project progresses through the development stages. The timelines are adjusted if the project is delayed. While this software is useful in tracking projects and

predicting headcount and budget needs for the upcoming year, it does not determine resource needs beyond the next year or analyze how resource needs of different projects in the portfolio overlap.

Prior to this project and model, the Development approach for strategic planning was to manually cut and paste a project template over multiple years for the forecasted number of projects from Research. Then as the projects progressed through the development stages, the template was changed to account for each projects' specific timeline. This was a very time consuming process. This method delivered a single number for a headcount forecast output, which gave no information about probability of occurrence or risk.

Monte Carlo simulation models allow for a random sampling as input variables; therefore they account for variability within the input factors as defined by probability distributions and show a probability of occurrence for output factors. This allows the user to evaluate the risk associated with strategic planning. Crystal Ball is a commercial Monte Carlo simulation software program. I chose Crystal Ball because it interfaces with Microsoft Excel spreadsheets and is easy to use. In addition, Novartis already owned a version of the software and I thought I could easily adapt it to a Development strategic planning model.

The basic principle of a simulation model is "putting into a single framework the best available information and knowledge about the strategy or structure of the system being studied, the outcomes of interest, and the risks, rates and probabilities affecting each action." (Stahl, 2008) I chose this approach because more industry historical data was available than Novartis historical data. I also want to capture the portfolio uncertainty, but avoid accounting for project specific data. The model runs a portfolio simulation in a few hours by changing one sheet of input variables, rather than manually adjusting an assortment of projects.

Benchmarking

Strategically, Novartis is motivated to compete with two successful biotech firms, Amgen and Genentech. Novartis partnered with Genentech on two successful biologics in the past few years. Although Genentech completed the process development steps for both of these drugs and helped design the scaled-up manufacturing processes, Novartis learned and profited immensely from these projects. Novartis is investing in building biologic capabilities in Research and Development and adapting organizationally and technically to augment its knowledge gains. Genentech and Amgen have well defined process development steps and cell lines. Novartis recently acquired a new, robust

cell line and is rapidly improving the speed and quality of process development technical capabilities. One approach is to match the resources that these biologics organizations devote to the first stage of process development. Committing more resources up front to perform process development activities at risk, prior to passing the first clinical trial, may require a larger workforce, but the tradeoff is less work in later development stages and a faster track through scale up manufacturing activities.

I spoke with employees at Amgen about portfolio modeling techniques for resource planning in development stages. Similar to Novartis, they use an Excel model that is linked to a Microsoft Access database of project information. They manually run portfolio scenarios through an Access macro, but it does not provide all the desired outputs. They are interested in a better way to model the risk and uncertainty of the development portfolio.

Organizational Interviews

One of the biggest challenges Novartis faces in growing its biologic capabilities is efficiently constructing this new organization. I spoke with 15 leaders in Development, Operations and Portfolio Management to understand how the organization is dealing with its changing structure. The project managers are responsible for the technical development activities and material production for clinical trials. They work in matrixed teams to coordinate the timeline of development activities with the clinical trial schedule. While they plan the project schedule years in advance, they encounter time delays that jeopardize the material supply for clinical trials. Some of the time delays are due to the variability of the project's success in process and analytical development activities. Others are due to the yield from the pilot plant campaigns. Both of these issues occur because new methods and technological advances are being implemented and standardized. As more projects progress down the development path, the organizational efficiencies will improve and the project managers will have an easier time coordinating development activities.

The functional group leaders in Development have a different view of the organizational changes. They are already dealing with the increasing number of projects and pressure to perform more activities with the same number of people. As they hire more scientists to accommodate the increasing growth, they become cramped for both laboratory and pilot plant capacities. Therefore the organization spreads out into new spaces and breaks off into more segmented functional groups. This leads to communication challenges and more tech transfers, actions that tend to delay a project.

These group leaders have resource planning models to plan the number and type of scientists in each of their groups. Models account for the uncertainty around when projects start and how far they advance in the development pipeline. However they are manually intensive and segmented by group, so not easy to duplicate for a larger, more diverse group.

The business groups have a different view of biologics and portfolio modeling. I spoke with the Development and Corporate finance teams as well as the Development portfolio management teams. The finance teams are responsible for forecasting budgets for the next year. They work closely with the project managers and functional group leaders to predict their project and group needs for the upcoming year. While they are heavily involved in strategic planning, they do not use a specific model to forecast budget and investment needs. They would like a model to gain a better idea of the probabilities associated with their budget projections. They run high and low risk variations of the budget, but these are manually intensive. The portfolio management teams use modeling extensively. Most of the models I saw were Excel based or variations of financial modeling software. They are more concerned with portfolio net present value (NPV) projections and how time and probabilities of success affect NPVs. They revise forecasts as projects progress down the development pipeline. The Development portfolio management group is organized by disease area, so they do not separate biologics from small molecule projects. They have not seen a biologic project progress entirely through the Novartis pipeline, so they have limited historical data for the models. They use Novartis small molecule historical data and adjust it slightly with biotech industry historical data. As Novartis launches its own biologics and develops data about company specific timelines and probabilities of success, that data should be used to forecast biologic NPVs. I believe as the percentage of biologics in Novartis' portfolio grows a difference in risk and uncertainty will appear. I did not speak with any marketing groups, but it would be interesting to see how they view the difference between biologics and small molecule products.

Summary

Overall, the literature review of drug development resource modeling reveals the need for a simulation model to quantify risk and variability. Such a model leads to better strategic planning decisions in an uncertain business and scientific environment. While there are multiple options, a Monte Carlo simulation model fits the desired business and scientific inputs and outputs. Crystal Ball is a user-friendly software program that allows for Monte Carlo simulations and calculations in

an Excel spreadsheet format. Although there is no industry standard model, learning how biotech companies manage the uncertainty of biologic development is useful and important in this competitive space. Organizational structure impacts resource planning strategies and decisions. Novartis has changed the Development organizational structure as they adjust internal capabilities with external comparisons. As these changes settle out, groups solidify, and processes become standardized, organizational efficiency and productivity will improve even more.

RESOURCE PLANNING MODEL

Model Statement

To aid in strategic planning, a simulation model determines headcount requirements by year. The model also attempts to express the variability in the requirements by providing a forecast range and associated probability of occurrence.

Approach

This is possible with the use of Crystal Ball, a Monte Carlo simulation software. The model is described in this chapter and is included in Appendix A. An example scenario analysis and associated strategic recommendations are also included. A user guide is written in Appendix B. Data in this thesis is altered for demonstrative purposes and does not reflect actual Novartis data.

Data Collection

The first task is to gather data on project activities and associated working days in order to create a template for the headcount required per project. Templates were created to account for different models of monoclonal antibody (mAb), microbial, and biosimilar development. The templates include Development and Operations activities in the following groups: Process Development, Analytical Development, Drug Substance (DS) Production, Drug Product (DP) Production, Quality Control, Formulation and Project Management. The activities are further broken down by development stage. Each activity is listed under the corresponding stage and group along with the total number of associated working days. These working days are then allocated to a cell(s) corresponding to the specific quarter(s) along the development timeline in which they occur. The result is a matrix of activities by quarter that can be summed to find headcount per quarter and then simplified into a matrix of headcount by phase by group. The headcount is calculated by multiplying the number of working days by the ratio [1 FTE = 200 working days] and the ratio [1 headcount = 80% project work per FTE]. This percentage of project work per FTE is variable, but is assumed to be 80%. The simplified matrices for three of the templates are shown in Figure 1, Figure 2, and Figure 3. These form the main data input for the model.

Choose one: Manual assumptions		Process Development	Analytical Development	Production DS	Production DP	Quality Control	Formulation	Project Management
Project Headcount								
Preclinical	14	5.0	5.0	0.0	0.0	2.0	1.0	1.0
PhI\PoC\PhIIa	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
PhIIb	14	5.0	5.0	0.0	0.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
PhIII	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
Submission	3	0.0	0.0	0.0	0.0	2.0	0.0	1.0
Total Headcount/project	**136**	35	35	25	10	16	7	8

Figure 1: mAb Headcount Template Matrix

Choose one: Manual assumptions		Process Development	Analytical Development	Production DS	Production DP	Quality Control	Formulation	Project Management
Project Headcount								
Preclinical	14	5.0	5.0	0.0	0.0	2.0	1.0	1.0
PhI\PoC\PhIIa	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
PhIIb	14	5.0	5.0	0.0	0.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
PhIII	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
Submission	3	0.0	0.0	0.0	0.0	2.0	0.0	1.0
Total Headcount/project	**136**	35	35	25	10	16	7	8

Figure 2: microbial Headcount Template Matrix

Choose one: Manual assumptions		Process Development	Analytical Development	Production DS	Production DP	Quality Control	Formulation	Project Management
Project Headcount								
Start	14	5.0	5.0	0.0	0.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
Preclinical	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
PhI	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
PhIII	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
	21	5.0	5.0	5.0	2.0	2.0	1.0	1.0
Submission	11	0.0	0.0	5.0	2.0	2.0	1.0	1.0
	4	0.0	0.0	0.0	0.0	2.0	1.0	1.0
Total Headcount/project	**134**	30	30	30	12	16	8	8

Figure 3: biosimilar Headcount Template Matrix

The standard project timeline is shown at the top of each template. This includes the Milestones, Tox Studies, Clinical Studies and Material Campaigns distributed along the eight year timeline. The phases are listed above the years and are defined by the following times:

mAb and microbial timeline			**biosimilar timeline**	
Preclinical	Year 1		Start	Year 1 and 2
PhI\PoC\PhIIa	Year 2 and 3		Preclinical	Year 3
PhIIb	Year 4 and 5		PhI	Year 4
PhIII	Year 6 and 7		PhIII	Year 5 and 6
Submission	Year 8		Submission	Year 7 and 8

It is also possible to manually select assumptions for the headcount by phase by group matrix. Other desired headcount numbers, such as data obtained from benchmarking with other companies, can be entered into a headcount matrix in the data templates. There is a drop-down list included in the model to choose either "Novartis data templates" or "Manual assumptions" as the source of the headcount matrix. This feature maintains the link between the model and the data templates while allowing for easy changes to the headcount assumptions.

Model Description

The goal is to develop a model to forecast resource needs across a portfolio of biologic development projects. By defining input variables with probability distributions, the model uses Crystal Ball to predict a range of headcount requirements with an associated probability of occurrence.

The Input Variables tab, as shown in Figure 4, uses both manual (yellow-highlighted cells) and Crystal Ball (green-highlighted cells) variables. There are two types of manual variables and three types of Crystal Ball variables.

Incoming Projects

Year	mAb - 3 step Target	mAb - 2 step Target	microbial Target	microbial biosimilar & vaccine Target	mAb biosimilar Target
1	5	0	1	1	2
2	5	5	1	1	3
3	5	5	1	1	4
4	8	7	1	1	5
5	10	7	1	1	5
6	10	7	1	1	5
7	10	7	1	1	5
8	10	7	1	1	5

Time in Phase (years)

mAb and microbial	likeliest	min	max
Preclinical	1	0.75	2.00
PhI\PoC\PhIIa	2	1.75	3.00
PhIIb	2	1.75	3.00
PhIII	2	1.75	3.00
Submission	1	0.75	2.50
Total	8		

biosimilar	likeliest	min	max
Start	2	1.75	3.00
Preclinical	1	0.75	2.00
PhI	1	0.75	2.00
PhIII	2	1.75	3.00
Submission	2	1.75	3.00
Total	8		

Probability of Success

mAb and microbial	mean	std dev
Preclinical - PhI	75%	10%
PhI - PhIIb	75%	10%
PhIIb - PhIII	42%	10%
PhIII - Approval	60%	10%

biosimilar	mean	std dev
Start - PhI	80%	10%
PhI - Approval	90%	10%

% at risk	mAb - 3 step	mAb - 2 step	microbial
PhIIb Dev. Activities Performed at Risk	25%	0%	25%
PhIII Dev. Activities Performed at Risk	25%	25%	25%

Figure 4: Model Input Variables Tab

The first manual input is the current number of projects per phase, which can be obtained from the current project pipeline. The input cells are shown in Figure 5.

Current Projects

expected timeline year	mAb and microbial phases	mAb - 3 step	mAb - 2 step	microbial	microbial biosimilar & vaccine	biosimilar phases	mAb biosimilar
1	Preclinical	5	0	0	0	Start	5
2	PhI\PoC\PhIIa	5	0	1	1		2
3		0	0	0	1	Preclinical	0
4	PhIIb	3	0	3	1	PhI	0
5		0	0	0	0	PhIII	3
6	PhIII	2	0	2	2		0
7		0	0	1	0	Submission	0
8	Submission	0	0	0	0		0

Figure 5: Manual Input - Current Number of Projects per Phase

The second manual input is the percentage of projects to be performed at risk (development work completed prior to outcome of phase transition data or decision). For example, the Phase IIb activities performed at risk occur prior to the results of the Phase I\PoC\PhIIa clinical trial. The input cells are shown in Figure 6.

% at risk	mAb - 3 step	mAb - 2 step	microbial
PhIIb Dev. Activities Performed at Risk	25%	0%	25%
PhIII Dev. Activities Performed at Risk	25%	25%	25%

Figure 6: Manual Input - Percentage of Projects Performed At Risk

The first type of Crystal Ball input variable is the number of incoming projects, which are defined by discrete, custom distributions, as shown in Figure 7. The likeliest target from Research is given the highest probability of occurrence. A minimum and maximum are also included with lower probabilities. These variables differentiate between mAb, microbial, and biosimilar projects, include in-licensed projects but exclude outsourced projects. There are separate variables for eight years.

