Long Range Planning of Biologics Process Development and Clinical Trial Material Supply Process

By

Emily Edwards

B.S.E., Chemical Engineering
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Submitted to the MIT Sloan School of Management and the Engineering Systems Department
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ABSTRACT

This thesis investigates the feasibility of using a complex model with a Monte Carlo simulation model to forecast the financial, personnel, and manufacturing capacity resources needed for biologic drug development. Accurate forecasting is integral across industries in order to make strong long-term, strategic decisions and an area many companies struggle with. The resources required for the development of a biologic drug are especially hard to estimate due to the variability in the time and probability of success of each development phase. However, in the pharmaceutical industry getting products to market faster allows the company more time to recoup the substantial development investments before the patent expires and also potentially has a large impact on a company's market share.

For these reasons, Novartis Biologics wanted to develop a simulation model to provide an objective opinion and assist them in their long-range planning. This thesis describes the design, development, and functionalities of the resultant model. During validation runs, the model demonstrated accuracy of greater than 90% when compared against historical data for headcount, number of campaigns, costs, and projects per year. In addition, the model contains Monte Carlo simulation capabilities to allow users to forecast variability and test the sensitivity of the results. This proves the model can be confidently used by project management, operations, and finance to predict their respective future resource needs.

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BIOGRAPHICAL NOTE

Emily Edwards was born in Greensboro, North Carolina and has lived in North Carolina, Kentucky, Pennsylvania, Massachusetts, Australia, and Switzerland. Emily graduated from Bucknell University – College of Engineering in Lewisburg, Pennsylvania in 2005 with a B.S.E in Chemical Engineering. After college, Emily worked for Osram Sylvania in their Associate Development Program assuming positions of increasing responsibility. Prior to matriculating at MIT, Emily was the Product Manager for the Incandescent line. After graduating from the LGO program, Emily looks forward to joining Altman Vilandrie as a consultant.

1 Introduction and Overview

1.1 Problem Statement

The resources required for the development of a biologic drug are hard to estimate due to the variability in the time and probability of success of each development phase. The biotech company Amgen states that only one in ten new drugs that makes it into human testing actually makes it to market [1]. A recent study by the consulting firm Bain and Company reported that the cost for discovering, developing and launching (incorporates marketing and other business expenses) a new drug (along with the prospective drugs that fail) rose over a five year period to nearly $1.7 billion [5]. Decisions on questions such as capacity and personnel expansion in the form of updating existing facilities, breaking ground on new facilities, or striking a strategic partnership must be made years in advance despite limited means for predicting future needs.

1.2 Motivation

The motivation behind the project is that the Novartis Biologics group wants to expand its capacity to handle the increasing number of biologic projects. Previous LGO work provided the group a means to forecast personnel requirements amongst sites but an evolving division rendered the tool out of date with current site capabilities and division structure. In addition, the group needed a tool to accurately forecast cost requirements. A model with costing functionality will give a more complete picture, gain the confidence of the financial arm of the organization, and therefore help the organization to make important strategic recommendations to senior management.

1.3 Hypothesis

I believe I can integrate financial information, site capabilities, and development step personnel requirements to successfully model headcount and capacity and financial needs. This information can be presented in such a way to aid in long-term strategic decision making.

1.4 Goals

From a macro perspective, my project is designed to be an analytical resource and personnel planning tool. The drug development timeline is very long and the organization struggles to plan for projects five – ten years down the road. From a micro perspective, my project is designed to weave planning through the many sites and organizations that comprise biologics development. The final model should forecast 1) full time equivalent employees across functional groups across product types, 2) manufacturing capacity and site allocation, 3) product campaigns, and 4) financial resources. A robust model should also provide a forecast range and associated probability of occurrence.

1.5 Results

During validation runs, the model demonstrated accuracy of greater than 90% when compared against historical data for headcount, number of campaigns, costs, and projects per year. In addition, the model contains Monte Carlo simulation capabilities to allow users to forecast variability and test the sensitivity of the results. This proves the model can be confidently used by project management, operations, and finance to predict their respective future resource needs.

1.6 Thesis Overview

This thesis is organized into five chapters. The first chapter presents an introduction to and overview of the thesis and its contents. Chapter two provides background on the pharmaceutical industry, the drug development process, biotechnology, and Novartis. The third chapter dives into forecasting, common forecasting techniques, Novartis' forecasting method, and pharmaceutical risk hedging. The fourth chapter presents the specifics of the model by explaining the input, outputs, and functionalities of the two key components of the model. In addition, chapter four discusses dealing with uncertainty and the outcomes of the model validation. Finally chapter six summarizes key findings and conclusions.

2 Company Background

2.1 Industry Overview

The goal of the pharmaceutical industry is to discover, develop, produce, and sell therapeutic drugs to mitigate patients' diseases and symptoms. Though the dollar amounts quoted vary, bringing a therapy to market from idea inception costs over $1 billion and takes 10 – 12 years to go through development and regulatory approval. A recent study by the consulting firm Bain and Company reported that the cost for discovering, developing and launching (incorporates marketing and other business expenses) a new drug (along with the prospective drugs that fail) rose over a five year period to nearly $1.7 billion [5]. This statistic integrates the attrition over the development period. Amgen states that only one in ten new drugs that makes it into human testing actually makes it to market [1]. Drugs are stopped along the development process for a litany of reasons. The most common reasons are poor clinical results and toxicological and safety concerns. In addition, drug

development is occasionally halted when a competitive product reaches the market first and the market is deemed saturated.

Pharmaceutical Research and Manufactures of America (PhRMA) identifies five major trends changing the industry: "increased complexity of the research and development process; continued investment in Research and Development; increased use of medicines in health care; increased value for today's patients; and continued importance of patent incentives for innovative medicines" [10].

2.1.1 Drug Development

The development and bringing to market of a new entity can be thought of in two distinct phases: Drug Discovery and Drug Development. Drug discovery is the process by which NMEs are discovered or designed. Drug development is the process that results after a NME has been identified as a potential drug to turn it into a market viable product. This process converts a complex, small-scale, and unsafe procedure from the laboratory to an efficient, large-scale, and safe process that can be commercially manufactured. Drug development does not produce material that is available for sale.