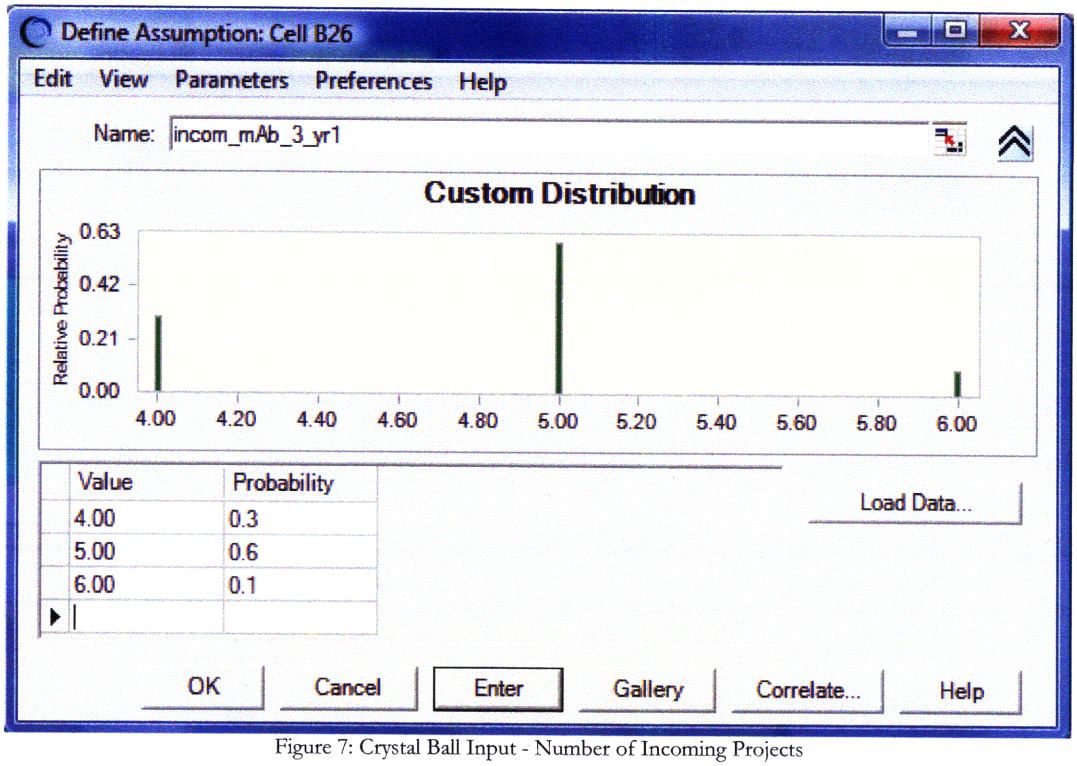


Figure 7: Crystal Ball Input - Number of Incoming Projects

The second type of Crystal Ball input variable is more of a stated assumption than a user-changed input. The time per development phase is defined by a BetaPERT distribution with historical minimum and maximum times per phase. The BetaPERT distribution is commonly used in project management models to estimate task and project duration. The likeliest time per phase is assumed to match the project timeline used in the headcount templates. The distributions for each of the five phases in mAb and microbial development are shown in Figure 8 through Figure 12.

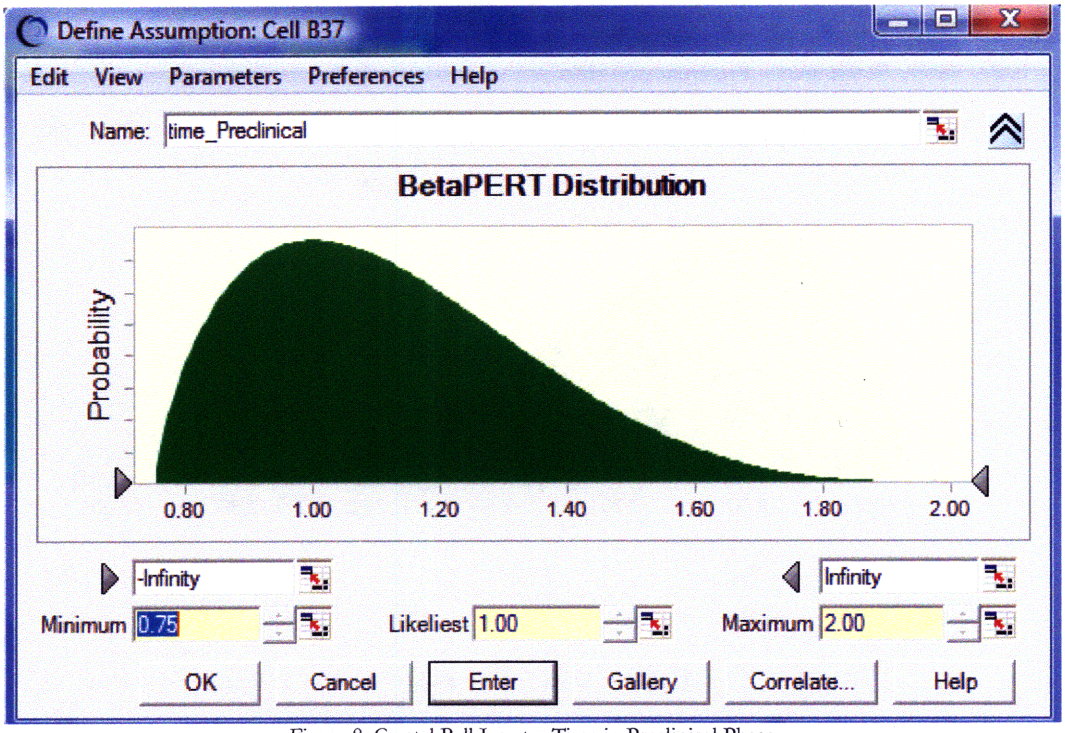


Figure 8: Crystal Ball Input – Time in Preclinical Phase

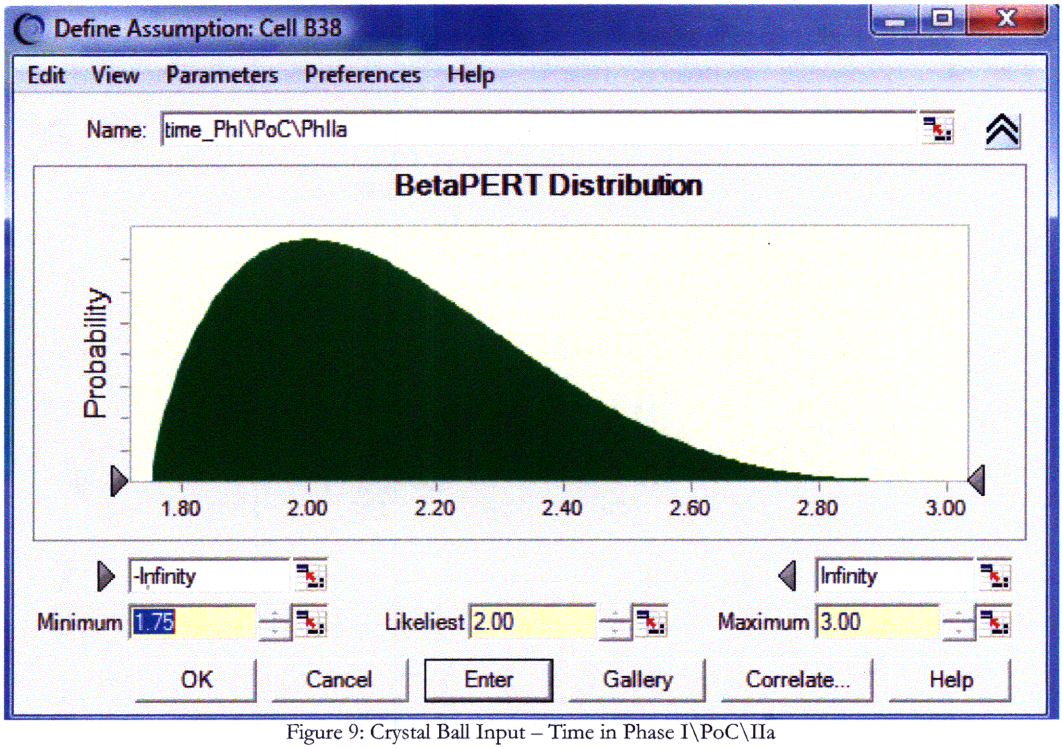


Figure 9: Crystal Ball Input – Time in Phase I\PoC\IIa

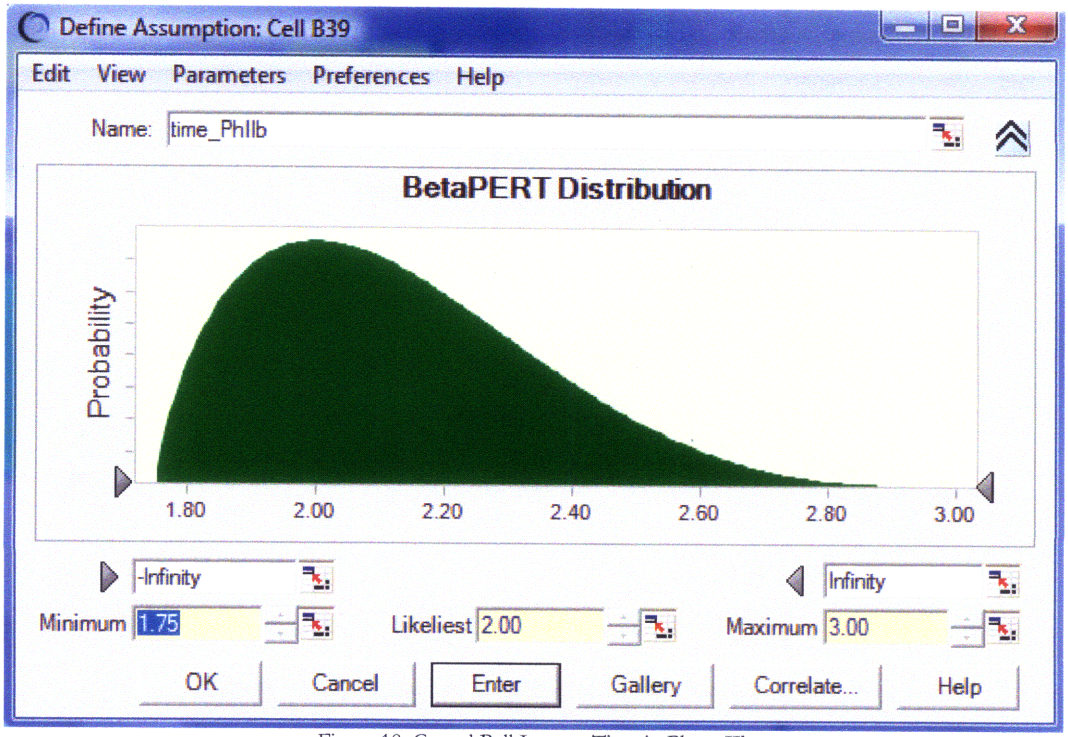


Figure 10: Crystal Ball Input – Time in Phase IIb

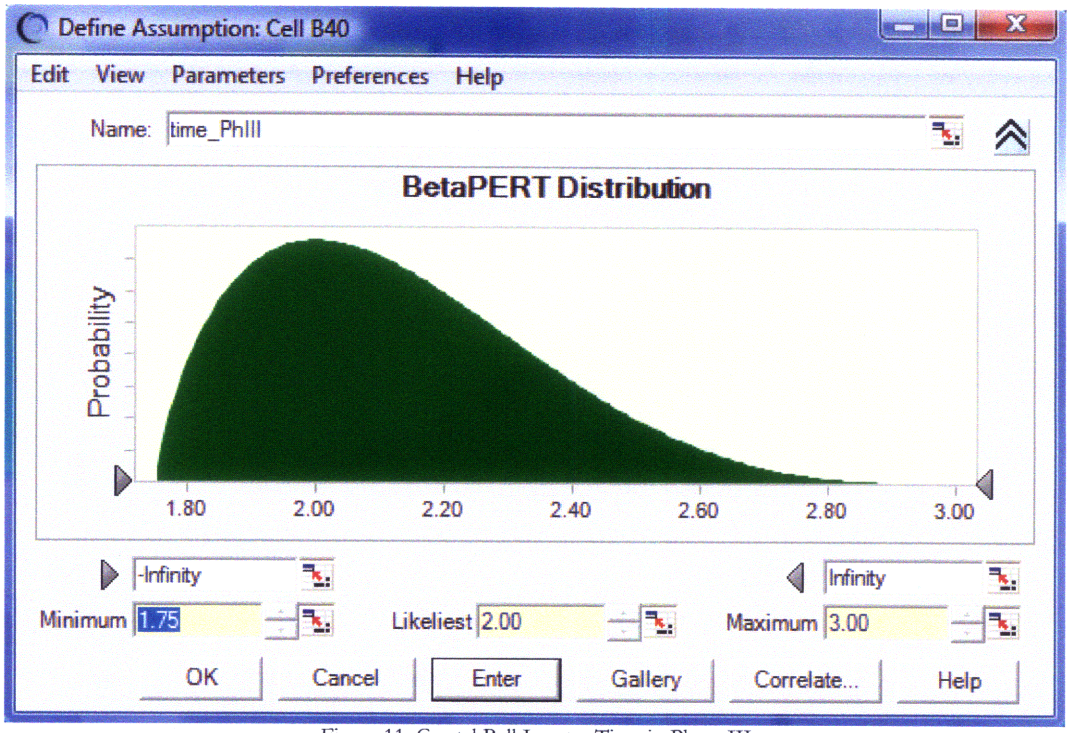


Figure 11: Crystal Ball Input – Time in Phase III

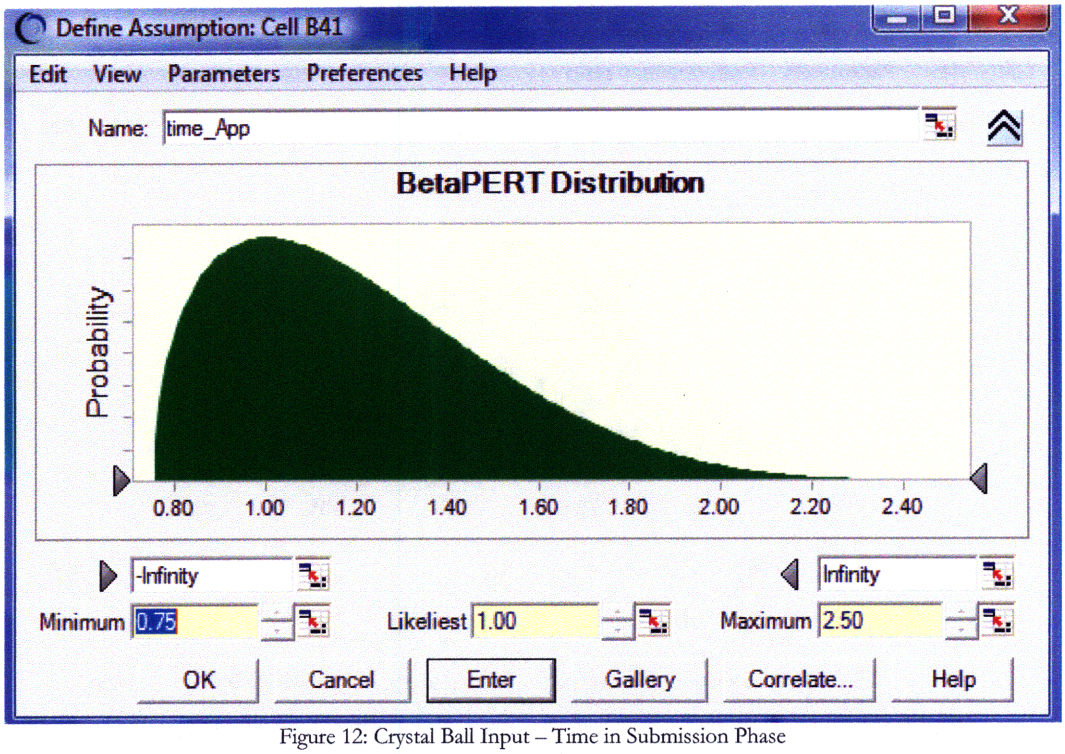


Figure 12: Crystal Ball Input – Time in Submission Phase

The third Crystal Ball input is also more like a stated assumption. The probability of success for each phase is defined by a normal distribution with a standard deviation. The normal distribution was chosen because the historical average is a good indication of the outcome of a large group of projects, like the Development portfolio. This follows the central limit theorem, which states conditions under which the sum of a sufficiently large number of independent random variables, each with finite mean and variance, will be approximately normally distributed. (Rice, 1995) The four phase transition probabilities of success in mAb and microbial development are shown in Figure 13 to Figure 16. The mean originates from the Tufts Center for the Study of Drug Development 2007 study on *The Cost of Biopharmaceutical R&D.* (DiMasi, 2007)

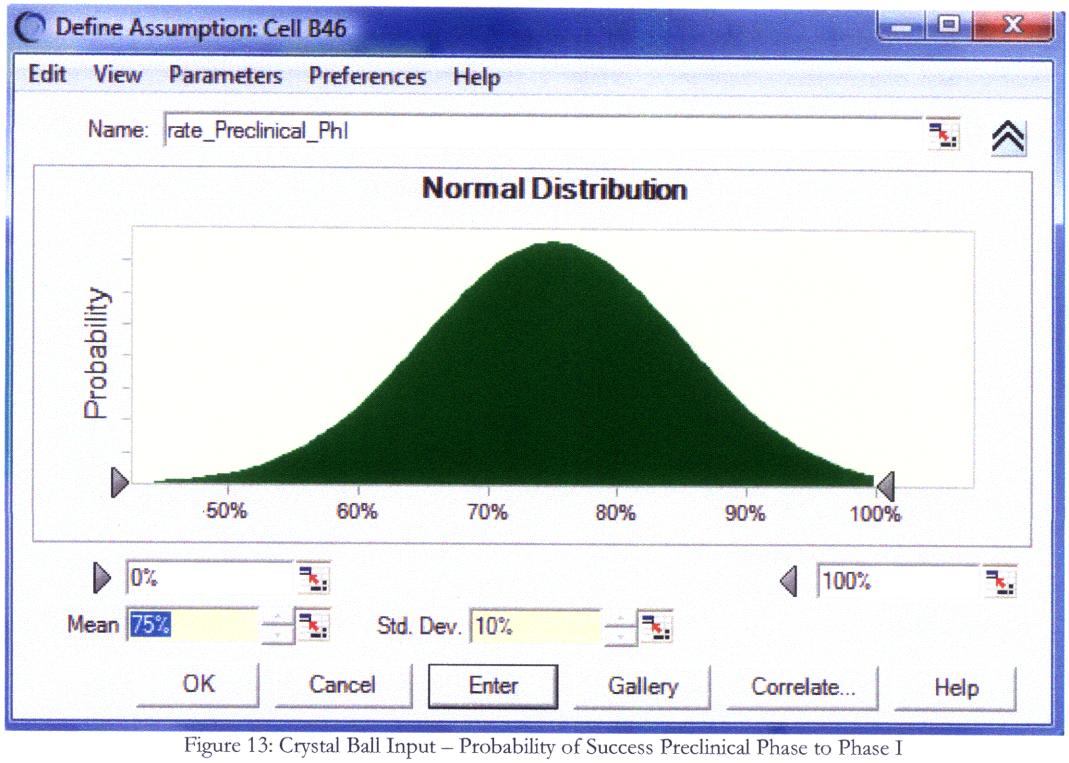


Figure 13: Crystal Ball Input – Probability of Success Preclinical Phase to Phase I

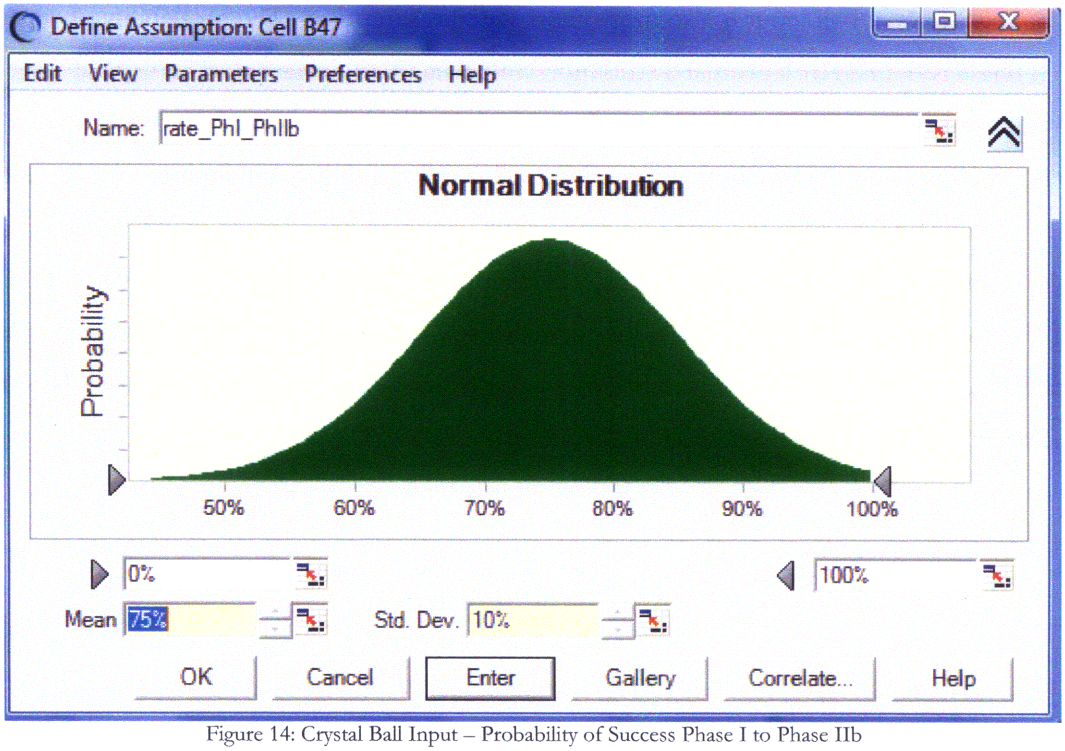


Figure 14: Crystal Ball Input – Probability of Success Phase I to Phase IIb

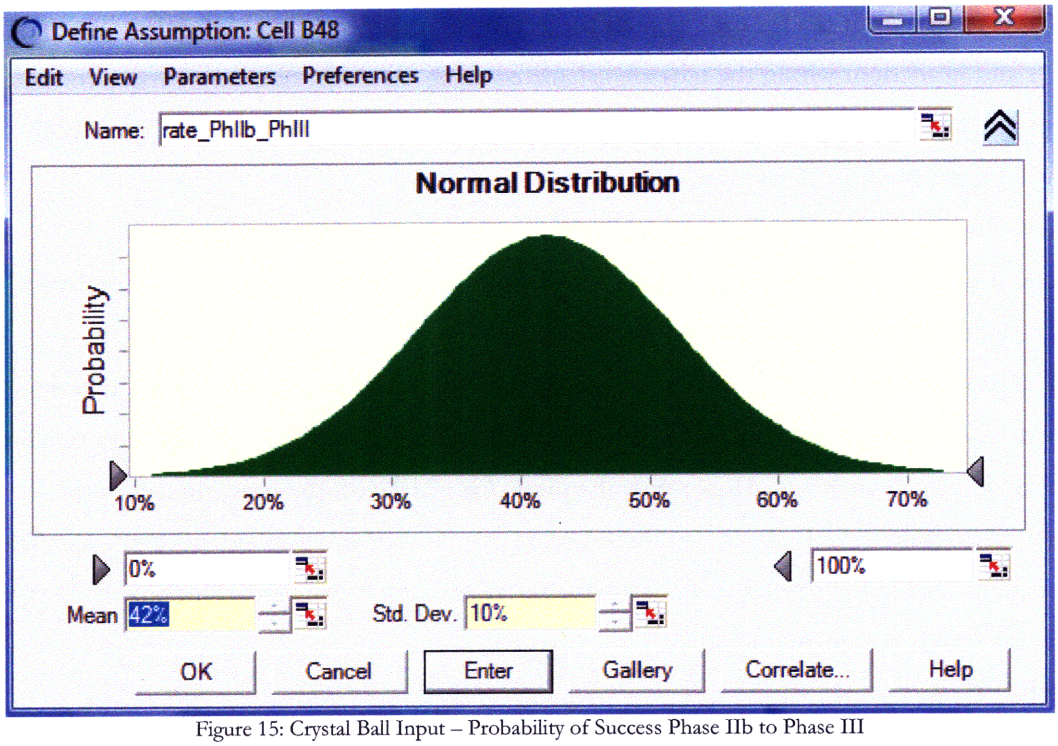


Figure 15: Crystal Ball Input – Probability of Success Phase IIb to Phase III

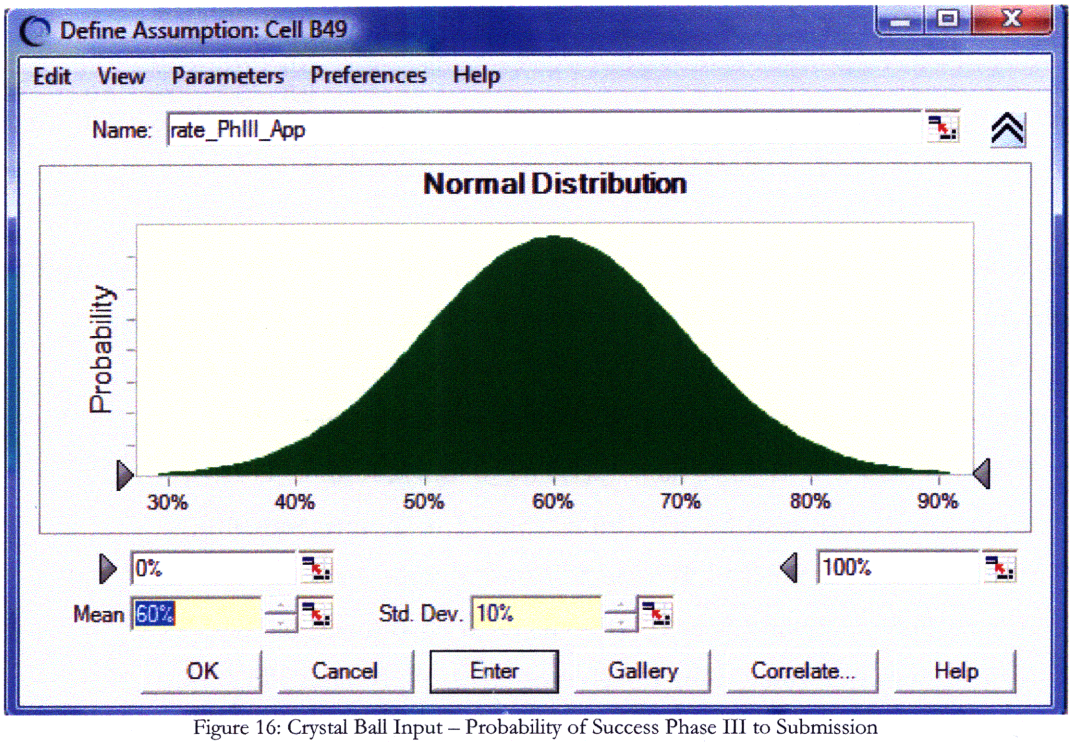


Figure 16: Crystal Ball Input – Probability of Success Phase III to Submission

There is an output tab for each type of project: mAb, microbial, and biosimilar. The number of projects and headcount within the tabs are calculated using the target number or mean for number of incoming projects, time in phase, and probability of success for a phase. The Crystal Ball output forecasts appear in separate windows.

The model calculates headcount requirements per year with this formula:
Headcount per year = Number of projects * Probability of success that a project progresses * Time factor * Headcount for current phase * At risk factor

The project time factor tracks if a project uses the full headcount allotted in the year designated for the normal corresponding phase. If the project progresses according to the likeliest timeline, the project time factor equals 1.0. However if the project gets delayed, the headcount for the delayed phase(s) are stretched out over the number of years that it takes to complete those phases. The projects transition to the subsequent phase the year after completing the current phase. The project time factor matrix is shown in Figure 17.

project time factor													
Preclinical	1.0	0.0											
PhI\PoC\PhIIa		1.0	0.0	0.0									
			1.0	0.0	0.0								
PhIIb				1.0	0.0	0.0	0.0						
					1.0	0.0	0.0	0.0					
PhIII						1.0	0.0	0.0	0.0	0.0			
							1.0	0.0	0.0	0.0	0.0		
Approval								1.0	0.0	0.0	0.0	0.0	0.0

Figure 17: Model Calculation - Project Time Factor

The model uses a nested if statement to calculate each cell in the project time factor matrix. For example, the third year of the Approval phase correlates to the following if statement:

=IF(time_Preclinical>1, IF(time_PhI\PoC\PhIIa>2, IF(time_PhIIb>2, 0,
IF(time_PhIII>2, 0, IF(time_Sub>1, (1/time_Sub),1))), IF(time_PhIIb>2,
IF(time_PhIII>2, 0, IF(time_Sub>1, (1/time_Sub),1)), IF(time_PhIII>2,
IF(time_Sub>1, (1/time_Sub),1), IF(time_Sub>1, 1-(1/time_Sub),0)))),
IF(time_PhI\PoC\PhIIa>2, IF(time_PhIIb>2, IF(time_PhIII>2, 0,
IF(time_Sub>1, (1/time_Sub),1)), IF(time_PhIII>2, IF(time_Sub>1,
(1/time_Sub),1), IF(time_Sub>1, 1-(1/time_Sub),0))), IF(time_PhIIb>2,
IF(time_PhIII>2, IF(time_Sub>1, (1/time_Sub),1), IF(time_Sub>1, 1-
(1/time_Sub),0)), IF(time_PhIII>2, IF(time_Sub>1, 1-(1/time_Sub),0), 0))))

The model creates a matrix with the number of projects in each phase in each year, which includes current and incoming groups of projects. The way that each group of projects progress from year to year depends on the probability of success of phase transition and the time factor. Both effects have been included in the matrix in Figure 18.