The drug development phase involves several phases of clinical trials to ascertain the safety of the drug and determine appropriate formulation and dosing. There are generally three distinct steps: a pilot plant campaign, a medium-sized manufacturing campaign, and a full-scale validation campaign. The purpose of the campaigns is twofold. Every campaign produces three to five batches of material that is used in clinical trials. In addition, the material yielded through the campaigns undergoes rigorous quality testing and the campaigns themselves test process design and improvements. At least one of the full-scale validation campaigns must occur at the final production site of the drug because regulatory agencies approve specific manufacturing processes at a plant.

Players in the pharmaceutical field combat the high failure rate in a variety of ways. Large multinational corporations are often vertically integrated and control all aspects of drug discovery and development. The high cost of late stage development which is very capital intensive has led many smaller companies to focus on one or two phases of the process such as formulation.

2.1.2 Biotechnology

Today, the pharmaceutical industry can be broken into two classes of therapeutic drugs: small molecule therapeutics and biologic therapeutics. Small-molecule therapeutics such as aspirin are composed of chemical compounds and are synthesized. Biologics are derived from living organisms and include proteins, DNA vaccines, monoclonal antibodies, and peptibodies. They are manufactured inside living cells in a more complex process than the traditional chemical synthesis. The manufacturing equipment required for these classes of drugs varies greatly and equipment cannot be shared between these two processes.

Hungarian engineer, Karl Ereky, coined the term biotechnology in 1919 to describe the interaction of biology and human technology. The United Nations Convention on Biologic Diversity defines biotechnology as "any technology application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use" [1]. The industry took time to get off the ground from the days of Ereky. The first FDA approved biologic medicine was human insulin in 1982 made via recombinant DNA technology [1]. Modern biotechnology often focuses on understanding the metabolic pathways related to a disease state or pathogen and how to effectively manipulate these pathways using molecular biology or biochemistry.

2.1.3 Biotechnology vs. Small Molecule Therapeutics

Figure 1 below summarizes the key differences between biologics and small molecule therapeutics.

Figure 1: Biologics vs. Small Molecule Therapeutics

Key Differences Between Biologics (Large Molecule) and Small Molecule				
	Drug Charateristics	**Target**	**Side Effects**	**Manufacturing**
Biologics	Dosed weekly - monthly Mostly injections Intensive assay development	Mostly outside of cells Good at protein interactions	Rare due to low off target toxicity	Challenging Causes large investments
Small Molecule	Dosed hourly - daily Variable intake Standard assays	Any druggable target Enzymes / receptors / channels	More frequent due to action on / in multiple pathways	Easier compared to Biologics

Biologics have the potential to be more patient friendly than small molecule therapeutics. Because biologics are more selective and specific, as they "attack" they only target the intended disease and do not affect healthy tissues or cells; they typically produce fewer side-effects than traditional small molecule therapeutics. Biologics are proteins and as such are degraded exactly the same way as other proteins in the body. In addition, the long half-life of biologics leads to less frequent administration. The therapeutic antibody activity can remain effective for 2 to 4 weeks [6].

2.2 Novartis Overview

2.2.1 Background

Novartis AG is a diversified healthcare company consisting of four divisions: Pharmaceuticals, Vaccines and Diagnostics, Sandoz (Generics), and Consumer Health (Over the Counter, Animal Health, and Ciba Vision). Novartis was created in 1996 with a merger between the Swiss companies Ciba-Geigy and Sandoz. The company's mission statement is "to discover, develop and successfully market innovative products to prevent and cure diseases, to ease suffering and to enhance the quality of life [9]."

Novartis is headquartered in Basel, Switzerland with 119, 418 employees spread across 140 countries around the globe. Novartis posted $50.6 billion in net sales and $10 billion in net income for 2010 [8]. Novartis plows a large portion of its revenue back into research and development (R&D) with a

total expenditure of $8.1 billion in 2010. Pharma AG (the pharmaceuticals division) is the largest division and generates the most revenue with net sales of $30.6 billion in 2010. Currently their portfolio of patented prescription drugs contains over 50 key marketed products. A number of these products are leaders in their field including cardiology, neuroscience, oncology, and respiratory.

In 2009, Novartis received over 25 positive regulatory decisions in the United State, Europe, and Japan. In addition, their product development pipeline has 147 projects in a litany of stages of clinical development. While historically small molecule pharmaceuticals have been a very successful area for the company, they are also expanding into biologics.

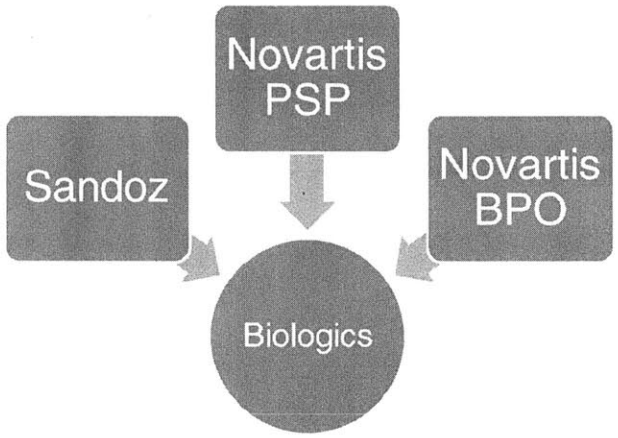
2.2.2 Biologics Group

The Novartis Biologics Group (NBx) launched in 2007 is the large molecule drug development group and is within the development division of Novartis Pharma. NBx is a small but growing part of the Novartis organization comprised of about 550 employees in Switzerland and the United States. For the past two years, the NBx group has been growing strongly at 33% a year. The organization has a strong track record of delivering medicines to patients. At present, biologics represent a quarter of the overall Novartis research and development pipeline [6]. Novartis' Biologics pipeline ranks in the top five in the industry behind Roche, Pfizer, and Amgen.

NBx is responsible for biologic projects from protein or antibody design up through the completion of Phase II of clinical development. In addition, the group also provides support for biologic projects during later stages of development and commercial production. Biologics development is governed by three different organizations: Sandoz, Novartis PSP (Process Science Production), and Novartis BPO (Biologics Pharmaceutical Organization). Sandoz operates several biologics facilities that are designated for future use in developing and producing biosimilars.