Number of Projects (including time factor and success rates)	expected timeline year											
Preclinical	1	5.0	5.0	5.0	5.0	8.0	10.0	10.0	10.0	10.0	10.0	10.0
PhI\PoC\PhIIa	2	5.0	3.8	3.8	3.8	3.8	6.0	7.5	7.5	7.5	7.5	7.5
	3	0.0	5.0	3.8	3.8	3.8	3.8	6.0	7.5	7.5	7.5	7.5
PhIIb	4	3.0	0.0	3.8	2.8	2.8	2.8	2.8	4.5	5.6	5.6	5.6
	5	0.0	3.0	0.0	3.8	2.8	2.8	2.8	2.8	4.5	5.6	5.6
PhIII	6	2.0	0.0	1.3	0.0	1.6	1.2	1.2	1.2	1.2	1.9	2.4
	7	0.0	2.0	0.0	1.3	0.0	1.6	1.2	1.2	1.2	1.2	1.9
Submission	8	0.0	0.0	1.2	0.0	0.8	0.0	0.9	0.7	0.7	0.7	0.7
Total Number of Projects		**15.0**	**18.8**	**18.7**	**20.3**	**23.5**	**28.1**	**32.4**	**35.4**	**38.2**	**40.0**	**41.2**

Figure 18: Model Calculation – Number of Projects Matrix

The at risk factor accounts for the development work that was completed on projects that fail to transition to the following phase. Because the development work was already completed, the headcount needs to be accounted for even though the project has failed. At risk work only applies to Process Development, Analytical Development, Formulation, and Project Management group activities. The at risk factor matrix is shown in Figure 19. The factor is based on the variable percentage that is manually entered on the Input Variable tab, as described above and shown in Figure 6.

at risk factor	expected timeline year										
Preclinical	1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
PhI\PoC\PhIIa	2	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06
	3	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06
PhIIb	4	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06
	5	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06
PhIII	6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	7	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Submission	8	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 19: Model Calculation – At Risk Factor

To calculate the at risk factor, the model multiplies the projects that fail by the at risk percentage and then adds that to the projects that proceed. The following formula is an example of the at risk factor for the first year of PhIIb development work:

=1+ (1-rate_PhI_PhIIb)*at_risk_PhIIb_mAb3

The headcount per phase is taken from the appropriate headcount template matrix, as described above and shown in Figure 1, Figure 2, and Figure 3. The user chooses between

"Novartis data templates" or "Manual assumptions" as the source of the headcount matrix from the drop-down menu above the upper right headcount matrix on each project type tab. The headcount per year for each group is calculated according to the formula above and is shown in matrices by phase and year. Each output tab has six matrices. In addition, a graph displays the totals for each group, as shown in Figure 20.

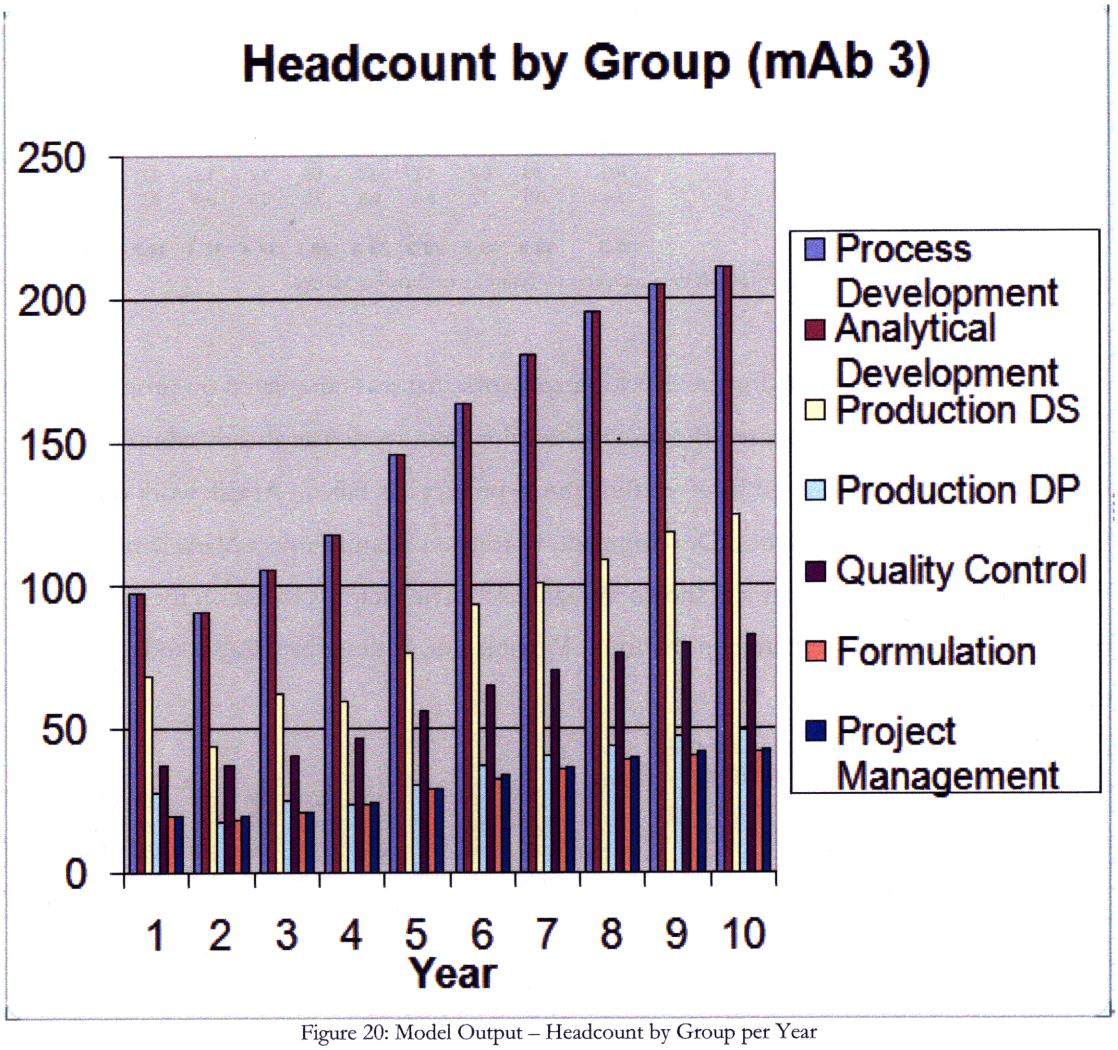


Figure 20: Model Output – Headcount by Group per Year

A Total Headcount by year matrix is obtained by summing the headcount in each group by phase and year. The model allows for display of Total Headcount or Development Headcount, which are calculated using the percentages from the headcount templates. A sample matrix is shown in Figure 21.

Choose one:												
Total												
Total Headcount	expected timeline year											
Preclinical	1	70.0	70.0	70.0	70.0	112.0	140.0	140.0	140.0	140.0	140.0	140.0
PhI/PoC/PhIIa	2	105.0	81.6	81.6	81.6	81.6	130.5	163.1	163.1	163.1	163.1	163.1
	3	0.0	108.8	81.6	81.6	81.6	81.6	130.5	163.1	163.1	163.1	163.1
PhIIb	4	42.0	0.0	55.3	41.5	41.5	41.5	41.5	66.4	83.0	83.0	83.0
	5	0.0	65.3	0.0	81.6	61.2	61.2	61.2	61.2	97.9	122.3	122.3
PhIII	6	42.0	0.0	26.5	0.0	33.1	24.8	24.8	24.8	24.8	39.7	49.6
	7	0.0	42.0	0.0	26.5	0.0	33.1	24.8	24.8	24.8	24.8	39.7
Submission	8	0.0	0.0	3.6	0.0	2.3	0.0	2.8	2.1	2.1	2.1	2.1
Total		**259**	**368**	**318**	**383**	**413**	**513**	**589**	**646**	**699**	**738**	**763**

Figure 21: Model Output – Total Headcount by Year Matrix

The sum across the different project types is displayed on the Total Output tab. Either Total or Development must be chosen on each of the project type tabs in order to correctly add the headcount. This data is also portrayed as a graph, as shown in Figure 22.

Year	0	1	2	3	4	5	6	7	8	9	10
Total Headcount											
mAb	259	368	388	610	669	873	1010	1108	1211	1262	1297
microbial	126	145	88	89	64	74	73	77	78	78	78
microbial bs & v	98	109	84	77	67	72	72	78	79	79	79
biosimilar	175	238	189	310	389	464	477	512	545	572	583
Total	658	859	750	1087	1189	1483	1631	1775	1912	1991	2036

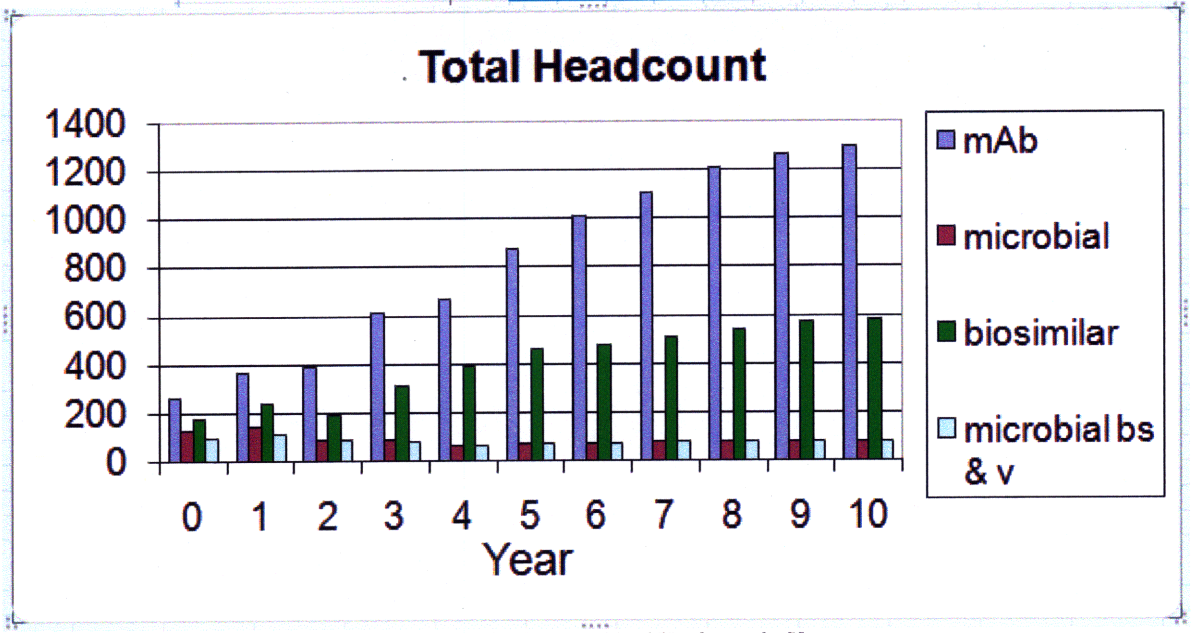


Figure 22: Model Output – Total Headcount by Year

The Total Output tab also displays aggregated Process Development Headcount, Analytical Development Headcount, and Number of Projects in matrices and graphs.

Model Output

While the output matrices and graphs give specific numbers for headcount requirements for each year, the Crystal Ball output forecasts show the range of headcount requirements for each year with an associated probability distribution. The forecasts can be shown for each year, as shown in Figure 23, or combined for multiple years, as shown in Figure 24 and Figure 25.

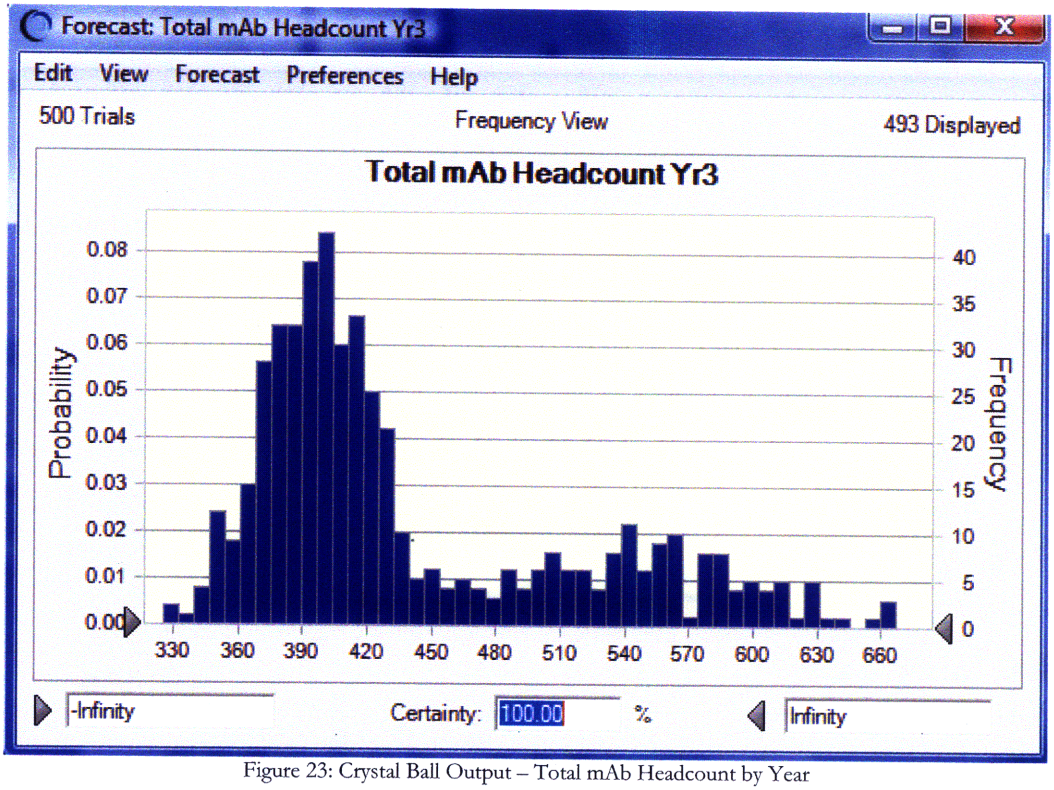


Figure 23: Crystal Ball Output – Total mAb Headcount by Year

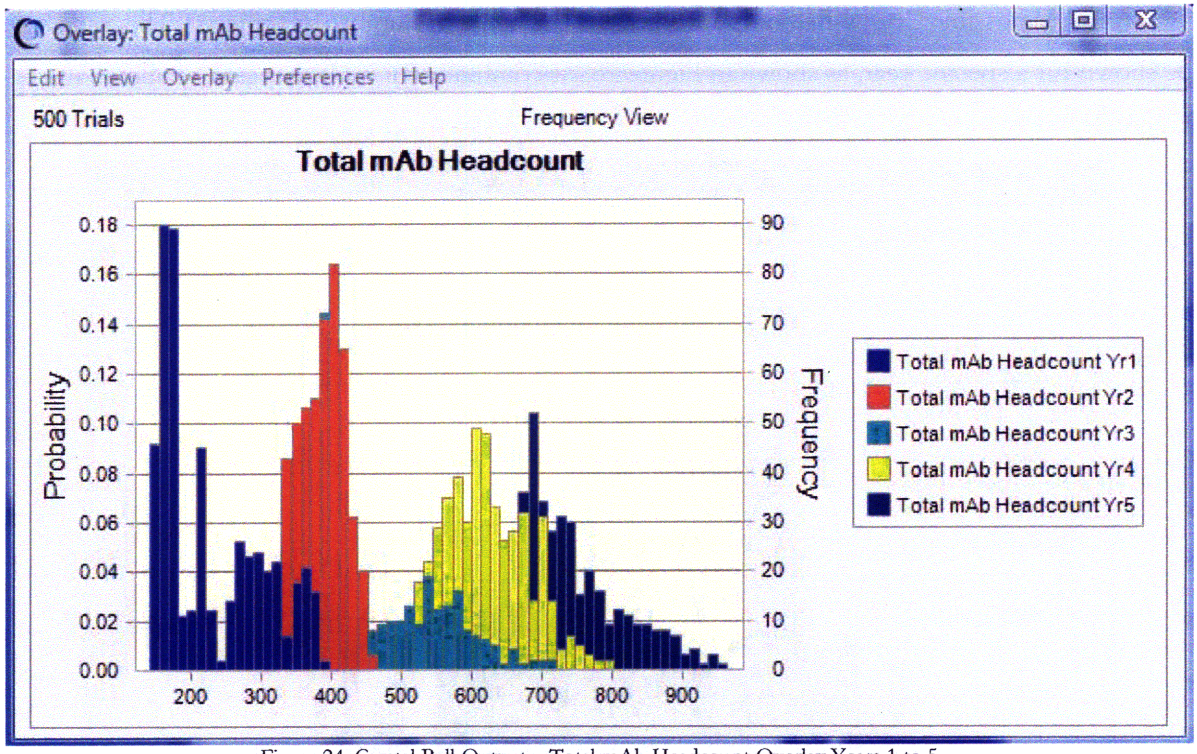


Figure 24: Crystal Ball Output – Total mAb Headcount Overlay Years 1 to 5

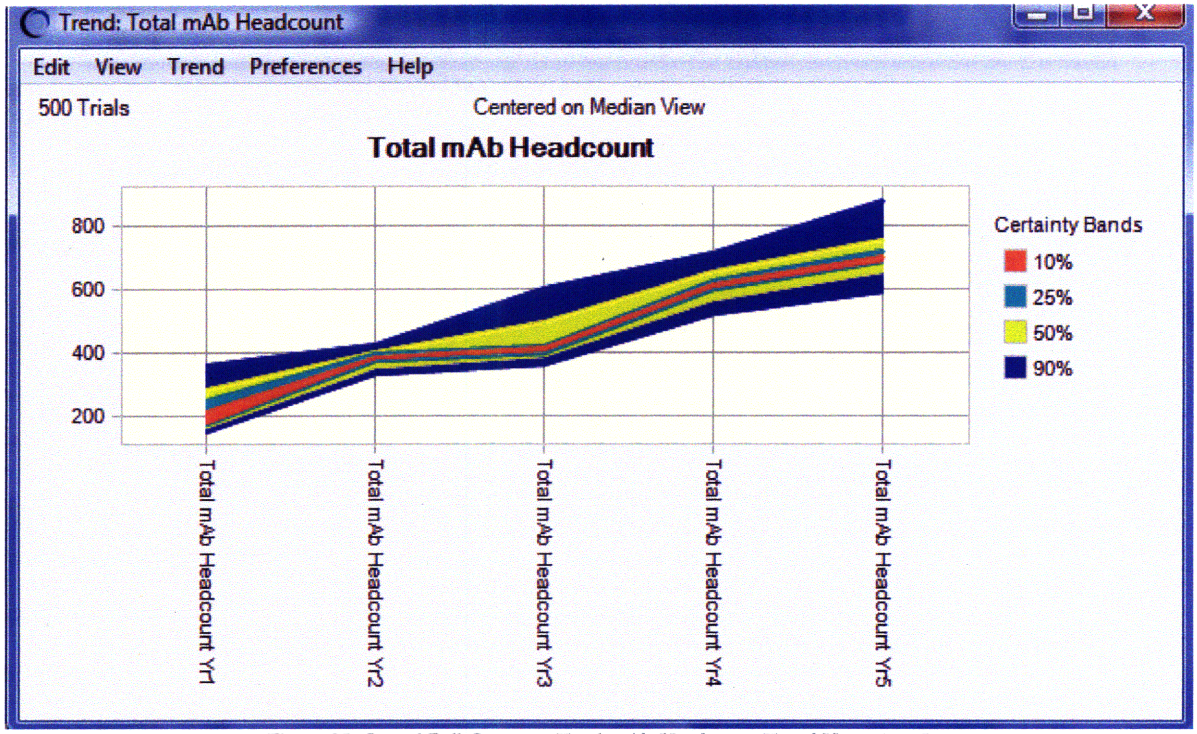


Figure 25: Crystal Ball Output – Total mAb Headcount Trend Years 1 to 5

Another possible Crystal Ball output forecast is the range of number of projects. This can also be shown for a specific year, as shown in Figure 26, or combined for multiple years, as shown in Figure 27.

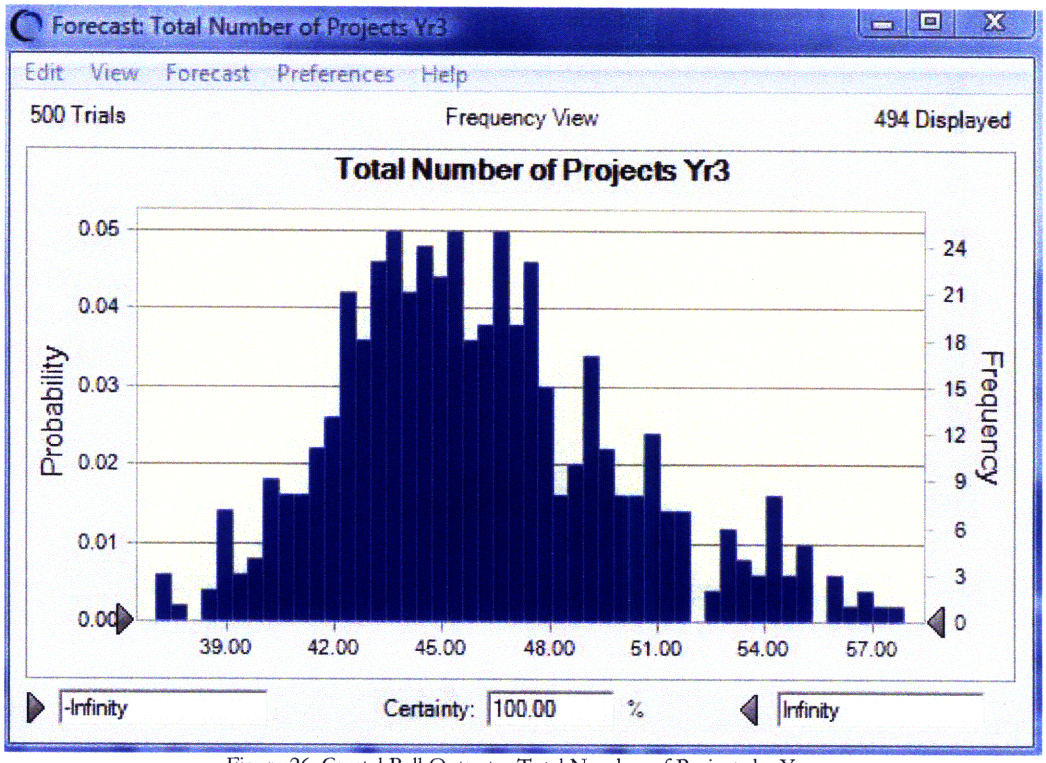


Figure 26: Crystal Ball Output – Total Number of Projects by Year

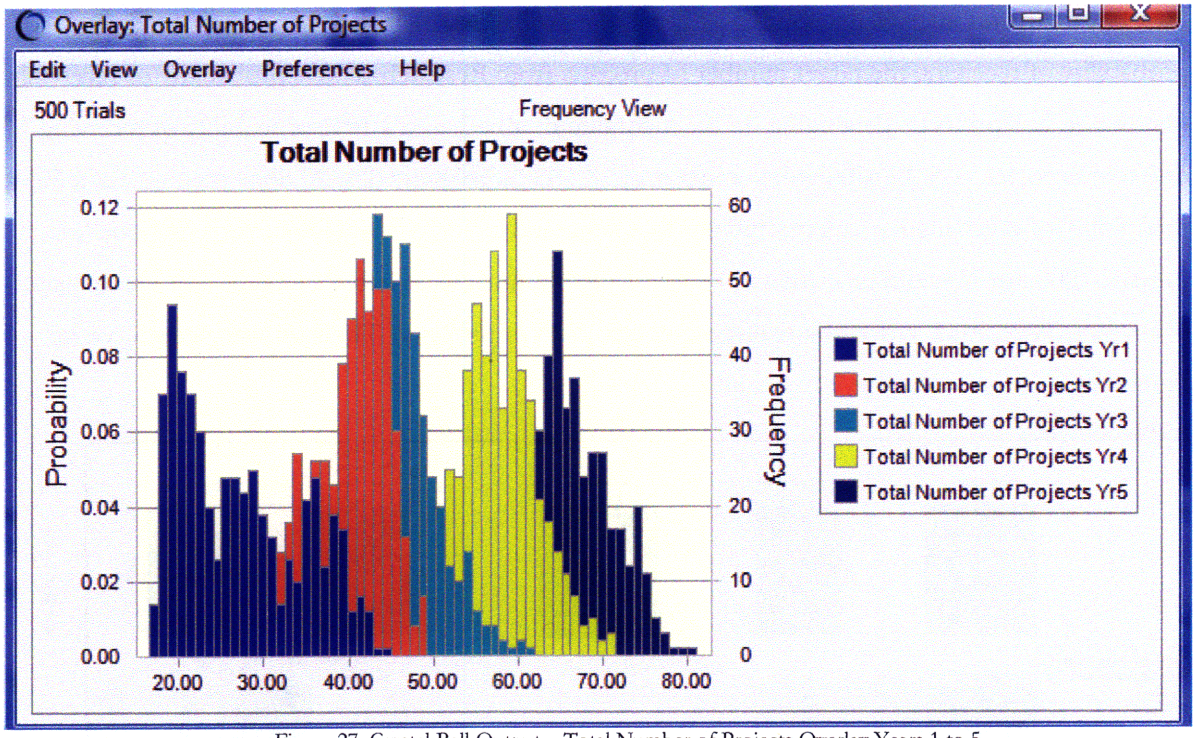


Figure 27: Crystal Ball Output – Total Number of Projects Overlay Years 1 to 5

Scenario Analysis

To make a strategic recommendation on headcount I chose an example portfolio scenario. This demonstrates how to think about input selection and assumption limitations as well as how to interpret the output forecasts and translate the graphs into a strategic plan.

As inputs, the current project portfolio was translated into the model's current projects matrix, as shown in Figure 28. In general, it is better to count projects as whole numbers in order to best account for their resource needs in later stages. Projects that are outsourced are not included. Outsourcing is discussed in the following section on Strategic Recommendations.

Current Projects

expected timeline year	mAb and microbial phases	mAb - 3 step	mAb - 2 step	microbial	microbial biosimilar & vaccine	biosimilar phases	mAb biosimilar	Total
1	Preclinical	5	0	0	0	Start	5	10
2	PhI\PoC\PhIIa	5	0	1	1		2	9
3		0	0	0	1	Preclinical	0	1
4	PhIIb	3	0	3	1	PhI	0	7
5		0	0	0	0	PhIII	3	3
6	PhIII	2	0	2	2		0	6
7		0	0	1	0	Submission	0	1
8	Submission	0	0	0	0		0	0
		15	0	7	5		10	37

Figure 28: Example Scenario - Current Projects

For mAb and microbial incoming projects, the probability distributions account for a 60% probability of receiving the target number of projects from Research, a 30% probability of receiving one or two less projects (depending on the incoming number), and a 10% probability of receiving one more project. For biosimilar incoming projects, the probability distributions account for a 50% probability of receiving the target number of projects and a 50% probability of receiving one less project. The timeline and probability of success distributions were left as defined. For percentage of projects developed at risk, the realistic choice is 25% of projects. These choices are shown in Figure 29.