The immediate Novartis owner of this project, Philippe Marschal is in charge of operations for the Novartis Process Sciences and Production (PSP) organization. The PSP group is responsible for process development and production across four groups: Process Sciences, Clinical Manufacturing, Quality Control, and Project Management. The figure below shows the organizational makeup of the Biologics division.

Figure 2: Biologics Organizational Makeup



NBx has four main products:

- Biosimilar cell culture – generic version of a drug that is nearing patent expiration and is produced using mammalian cell culture
- Biosimilar microbial – generic version of a drug that is nearing patent expiration and is produced using microbial expression systems
- Microbial – NMEs produced using a microbial expression system such as *E. coli* or yeast. This manufacturing method requires different manufacturing steps and different equipment than cell culture products
- Monoclonal Antibody – antibody produced by cells that are all derived from a single antibody-producing cell. Once a cell capable of generating an antibody with desired therapeutic characteristics is selected, laboratory processes are used to clone (make large

numbers of) these cells. Since the cells are all identical and can be used to continuously produce identical antibody molecules with these same therapeutic characteristics [1]

Figures 3 and 4 illustrate the development differences at Novartis between New Molecular Entities and Biosimilars [11].

Figure 3: New Molecular Entity (cell culture and microbial) Development Path [14]

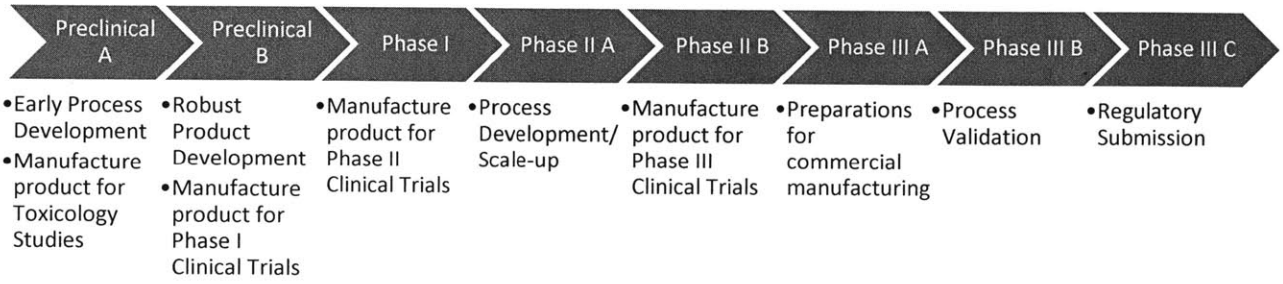
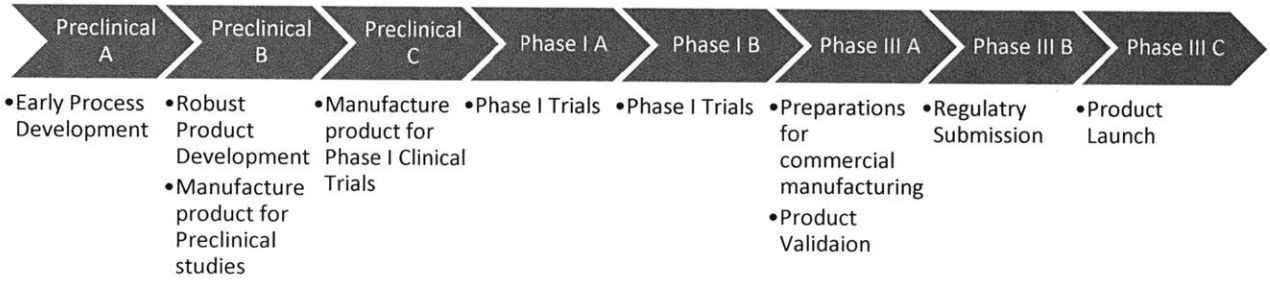


Figure 4: Biosimilar (biosimilar cell culture and biosimilar microbial) Development Path [14]



2.3 Organizational Assessment: Three Lens Analysis

Dr. Bela Banathy developed an approach to analyze organizations using three types of interrelated models to give a multi-dimensional view he coined the Three Lenses. His model is comprised of the strategic design, cultural, and political lenses [15].

2.3.1 Strategic Design

The strategic design lens examines how the flow of tasks and information is designed, how people are sorted into roles, and how the roles are related. Ultimately this lens demonstrates how the organization can be rationally optimized to achieve its goals [15].

The basic strategy of the organization is to heavily ratchet up the number of projects in the Novartis Biologic pipeline. At present, biologic drugs at Novartis make up 25% of projects in the overall company pipeline. This represents a significant increase and is directly related to this project because biologic development is an unknown.

Novartis is a company with very independent divisions. Thus jobs are designed with one particular organization in mind. This factor makes doing a project with stakeholders in three separate and sometimes diverging divisions a challenge. Similar to most large companies, collaboration between divisions could be significantly improved.

2.3.2 Cultural

The cultural lens examines how history has shaped the assumptions and meanings of different people and how certain practices take on special meaning and even become rituals. In additions, this lens analyzes how stories and other artifacts shape the feel of an organization [4].

The project is related to basic organizational assumptions and levels of acceptable risk. The project process and ultimate output will either change or reinforce these commonly held beliefs. Due to the project duration, management is hesitant to tout potential results without having a finished model.

The symbolic meaning of the project for the organization is that the resultant model will be representative of recent organizational changes. The MIT name also has an interesting symbolic meaning at Novartis. Due to the heavily publicized continuous manufacturing project and support

from top management, the MIT name is very visible and highly revered. This adds a certain amount of pressure to perform on internship work.

There are anticipated different sub-cultural responses to this project. The BPO organization in the chart above has been largely absent from the project. The finance arm of Novartis PSP has diverging interests from the operations arm which has diverging interests from the entire Sandoz organization. The best cultural lever for getting this model accepted across stakeholder groups is to brand it as the MIT model. By introducing the model from an outside perspective, we hope to remove some of the political issues and more easily gain widespread use.