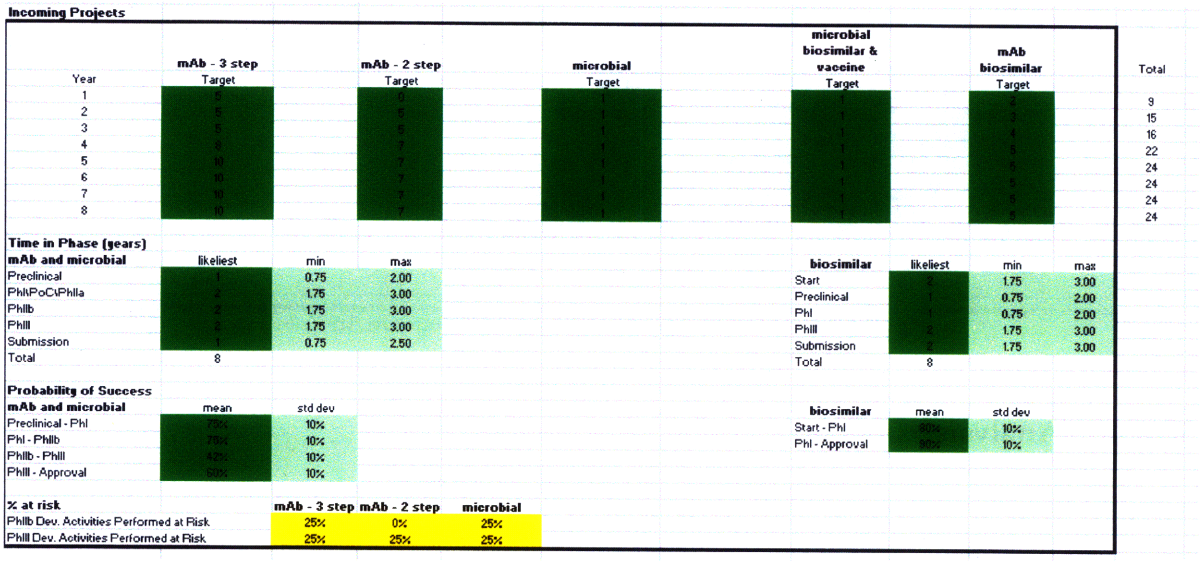
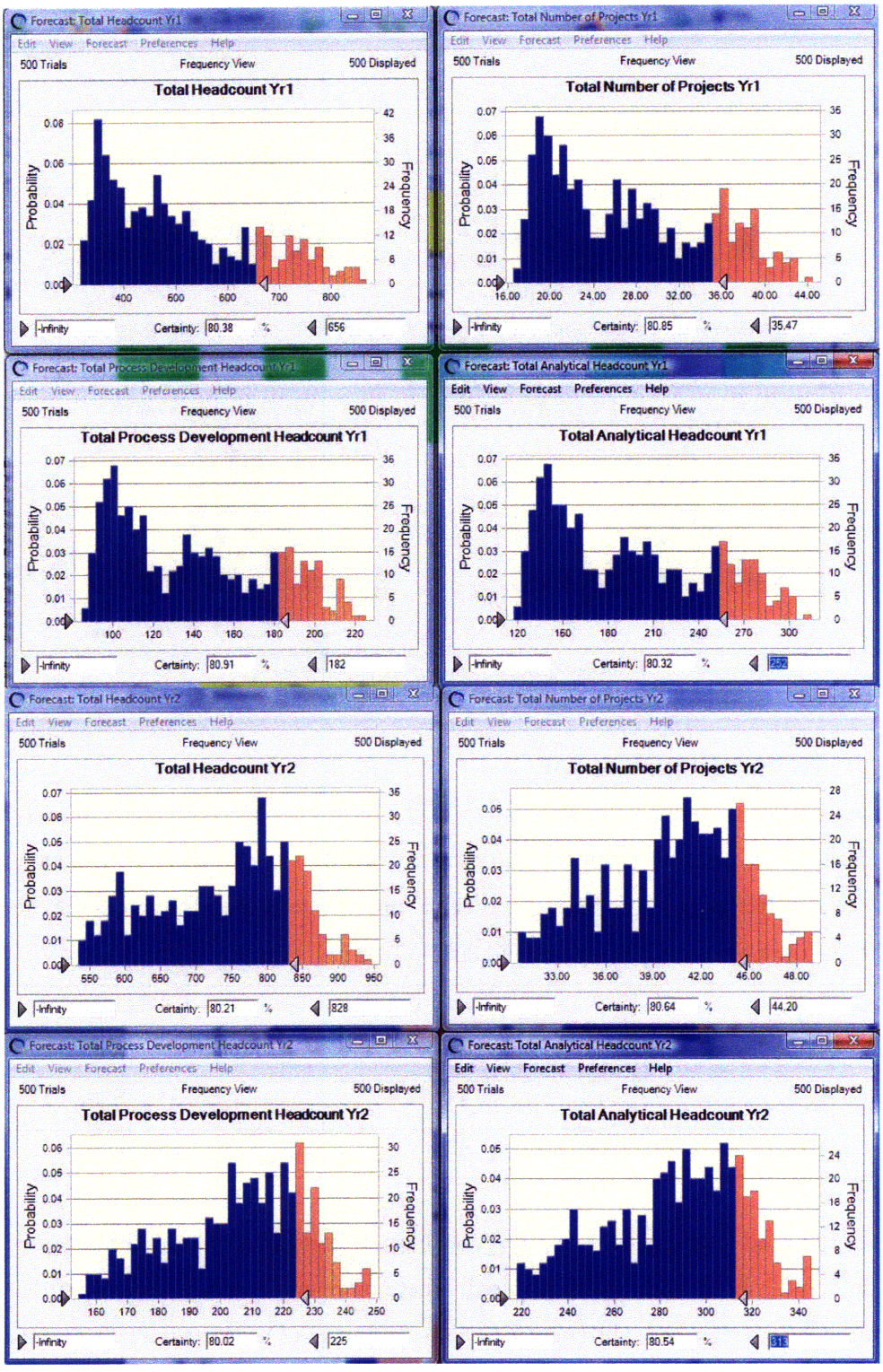


Figure 29: Example Scenario - Incoming Projects

These input choices led to the following headcount forecasts. Figure 30 displays the forecasts for Total Headcount, Total Number of Projects, Total Process Development Headcount and Total Analytical Development Headcount for year 1 through year 3.


Forecast: Total Headcount Yr1
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Headcount Yr1
Probability
Frequency
-Infinity
Certainty: 80.38 %
656
Forecast: Total Number of Projects Yr1
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Number of Projects Yr1
Probability
Frequency
-Infinity
Certainty: 80.85 %
35.47
Forecast: Total Process Development Headcount Yr1
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Process Development Headcount Yr1
Probability
Frequency
-Infinity
Certainty: 80.91 %
182
Forecast: Total Analytical Headcount Yr1
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Analytical Headcount Yr1
Probability
Frequency
-Infinity
Certainty: 80.32 %
Forecast: Total Headcount Yr2
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Headcount Yr2
Probability
Frequency
-Infinity
Certainty: 80.21 %
828
Forecast: Total Number of Projects Yr2
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Number of Projects Yr2
Probability
Frequency
-Infinity
Certainty: 80.64 %
44.20
Forecast: Total Process Development Headcount Yr2
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Process Development Headcount Yr2
Probability
Frequency
-Infinity
Certainty: 80.02 %
225
Forecast: Total Analytical Headcount Yr2
Edit View Forecast Preferences Help
500 Trials
Frequency View
500 Displayed
Total Analytical Headcount Yr2
Probability
Frequency
-Infinity
Certainty: 80.54 %

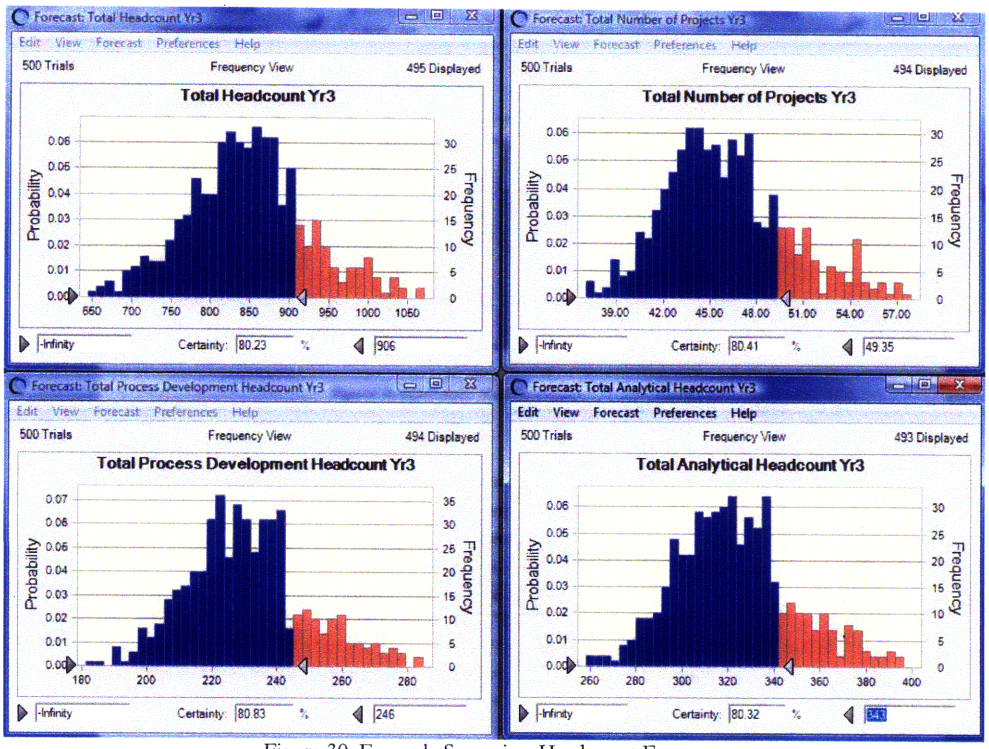


Figure 30: Example Scenario - Headcount Forecasts

Strategic Recommendations

To translate this data into a strategic statement, I look at the headcount requirements for a specific certainty level and then compare them across years. For example, choosing an 80% certainty level of developing the following number of projects corresponds to requiring the following headcount for years 2009 (year 1) to 2011 (year 3).

Year	Number of Projects	Total Headcount
2009	35	656
2010	44	828
2011	49	906

These forecasted numbers have an 80% probability of being needed or in other words I am 80% certain that this headcount will be required. These numbers should be used to set the headcount for the strategic plan, differentiating between Process Development and Analytical Development. One interesting conclusion is the rate of growth from year to year. There is a larger jump between 2009 and 2010 than between 2010 and 2011. This is mostly due to project delays and

phase transition points. This might be a point to consider outsourcing for a portion of the growth; a move that would increase flexibility until the higher number of projects is realized. If headcount growth is restricted at a number below the total headcount, outsourcing contracts should be considered to cover the expected increase in the number of projects. In this case, the model should be rerun with a lower number of incoming projects that year to account for the ones that will be outsourced. The difference in headcount will show the headcount saved and perhaps the monetary worth of a third-party contract.

Summary

This is one example of the data this model contains to answer strategic planning questions. There are several other questions that can be answered around the number of projects, facilities required, budgets, etc. Multiple scenarios should be run and different output forecasts shown to gain a better understanding of the model's full capabilities.

CONCLUSION

Conclusion

In summary, I would like to highlight three major findings. First, the model developed in this work is a useful tool for forecasting not only headcount requirements across a growing biologics portfolio, but also generally helpful for project planning where there are multiple areas of uncertainty. Development and Operations leaders can use it to jointly determine a flexible and responsive headcount strategy to cover the expected growth in mAb, microbial, and biosimilar projects in the next five years. Secondly, the portfolio modeling techniques employed in this thesis are useful to multiple groups within Biologics. Displaying the effects of time and attrition on a prospective portfolio is essential to discussing the best strategic plan to grow an organization. Comparing the forecasted outcomes of multiple scenarios gives managers an opportunity to define options to mitigate potential risks with alternative strategic plans. Thirdly, workforce flexibility is an important aspect of headcount strategy, such as transferring an idle group in Operations to an overworked division in Development. Outsourcing contracts with flexible numbers of projects is another option to moderate internal growth. Overall, this model is effective in creating data to enrich management discussions about headcount planning and other strategic decisions across the biologics industry.

However, as this strategic planning model forecasts how projects progress, it still relies on historical data for the timeline and probabilities of success. Since Novartis Biologics is a young organization, the data included may not be the best predictor of future success. As discussed in *The Black Swan* by Nassim Nicolas Taleb, outlier events are almost impossible to predict from historical data. There is always a chance that all the projects will succeed or fail depending on diverse results from the science and the clinical trial designs. There is also a chance that events external to Development or Novartis will have a more significant impact on the projects than desired or predicted. Users should therefore be aware that this is a finite model that will give outputs only as reliable as the data it contains. (Taleb, 2007)

Although unpredictable clinical effects create risk and uncertainty in biologics development, Novartis is making a sound investment in strengthening its biologics portfolio and platform. This long-term investment should pay off with a stronger, broader portfolio. In the short-term, Novartis

is in a great position to use its diversified portfolio to generate quarterly profits and expand its research and development budgets.

Future Adjustments

This model can be adapted as an organizational learning tool for use in development and production activities. Changes could be made to reflect interfaces between the two groups. I recommend that the Development and Operations strategic planning team review the data templates, timelines, and probabilities of success at least once per year. The model assumptions can then be tested against actual data. The data templates were formatted to allow for straightforward changes in number or allotment of working days per activity, new activities and percentage of work occurring within Development. In addition, I recommend the current and projected portfolio be reviewed quarterly to adjust the current and incoming number of projects assumptions. This could occur in conjunction with running and analyzing a new scenario.

Further Research Considerations

In the future, it would be useful to involve finance in adapting this model to assess portfolio cost projections. Since headcount drives internal costs, this should be straightforward. This would allow for more data on long-range budget forecasts. I tested one prototype of the model with this in mind and presented the results to the CFO and finance team. While they liked the idea, they requested validation testing be performed prior to implementation.

In retrospect I would have involved the strategic planner from Operations earlier in the process to provide feedback while formatting the model. I also would have run more scenarios with the Development management team to provide feedback on the model capabilities and output format. Novartis plans to continue this project and expand the model to incorporate other groups within Development. Another idea is to explore Human Resources' view on how productivity might be affected during a high growth phase.

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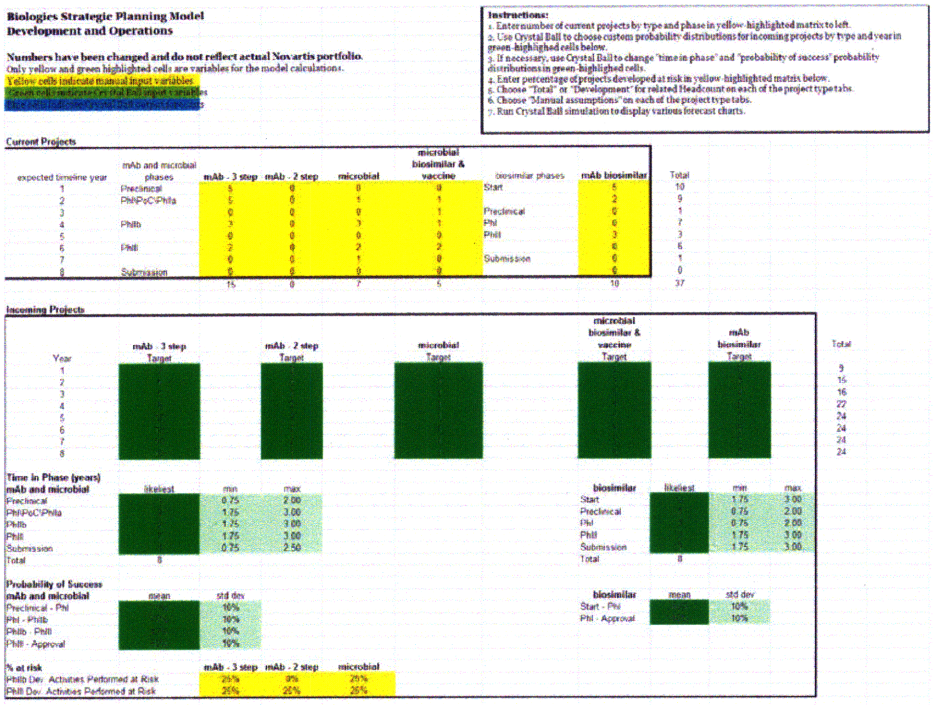
APPENDIX A

Model File

Biologics Model v5_thesis.xls

Input



Biologics Strategic Planning Model
Development and Operations

Numbers have been changed and do not reflect actual Novartis portfolio.
Only yellow and green highlighted cells are variables for the model calculations.
Yellow cells indicate manual input variables
Green cells are forecast or Crystal Ball input variables
Blue cells indicate Crystal Ball output forecasts

Instructions:
1. Enter number of current projects by type and phase in yellow-highlighted matrix to left.
2. Use Crystal Ball to choose custom probability distributions for incoming projects by type and year in green-highlighted cells below.
3. If necessary, use Crystal Ball to change "time in phase" and "probability of success" probability distributions in green-highlighed cells.
4. Enter percentage of projects developed at risk in yellow-highlighted matrix below.
5. Choose "Total" or "Development" for related Headcount on each of the project type tabs.
6. Choose "Manual assumptions" on each of the project type tabs.
7. Run Crystal Ball simulation to display various forecast charts.

Current Projects

expected timeline year	mAb and microbial phases	mAb - 3 step	mAb - 2 step	microbial	microbial biosimilar & vaccine	biosimilar phases	mAb biosimilar	Total
1	Preclinical	5	0	0	0	Start	5	10
2	PhIPoC\PhIa	5	0	1	1		2	9
3		0	0	0	1	Preclinical	0	1
4	PhIIb	3	0	3	1	PhI	0	7
5		0	0	0	0	PhII	3	3
6	PhII	2	0	2	2		0	6
7		0	0	1	0	Submission	0	1
8	Submission	0	0	0	0		0	0
		15	0	7	5		10	37

Incoming Projects

Year	mAb - 3 step Target	mAb - 2 step Target	microbial Target	microbial biosimilar & vaccine Target	mAb biosimilar Target	Total
1						9
2						15
3						16
4						27
5						24
6						24
7						24
8						24

Time in Phase (years)

mAb and microbial	likeliest	min	max
Preclinical		0.75	2.00
PhIPoC\PhIa		1.75	3.00
PhIIb		1.75	3.00
PhII		1.75	3.00
Submission		0.75	2.50
Total	8		

biosimilar	likeliest	min	max
Start		1.75	3.00
Preclinical		0.75	2.00
PhI		0.75	2.00
PhII		1.75	3.00
Submission		1.75	3.00
Total	8		

Probability of Success

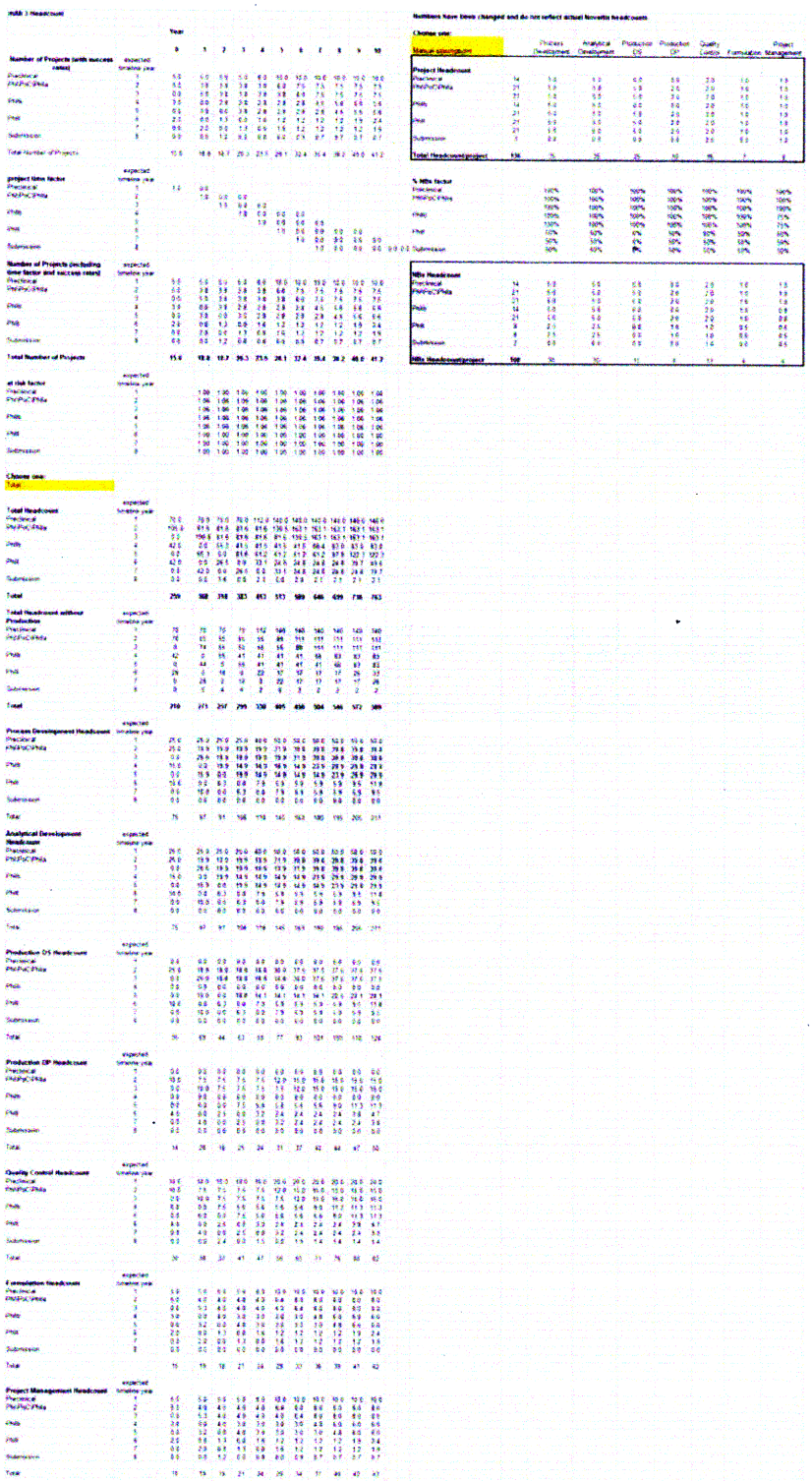
mAb and microbial	mean	std dev
Preclinical - PhI		10%
PhI - PhIIb		10%
PhIIb - PhII		10%
PhII - Approval		10%

biosimilar	mean	std dev
Start - PhI		10%
PhI - Approval		10%

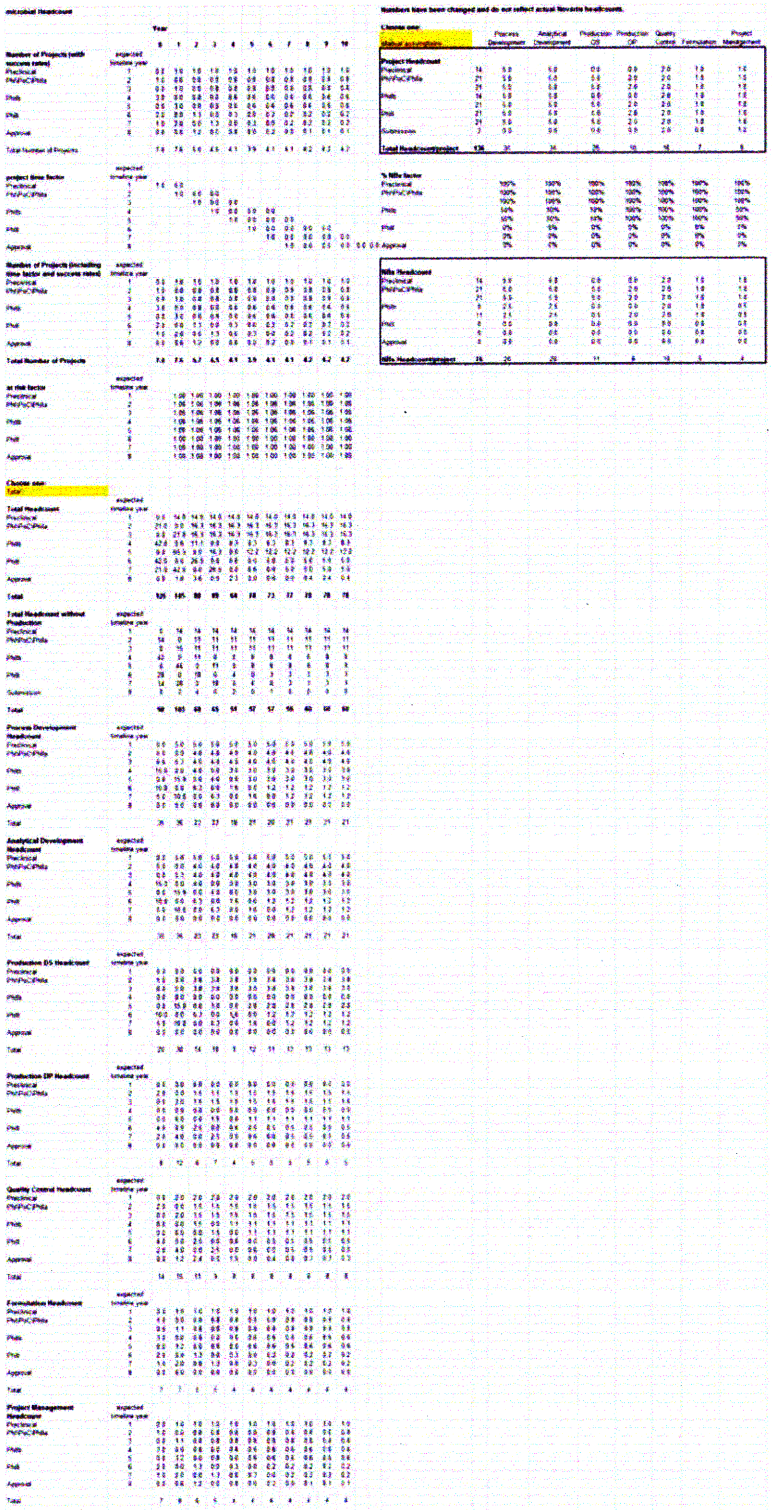
% at risk

	mAb - 3 step	mAb - 2 step	microbial
PhIIb Dev. Activities Performed at Risk	25%	0%	25%
PhII Dev. Activities Performed at Risk	25%	25%	25%