2.3.3 Political

The political lens examines how power and influence are distributed and wielded, how multiple stakeholders express their different preferences and get involved in decisions, and how conflicts can be resolved [4].

Stakeholder interests vary widely and are not always compatible. The finance arm of the organization wants a tool that pinpoints areas of financial waste that can ideally be eliminated or heavily reduced in the future. In addition, the finance arm wants a tool that can make the budgeting process less painful. The operations arm wants a tool that accurately predicts resource needs amongst sites many years down the road and helps save money from an operations perspective. At the end of the day, all stakeholders want to have an accurate and reliable tool that forecasts resource and personnel needs.

The biggest source of power is the operations arm of Novartis PSP. Sandoz seems to have less power as an organization than Novartis across the board. Sandoz largely makes generic drugs with significantly lower margins. Their facilities pale in comparison to those of Novartis and they seem

to be spoken of as second-class citizens. However they play an integral role in biologics manufacturing and will be likely producing the final products. They may gain more power with the model. There are no formal measures to allow less powerful parties to voice their interests.

3 Forecasting Procedures

3.1 What is Resource Forecasting?

All companies employ forecasting methods whether it is estimated demand for their specific goods and services next week or ten years from now. Having a robust forecasting system is imperative to resource planning and allocation – personnel, product, raw materials, and physical space. Companies use demand forecasts to make strategic decisions that they often will not realize the effects of for years down the road. In addition, forecasting helps companies identify where gaps exist between their desired state and their most probable state. Knowing their potential future shortcomings allows companies time to make changes before the shortcomings hit.

3.2 Common Forecasting Methods

Forecasting can be broken down into two distinct methodologies: 1) Manual Forecasting and 2) Simulation. The historical method, manual forecasting, is a very time consuming process by which specific functional groups provide estimates for a specific occurrence. An example of this would be all the sales representatives in a region estimating the sales volume for their territory for the following year. These figures would roll-up by region into corporate sales which would then make an estimate on sales volume for the company for the following year. With this figure, other groups within a company would be able to plan for personnel, production, etc. Manual forecasting is only

as accurate as all the aggregate pieces of information collected. It is slow, very time consuming, and challenging to alter if situations change such as the slow-down of the economy or a new competitive entrant into the market.

Most companies have been transitioning to the second school of thought in forecasting: simulation. This thesis focuses on simulation. The first component of simulation forecasting is developing a robust model. There are many off the shelf models available or companies can develop them in-house. Modeling uses historical data, market data, experimental design, and equations to calculate an expected outcome given a set of assumptions. Then the simulation varies the assumptions to provide a complete picture of future scenarios.

3.3 Pharmaceutical Risk Hedging

The long time period and inherent uncertainty of drug development described previously makes resources forecasting all the more important for the pharmaceutical industry. Computer modeling has been picking up steam in the pharmaceutical industry as companies realize the intrinsic value of using simulations for drug development and capacity planning decisions. In his book James Stahl, a healthcare modeling expert, states that models and simulations are used for the following reasons in pharmaceuticals: 1) To test something that is impossible to test through direct experimentation, 2) To better understand or predict the outcome of a complex system, and 3) To aid in decision making [13].

The key drivers for the pharmaceutical industry are manufacturing capacity and skilled personnel. Due to the lengthy regulatory approval process, additional manufacturing capacity often takes upwards of five years to design, build, test, validate, and gain regulatory approval in order to be commercially viable. David Ebersman of Genetech explains "Some of these phases could overlap if

we wanted to compress the schedule, but it would be difficult to complete a plant successfully in less than four and a half years. There are thousands of process steps and 100% process control and sterility are required [12]." From a personnel perspective, employees are highly skilled and it can take a year to find qualified applicants, take them through the hiring process, and provide them the necessary substantial training.

The high capital investments and lengthy process of building an FDA-approved manufacturing facility makes accurate long-term modeling very important for the long-term success of pharmaceutical companies. They cannot afford to delay drug development while waiting for new plants to come online but also cannot afford to let plants and operators sit idle if the huge variations in anticipated capacity end up on the lower end of the slope. In addition, the FDA requires new licensing to reengineer part of current production processes. David Ebersman of Genentech explains the ramifications of regulations. "When the FDA approves one of our drugs, they are approving the drug in the context of a specific manufacturing process in a specific location. If we tweaked any of the raw materials or process steps, we might need to go through the entire approval process again. That would entail stopping production and running tests again and again until we could prove that the product produced using the new process is identical to the original version that was tested with patients in clinical trials. If we saw any discrepancy, we might need to test the new version with patients, which could take several years [12]."

Ebersman's explanation of regulatory ramifications shows why pharmaceutical companies have attempted to develop ways to hedge risks. Because new facilities are very capital intensive and take up to five years to become fully operational, many pharmaceutical companies choose to outsource both development work and manufacturing to a Contract Manufacturing Organizations (CMO). These CMOs hedge risk for individual companies by building industry capacity in lieu of individual

companies building solo capacity which may outstrip their specific demand [2]. However there are downsides to contract manufacturing. Outsourcing is almost always more expensive on a per man-hour basis and requires time and internal resources. Additionally, in order to build a successful relationship with the CMO, the pharmaceutical company needs to share some of their production expertise with the CMO which may equate to building a future competitor.

3.4 Novartis' Forecasting Method

Prior to 2009, Novartis used a manual forecasting method. Novartis has a project management software program called SUCCEED that tracks each project's current status and costs. Each year the unit heads would use that information and apply a standard template to evaluate their needs for the coming year in terms of FTEs and resources. They made manual deviations from the template based on their own knowledge of the technical difficulty of each project, current delays, and projected future delays. Then management used these figures to construct three scenarios:

1) Stay flat
    - Keep current number of FTEs
    - Reshuffle FTEs as needed amongst funded projects
2) Stick to strategic plan
3) Support all products in pipeline
    - Might entail adding capacity and resources or making substantial investments

After defining the above scenarios, management would research each scenario and overlay it with the projected pipeline to determine the financial liabilities and benefits. This investigation involved looking at each scenario from both a bottom-up and top-down perspective. The bottom-up vantage point culminated in submitting all scenarios to upper management and the head of development finance. The top-down approach took the goals that were handed down from corporate finance and

synthesized them into the most likely scenario. To plan for the coming years, Novartis would take the chosen scenario and age it over multiple years with industry attrition rates.

Though the methodology described above is appropriate for keeping track of each project's status along the drug development process, it is very time consuming with many non-value added components and does not adequately take into account risk. Novartis does have two key advantages in hedging risk: 1) The Sandoz division, and 2) Strong relationships with CMOs. Sandoz is Novartis' generic division which also develops biosimilars and has excess manufacturing capacity.

Realizing their shortcomings and potential areas for improvement, Novartis Biologics brought in LGO student Tamara Conant in 2008 to examine their forecasting process and suggest improvements. Tamara designed and constructed a model to forecast full time equivalent employees or FTEs. This model is described in full in her thesis *Modeling Variability for Biologics Strategic Planning* [3]. In 2009, Novartis Biologics brought in LGO student Angela Thedinga to continue Tamara's work. More detail on this can be found in her thesis *Forecasting Resource Requirements for Drug Development Long Range Planning* [14].

4 Model Methodology

4.1 Model Goal

This model is intended to assist with five year strategic planning and strategic decision making (i.e. capacity expansion and outsourcing decisions) by estimating:

- Headcount
- Manufacturing Capacity

- Financial Resources (Internal and External)

for NBx TSS, NBx PSP and BPO development. A robust model should also provide a forecast range and associated probability of occurrence. The model should be simple enough to be used by personnel across the organization with minimal training.

4.2 Approach

I began the project with the aim of utilizing information from different areas of Novartis to design and construct a comprehensive resource, project and financial forecasting, and long-range planning model. There were seven major tasks associated with the project:

1) Baselining the current state of doing resource, project and financial forecasting, and long-range planning.
2) Determining the strengths and areas for improvement of the current model
3) Designing a future state model
4) Collecting data
5) Incorporating the data into the future state model
6) Validation
7) Creating a system for keeping the model up-to-date and relevant

The following sections will detail the culmination of this approach.

4.3 Model Description

The resultant model is comprised of two files: the front facing model and the back of the house work package. The reason behind this split is twofold. First, as the amount of data entered into the file grew during model design and construction, the file took an increased amount of time to process and crashed frequently. Splitting the work package and user dashboard dramatically decreasd

involuntarily Excel shut-downs. Secondly, the work package file contains the bulk of the assumptions and corresponding data. This data should not be changed unless there is a specific change to part of the drug development process i.e. a new step, productivity increases, etc. The actual model file is where the user enters inputs and views outputs.

4.4 The Workpackage

The workpackage assumes that each project can be described by one of seven "standard" project templates. The seven templates are mAb 3 step, mAb 2 step, microbial, mAb biosimilar, microbial biosimilar, vaccines/3rd party, and external. These seven templates define the headcount, materials and services, and campaign requirements considering all tasks required for a single project.

Within each of the seven templates is a list of tasks that need to be performed to take a drug from idea conception to readiness for commercial manufacturing. These standard platform activities were decided upon by the group heads in each of the various departments. Tasks were then bucketed into the following groups of Development and Operations activities: Process Development, Analytical Development, Drug Substance (DS) Production, Drug Product (DP) Production, Quality Control, Formulation, Toxicology, IBP Cell Culture, IBP Microbial, and Project Management. A few examples of developmental and operational activities are below:

- Manufacturing of non-GMP tox material – Product Development
- Cell line generation initial stage – IBP Cell Culture
- Tissue cross reactivity study (Monkey, Human, Mice) – Toxicology
- Virus validation study – Product Development

The list of activities varied slightly depending product family. For example, the mAb 3 step template lists 155 activities while the microbial template lists 147 activities.

Each activity is listed with the total number of associated working days, external cost in dollars, number of campaigns, group, and site. The developmental timeline shown below is used to specify activities for each project into a certain time period. The duration of time a project spends in each stage of the developmental timeline can be altered as the process efficiency increases.

Figure 5: Development Stage Definitions

Development Stage Definitions			
Year	**mAb/microbial activities**	**biosimilar activities**	**vaccines/3rd party activities**
1	**Candidate Selection Phase:** *Cell line development *Phase I(& II if two step) development *Non-GMP Tox campaign	**Preclinical Phase Year 1:** *Cell Line Development	**Candidate Selection Phase:** *Phase I(& II if two step) development *Non-GMP campaign
2	**Preclinical Phase:** *Phase II process development *Phase I campaign	**Preclinical Phase Year 2:** *Process Development	**Preclinical Phase:** *Phase II process development *Phase I campaign
3	**Clinical Phase I/PoC/Phase IIa:** *No major PD activities *Phase II campaign	**Preclinical Phase Year 3:** *GMP Phase I Manufacturing *Preclinical Studies	**Clinical Phase I/PoC/Phase IIa:** *No major PD activities *Phase II campaign
4	**Clinical Phase IIb Year 1:** *Phase III process development	**Clinical Phase I Year 1:** *Phase I studies	**Clinical Phase IIb Year 1:** *Phase III process development
5	**Clinical Phase IIb Year 2:** *Phase III campaign *Process Characterization	**Clinical Phase I Year 2:** *Phase I studies	**Clinical Phase IIb Year 2:** *Phase III campaign
6	**Clinical Phase III Year 1:** *Phase III re-supply campaign	**Clinical Phase III Year 1:** *Phase III Studies	**Clinical Phase III Year 1:** *Phase III re-supply campaign
7	**Clinical Phase III Year 2:** *Process validation *Validation	**Clinical Phase III Year 2:** *Phase III Studies *Submission	**Clinical Phase III Year 2:** *Validation
8	**Clinical Phase III Year 3:** *Submission *Registration/Launch	**Clinical Phase III Year 3:** *Registration/Launch	**Clinical Phase III Year 3:** *Submission
Launched	**Lifecycle Management**	**Lifecycle Management**	**Lifecycle Management**

The total number of working days needed for each activity is then allocated to a cell(s) corresponding to the specific quarter(s) along the development timeline. The external cost and number of campaigns are allocated to a cell (s) corresponding to the developmental year in which the cost hits Novartis' budget.