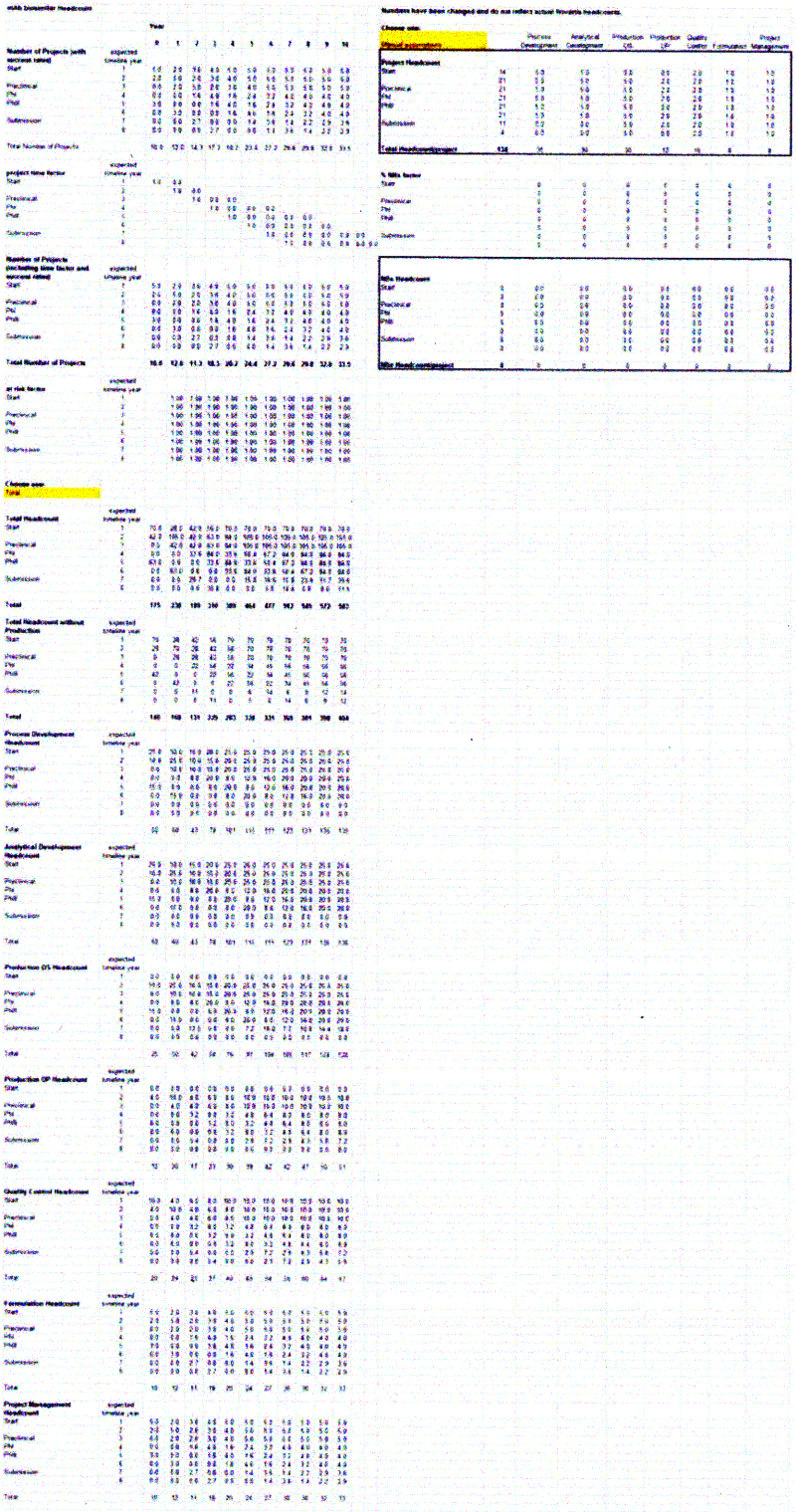
mAb calculations



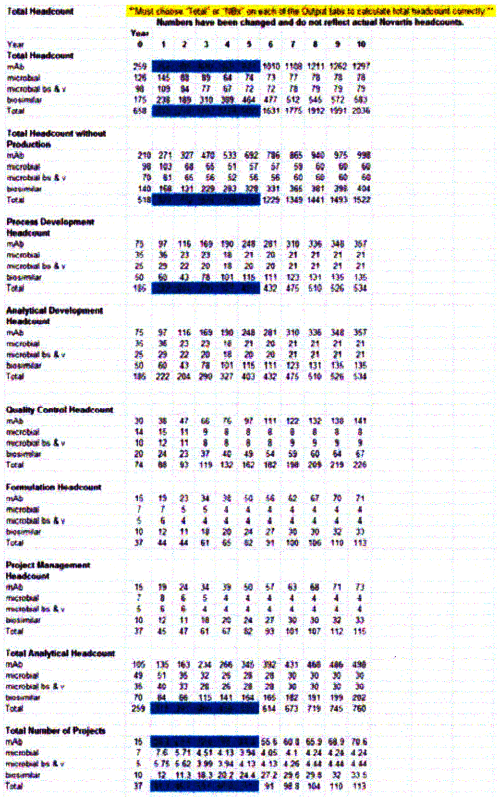
microbial calculations



biosimilar calculations



Output



Total Headcount	"Must choose "Total" or "NBs" on each of the Output tabs to calculate total headcount correctly." Numbers have been changed and do not reflect actual Novartis headcounts.									
Year	Year 0	1	2	3	4	5	6	7	8	9	10
Total Headcount											
mAb	259	[redacted]					1010	1109	1211	1262	1297
microbial	126	145	88	89	64	74	73	77	78	78	78
microbial bs & v	98	109	94	77	67	72	72	78	79	79	79
biosimilar	175	238	189	310	309	464	477	512	546	572	583
Total	658	[redacted]					1631	1775	1952	1991	2036
Total Headcount without Production											
mAb	210	271	327	470	533	692	786	865	940	975	998
microbial	98	102	66	65	51	57	57	59	60	60	60
microbial bs & v	79	81	65	56	52	56	56	60	60	60	60
biosimilar	140	168	121	229	283	328	331	365	381	396	404
Total	518	[redacted]					1229	1349	1441	1493	1522
Process Development Headcount											
mAb	75	97	116	169	190	248	281	310	336	348	357
microbial	35	36	23	23	18	21	20	21	21	21	21
microbial bs & v	25	29	22	20	18	20	20	21	21	21	21
biosimilar	50	60	43	78	101	115	111	123	131	135	135
Total	185	[redacted]					432	475	510	526	534
Analytical Development Headcount											
mAb	75	97	116	169	190	248	281	310	336	348	357
microbial	35	36	23	23	18	21	20	21	21	21	21
microbial bs & v	25	29	22	20	18	20	20	21	21	21	21
biosimilar	50	60	43	78	101	115	111	123	131	135	135
Total	185	222	204	290	327	403	432	475	510	526	534
Quality Control Headcount											
mAb	30	38	47	66	76	97	111	122	132	138	141
microbial	14	15	11	9	8	8	8	8	8	8	8
microbial bs & v	10	12	11	8	8	8	8	9	9	9	9
biosimilar	20	24	23	37	40	49	54	59	60	64	67
Total	74	88	93	119	132	162	182	198	209	219	226
Formulation Headcount											
mAb	15	19	23	34	38	50	56	62	67	70	71
microbial	7	7	5	5	4	4	4	4	4	4	4
microbial bs & v	5	6	4	4	4	4	4	4	4	4	4
biosimilar	10	12	11	18	20	24	27	30	30	32	33
Total	37	44	44	61	65	82	91	100	106	110	113
Project Management Headcount											
mAb	15	19	24	34	39	50	57	63	68	71	73
microbial	7	8	6	5	4	4	4	4	4	4	4
microbial bs & v	5	6	4	4	4	4	4	4	4	4	4
biosimilar	10	12	11	18	20	24	27	30	30	32	33
Total	37	45	47	61	67	82	93	101	107	112	115
Total Analytical Headcount											
mAb	105	135	163	234	266	345	392	431	468	486	498
microbial	49	51	35	32	26	28	28	30	30	30	30
microbial bs & v	35	40	33	28	26	28	28	30	30	30	30
biosimilar	70	84	66	115	141	164	165	182	191	199	202
Total	259	[redacted]					614	673	719	745	760
Total Number of Projects											
mAb	15	[redacted]					55.6	60.8	65.9	68.9	70.6
microbial	7	7.6	5.71	4.51	4.13	3.94	4.05	4.1	4.24	4.24	4.24
microbial bs & v	5	5.75	5.62	3.99	3.94	4.13	4.13	4.26	4.44	4.44	4.44
biosimilar	10	12	11.3	18.3	20.2	24.4	27.2	29.6	29.8	32	33.5
Total	37	[redacted]					91	98.8	104	110	113

APPENDIX B

User Guide

Although Crystal Ball 7.3.1 software is necessary to run the Monte Carlo simulations to arrive at a range of forecasted headcount requirements, it is possible to gain insight into portfolio scenarios for strategic planning just using Excel. The model file should be opened with Crystal Ball, if the user has installed the software. Otherwise it can be opened with Excel.

The model Input Variables tab displays instructions on how to input data into the model to run different scenarios, as shown in Figure 31. The Crystal Ball Getting Started Guide and User Manual are valuable tools if one is not familiar with this software. They are available as pdf files under the Start menu => Programs => Crystal Ball 7 => Documentation.

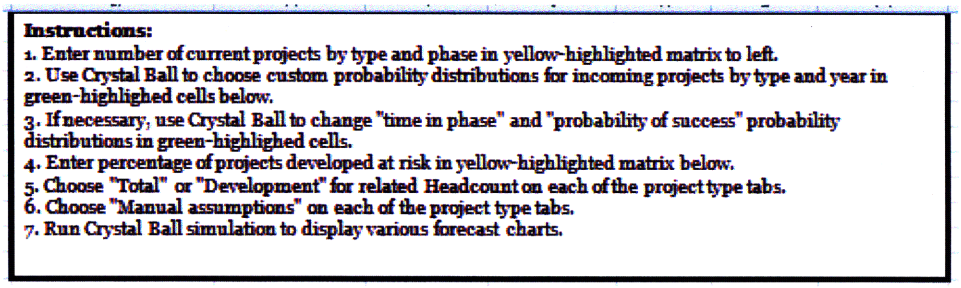


Figure 31: User Instructions

To begin, the current pipeline projects should be broken up by type (mAb, microbial, or biosimilar) and by phase (Preclinical, Phase I\PoC\PhIIa 1st or 2nd year, Phase IIb 1st or 2nd year, Phase III 1st or 2nd year or Submission for mAb and microbial projects and Start 1st or 2nd year, Preclinical, Phase I, Phase III 1st or 2nd year or Submission 1st or 2nd year for biosimilar projects). These numbers are entered into the top yellow-highlighted matrix.

Next, select one incoming project type and year cell (green-highlighted cells under target heading). Then click on the Define Assumption button on the Crystal Ball toolbar or under the Define menu. See Figure 32 for a description of the buttons on the Crystal Ball toolbar from the Crystal Ball Getting Started Guide.

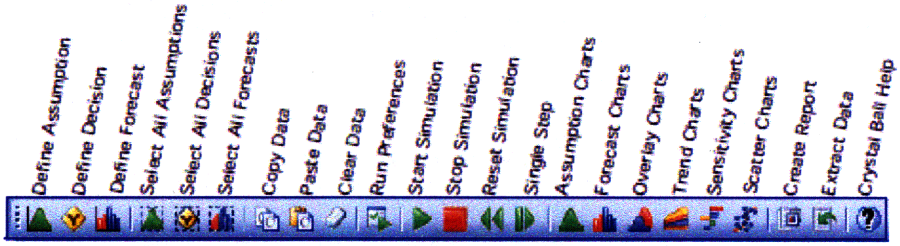


Figure A.1 The Crystal Ball toolbar

Figure 32: Crystal Ball Toolbar Descriptions

The Define Assumption window for the selected cell will open, as shown in Figure 33. Changes to the incoming number of projects must be made in this window. To add a new number, enter the number in the Value box and the probability in the Probability box located below the distribution chart. Then click the Enter button for the addition to appear in the distribution chart. To change a number that is already present, click on the green bar for the number desired to be changed and then change the Value and/or Probability in the boxes below the distribution chart. Again, click the Enter button for the change to appear in the distribution chart. To change the type of probability distribution, click on the Gallery button and choose another type. When the assumption for the selected cell has been defined, click the OK button to save the assumption and return to the Excel spreadsheet. Repeat this for each of the incoming project types and years. Without access to Crystal Ball, simply enter the number of projects desired to simulate in the cells under the target column. The number shown in the cell and the Crystal Ball probability distributions are not linked, so make sure that both agree to arrive at corresponding calculations.

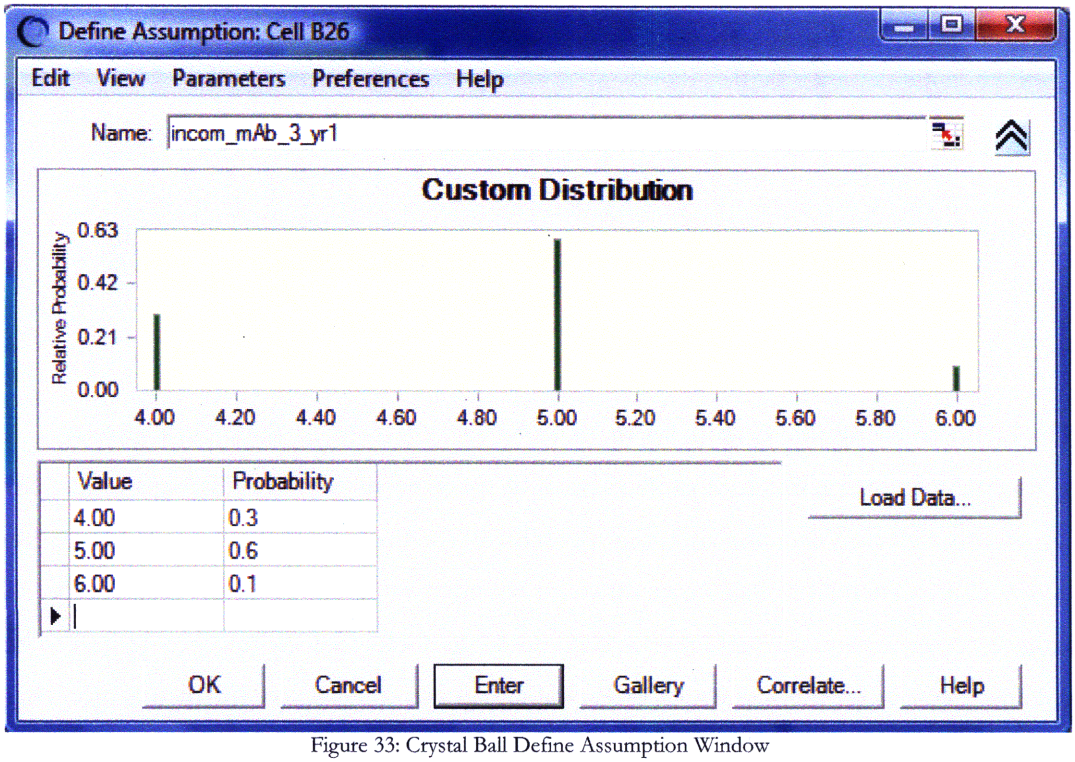


Figure 33: Crystal Ball Define Assumption Window

Similarly, to change the probability distributions for the time in phase or probability of success, select the cell desired to be changed, open its define assumption window, and make the desired changes as described above.

Then decide how many projects will have development activities performed at risk by project type and phase. Enter these percentages in the appropriate yellow-highlighted cell at the bottom of the Input Variables tab. See Figure 6 for more detail.

The final preparation step is to choose the type of headcount desired as an output, either Total or Development. The user must choose the same type on each of the project type tabs in order for the Total Output tab to display comprehensive numbers. In each of the project type tabs, select the yellow-highlighted cell under Choose One: and click on the arrow to the right to display the drop-down list. Pick one of the two choices: Total or Development. See Figure 21 for more detail.

In a similar manner, choose the source of the headcount data above the headcount matrix on the upper right. Select the yellow-highlighted cell under Choose One: and click on the arrow to the right to display the drop-down list. Pick one of the two choices: Novartis data templates or Manual assumptions.

At this point, the user will see the headcount in the matrices and on the chart on each project type tab and the Total Output tab. These numbers reflect the outcome of the likeliest numbers from your chosen scenario.

Finally, run the Crystal Ball simulation to display the forecast charts. Click the Start Simulation button in the Crystal Ball toolbar. Various forecast charts will appear as the software runs the simulation trials. Each forecast will display the headcount or number of projects range and associated probability. Moving the arrows along the x-axis of the chart displays probabilities for certain ranges. This is explained in more detail in the Scenario Analysis section. To see a specific chart, such as the one shown in Figure 23, click on the Forecast Charts button in the Crystal Ball toolbar and select the chart you wish to view. To display the outcomes on overlay or trend charts, as shown in Figure 24 and Figure 25, click on the Overlay Charts and Trend Charts buttons. Different assumption charts can be displayed by clicking on the Assumption Charts button.

To change the simulation parameters, click on the Run Preferences button. The user can change the number of trials to run under this window. To reset the simulation and clear the results, click the Reset Simulation button. To save the simulation results for future viewing, go to the Run menu in the Control Panel and select Save Results. Choose a file name and location in which to save the results. To restore saved results, go to the Run menu in the Crystal Ball Control Panel and select Restore Results. Then choose the file location and name of the results for viewing.

To display additional Crystal Ball forecasts, select the desired cell within one of the output tabs and click on the Define Forecast button in the Crystal Ball toolbar. The user will be asked to name the cell and the units. Then click OK and rerun the simulation. To display the new output forecast, click on the Forecast Charts button in the Crystal Ball toolbar and select the chart by its name.