4.5 The Model

The model contains a litany of color-coded tabs. The color key below is intended to help the casual model user with model operation.

Figure 6: Model Color Key

Color Key

Information	Information about the model and its use.
User Inputs	Inputs specified by the user.
Crystal Ball Inputs	Inputs defined through Crystal Ball. When a simulation is run, these cells change
	Outputs or reports generated by the model.
Assumptions	These tabs define the underlying assumptions and calculations and are normally hidden.

4.5.1 Model Assumptions

The model assumptions are integral to its operations and accuracy. Assumptions should be reviewed and updated annually or with any large business changes. The model contains both fixed and flexible assumptions.

The fixed assumptions are primarily found in the workpackage and cannot be changed without significantly changing the model structure. Fixed assumptions include:

- All projects are assumed to be represented by a "standard" project, requiring an average number of resources (FTEs, manufacturing capacity, and financial resources).
- The resources required for a "standard" project this year are assumed to be the same number of resources required for that type of project for the next ten years. No organizational efficiency (or improvement over time) is factored into the model.
- All employees within the same functional group at any site are equally capable of working on any type of project, and each employee can work on an unlimited fraction of projects. Each FTE is only limited by the number of work days in the year.

- Manufacturing sites are interchangeable and campaigns are assigned per the site allocation defined by the user.
- Activities in the next stage can only be started when all of the tasks in a previous stage are complete.
- The progression of projects through the pipeline is fractional, not discrete
- Fractional projects are added, so four projects that all have a 50% chance of progressing are considered as two full projects
- The organization is split into a definite number of groups and will remain that way for the period of the forecast (model does not predict organizational structure changes).
- The model assumes that for each simulation run, each development stage takes the same amount of time for all new molecular entity or biosimilar projects. For instance, if the simulation generates a 1.5 year duration for development stage 4, then all projects will take 1.5 years to complete stage 4 for all ten years of the forecast.
- No matter what the phase duration time is, the work required for that development stage is spread evenly over the years required to complete the work.
- The model assumes that all future projects will start in development stage 1. This is not the case for many in-licensed projects. Currently in-licensed projects can be considered by assigning the appropriate development stage to the current project parameter, but all future projects are assumed to enter the pipeline at development stage 1[14].

Many of the flexible assumptions double as the model inputs and can be changed easily based on changes in the business. These inputs will be detailed in the next section however there are a few key flexible assumptions that likely will not be changed by the casual user including:

- Resources required per development stage and per functional group

- Time required for each development stage
- Number of manufacturing weeks for each campaign broken out by development phase
- Working days per FTE

  One FTE works 250 days a year. After accounting for 25 days of vacation, sick leave, training, and administration, we assume that an FTE spends on average 80% of those 250 working days on project work. This equates to 1 FTE = 200 days of work.
- Inflation rate
- Exchange rate of the US Dollar to Swiss Franc and Euro

4.5.2 Model Inputs

The model inputs are listed below:

1) **Current Projects** – listing of projects and current development status, located on the "Current Projects" worksheet

The current projects are broken down by the development timeline illustrated in Figure 5. Projects can be listed as fractions totaling one across two development years depending on their progress. Occasionally due to limited resources, a delayed project will only show as a fraction of a project.

2) **Future Projects** – estimates of future new projects with a probability distribution, located on "Future Projects" worksheet

Figure 7 below shows the target for incoming projects by calendar year spread amongst the seven product categories. All data is fictitious. The Novartis model owner will update these figures based on corporate goals and R&D projections.

Figure 7: Future Projects Snapshot

Incoming Projects									
	mAb - 3 step	mAb - 2 step	microbial	external		microbial biosimilar	mAb biosimilar	Vaccines/ 3rd Party	
Year	Target	Target	Target	Target	NBx Total	Target	Target	Target	Grand Total
2010	2.5	1	0.5	1	5	0	1	1	7
2011	3	3	1	2	9	0.25	1	2	12.25
2012	4	4	1	3	12	0.25	2	3	17.25
2013	4	2	2	3	11	0.25	2	1	14.25
2014	3	5	2	3	13	0.25	1	2	16.25
2015	3	3	2	2	10	0.25	2	3	15.25
2016	2	4	3	3	12	0.25	3	3	18.25
2017	4	5	3	2	14	0.25	1	2	17.25
2018	2	7	3	3	15	0.25	2	2	19.25

3) **Probability of success between development stages** – fraction of projects that progress from one development stage to the next, located on the "Future Projects" worksheet

For each of the seven different defined product types, a probability of success is defined. An example of this for biosimilars and vaccines is shown in Figure 8 below. For the technical development step, it will most likely take three years. However there is a possibility of this step taking between two and four years. These probability distributions are used in the Monte Carlo simulations which are detailed later in the Uncertainty section of this document.

Figure 8: Biosimilar and Vaccines Probability of Success

biosimilar and vaccines	likeliest	min	max
TechDev/Preclinical	3	2.00	4.00
PhI	2	1.00	3.00
PhIII	2	1.00	3.00
Submission	1	0.50	1.50
Total	8		

4) **Percent of projects performed at risk** – percentage of projects that will process to the next development stage without pass/fail indication, located on "Future Projects" worksheet

Due to the limited patent life of a new product and the long development time line, pharmaceutical companies such as Novartis try to accelerate development activities to bring

products to market sooner to recoup the high costs of development. Companies do not want any delays in clinical trials due to waiting for test material, manufacturing development, etc. Most products follow the steps of development process in the chronological order detailed in Figures 3 and 4 depending on the product type. However at times, management may choose to perform some activities before the preceding activity is complete.

For instance, the results of a clinical trial either kill a project or push it further along the path of becoming a commercially viable product. Continuing along the development path without knowing the clinical outcome is precarious because development is proceeding at risk of a negative outcome. Thus these activities are said to be done at risk. If the product fails the clinical trial, these activities done at risk are a waste of resources that could have been better spent elsewhere. If the product excels in the clinical trial, then having already performed some of the activities in the next developmental step lessens the time until the drug can be introduced into the market. Getting products to market faster not only allows the company more time to recoup investments before the patent expires, but also potentially has a large impact on market share. Figure 9 below shows the percentage of activities performed at risk by product family.

Figure 9: Percentage of Activities Performed at Risk

% at risk	mAb - 3 step	mAb - 2 step	microbial
Year 2 activities performed at risk	50%	80%	80%
Year 3 activities performed at risk: Mainly Phase II supply	50%	80%	80%
PhIII Dev. Activities Performed at Risk before POC readout	25%	25%	25%
PC/PV Activities Performed at Risk	10%	10%	10%

5) **Site Allocation** – resources required are categorized into Competence Center (CC), Development Site (DS) or Launch Site (LS) activities. The proportion of these activities per site is defined in the "Site Allocation" worksheet.

Some functional groups are only located at one site and thus some activities must always be performed at the same site. These resources are defined as "fixed". Other activities could be sourced by different site (i.e. mAb development site activities could be performed by Basel or Kundl) and are defined as "flexible". Manufacturing campaign site availability depends on the capabilities of the various manufacturing sites, the product type, and the product development stage. The site allocation dictates the proportionality of the flexible activities.

Figure 10 is a snapshot of the site allocation for 2010. The grey cells represent a non-match between a site's capabilities and the drug type. The orange cells show potential sites where a project can be slotted based on drug type and needed development activities. Site allocations can be allocated manually by percentage or can be left blank for the model to find the most efficient allocation. For instance, 40% of the development activities performed in 2010 for the mAb 3 step product will be done in Basel and 60% will be done in Schaftenau.

Figure 10: Site Allocation for 2010

			2010											
Drug Type		Center	Basel	Cambridge	Huningue	Kundl	Menges	Oberhaching	Schaftenau	Vacaville	Low Cost Location	Other 1	Other 2
mAb3	CC	mAb3_CC	100%						0%				
	DS	mAb3_DS	40%						60%				
	LS	mAb3_LS			40%				60%				
mAb2	CC	mAb2_CC	100%										
	DS	mAb2_DS	40%						60%				
	LS	mAb2_LS			50%				50%				
Microbial	CC	mic_CC		50%		50%							
	DS	mic_DS				100%							
	LS	mic_LS				100%				0%			
Biosimilar mAb	CC	mAb_bsim_CC				25%		75%					
	DS	mAb_bsim_DS					85%		15%				
	LS	mAb_bsim_LS					100%		0%				
Biosimilar microbial	CC	mic_bsim_CC				100%		0%					
	DS	mic_bsim_DS				100%							
	LS	mic_bsim_LS				100%							
Vaccines/3rd party	CC	vac_CC				100%							
	DS	vac_DS				80%			20%				
	LS	vac_LS				100%			0%				

6) **FTE Adjustments** - a listing of all resources required that are not considered in the project assumptions for various reasons (i.e. Future LCM activities, plant support not proportional to number of projects, etc)

The FTE adjustments represents a small number of resources needed that fall outside of the platform process activities detailed in the workpackage. A 2010 example of an activity in this section was Copaxone bioanalytics for toxicity clinics. For 2010, the FTE adjustments section resulted in the forecasted addition of less than ten people.

4.5.3 Model Calculations

Once all the inputs described previously are entered, the model is able to begin calculations and does so without prompting each time data is added or updated. The output of the workpackage is a matrix of activities by quarter that can be summed to find headcount per quarter, external costs by development year, and campaigns by development year. This can then be simplified into a matrix of headcount, costs, and campaigns by phase by group. The gray calculation tabs in the model pulls in the resultant matrix of information from the workpackage.

One important component of model calculations that is not represented in the workpackage is headcount costs. Personnel costs are listed in the gray "Financial Template" tab in the model. Listed here are the average yearly salaries of employees in specific groups in specific sites. An example of such a group is process development employees located in Menges. In addition, other costs proportional to FTEs such as travel and training costs are listed here.

At a high level, the following calculations generated the output data for the model:

- Number of future projects in a given year = Current projects * Future projects * Probability of success that a project progresses * Time factor * At risk factor

- Total working days = Number of projects by development phase * Corresponding sum of working days per total development phase activities * Probability of success that a project progresses * Time factor * Headcount for current phase * At risk factor
- Total FTEs Cost = FTEs per group per site * (corresponding personnel costs per group per site + miscellaneous costs per FTE when applicable)
- Total Material and Services Cost = Number of projects by development phase * Corresponding Materials and Services costs by development phase
- Total Costs = Total FTE Cost + Total Material and Services Cost

4.6 Model Outputs

The model outputs were designed to be easy to read, comprehend, and use by the key stakeholders. The core outputs are shown below:

- **FTE Summary** – FTEs required per site per group per year, located on the "FTE Summary" worksheet

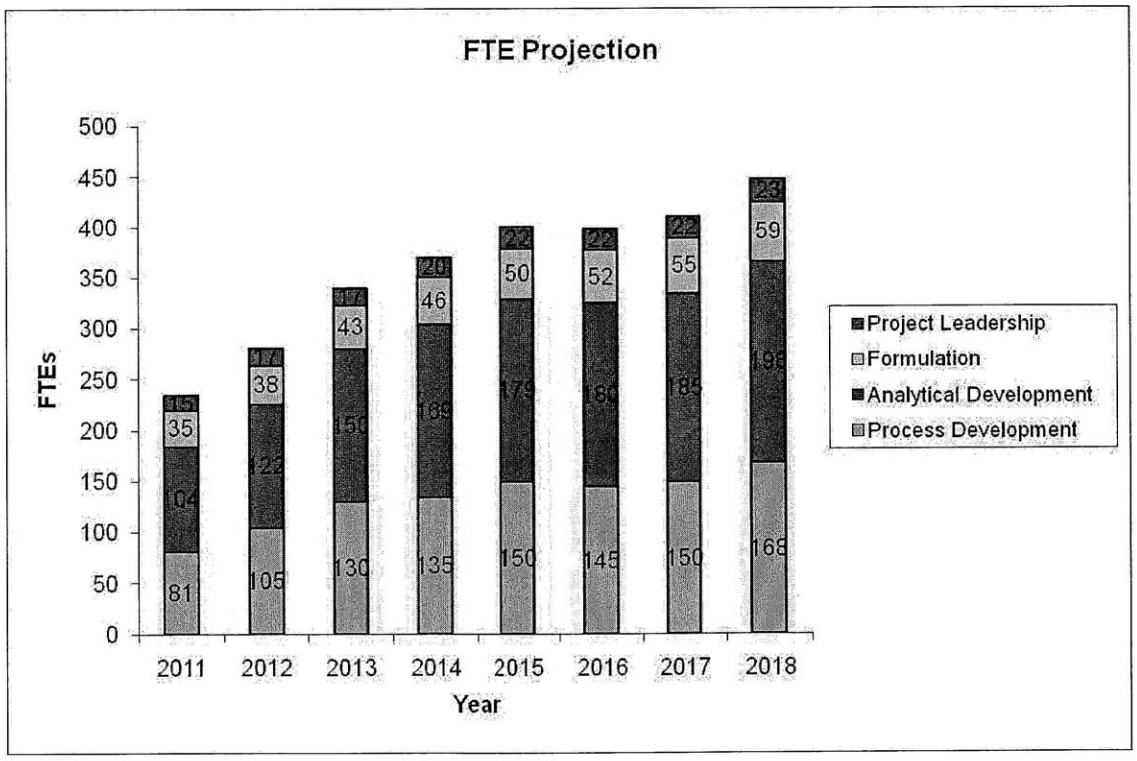
Figure 11 illustrates a potential headcount projection across two sites, Basel and Huningue, for the mAb product type for the current year until 2018. The headcount is broken down by functional group eg Process Development, Analytical Development. The Huningue site is focused primarily on cell culture and thus does not have the capability to perform activities bucketed into a number of functional groups such as Toxicology. Thus the projected headcount for Toxicology for Huningue is zero. The model contains these detailed headcount projections for each product type by functional group across all applicable Novartis sites.

Figure 11: mAb Headcount Projections

FTE Forecasts																			
		Basel								Huningue									
		2011	2012	2013	2014	2015	2016	2017	2018	2010	2011	2012	2013	2014	2015	2016	2017	2018
mAb	Process Development	104.4	131.5	135.0	158.7	174.5	177.4	191.5	168.3	20.9	12.4	12.3	18.3	19.0	19.7	17.8	18.6	21.9
	Analytical Development	118.3	148.9	169.5	189.0	198.0	209.6	223.1	234.5	9.3	9.8	11.0	13.8	13.2	12.3	12.3	13.7	15.5
	Quality Control	24.0	36.4	30.9	39.0	38.3	40.7	40.5	44.5	3.8	7.0	5.6	8.1	8.6	7.9	8.2	8.0	9.5
	Formulation	38.3	43.3	46.4	49.6	51.6	54.7	58.7	63.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Project Leadership	16.6	16.9	19.9	21.6	21.7	21.9	23.1	24.8	1.8	2.4	2.5	2.9	3.2	3.6	3.5	3.7	4.0
	Production DS	1.2	1.7	1.5	1.8	1.6	1.4	1.5	1.7	0.3	0.2	0.1	0.4	0.4	0.3	0.3	0.3	0.4
	Production DP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Management/Ope	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	IBP Cell Culture	4.8	5.6	5.1	5.6	5.1	4.6	6.1	6.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	IBP Microbial	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Toxicology	70.5	81.9	86.2	93.9	87.7	90.8	103.0	111.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	392.0	480.1	508.6	573.1	592.4	615.1	661.5	670.2	36.1	31.6	31.6	43.5	44.4	43.8	42.1	44.4	51.5

These FTE summary tables were well received by management and have been useful in making FTE projection charts for high-level resource meetings and the budgeting process.

Figure 12: FTE Projection Chart



Additionally, a few stakeholders expressed interest in having the FTE information easily available in less detail. Figure 13 below rolls up the all the individual group FTE forecasts and shows a representative output of FTE forecasts across two sites, Basel and Huningue, for the seven different product groups plus enabling technologies which is essentially an administrative function. Figure 13 was constructed in accordance with my sponsoring department's budget. A simple toggle switch on the main headcount page results in Figure 13 which allows the group to gain a 30,000 foot view of needed resources for budgeting.

Figure 13: Total Headcount Projections

		FTE Forecasts																	
		Basel								Huningue									
		2011	2012	2013	2014	2015	2016	2017	2018	2010	2011	2012	2013	2014	2015	2016	2017	2018
mAb	PSP Total	194.9	247.4	261.9	298.4	321.7	322.3	346.4	336.2	20.2	19.6	24.3	33.1	33.5	33.6	31.7	34.0	39.2
microbial	PSP Total	22.9	25.6	36.8	43.2	44.4	56.0	63.3	66.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
mab biosimilars	PSP Total	7.2	9.1	10.2	9.2	10.2	12.6	11.4	12.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
microbial biosimilars	PSP Total	0.7	0.2	0.3	0.4	0.5	0.5	0.5	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Vaccines/3rd Party	PSP Total	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
external	PSP Total	25.9	28.6	31.1	33.9	33.1	35.1	35.5	38.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Non generic tasks	PSP Total	8.5	8.5	7.5	7.5	7.5	7.5	7.5	7.5	9.8	3.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Enabling	PSP Total	18.6	23.0	24.6	27.9	30.0	31.1	33.4	32.3	2.3	1.6	1.6	2.3	2.4	2.4	2.2	2.3	2.7

- **Campaign Summary** - Campaign weeks per site required for development projects, located in the "DS Campaign Summary" and "DP Campaign Summary" worksheets

The campaign summaries are broken down by Drug Substance and Drug Product. The resultant tables follow the same format as the FTE summary. Figure 14 below gives a high-level view of Drug Substance Campaign Forecasts for the Kundl site across the product family types. The most important take away for the campaigns are the total number of campaigns in addition to the campaign weeks. This is because different campaigns require different number of batches

depending on the size of the clinical trial. Producing additional batches requires additional manufacturing weeks.

Figure 14: Drug Substance Campaign Forecasts - Total

	Output:	Kundl								
		2010	2011	2012	2013	2014	2015	2016	2017	2018
Total	Total Campaigns	8	6	7	6	7	7	7	8	9
	Total Campaign Weeks	92	58	75	66	73	71	77	83	92
mAb	Total Campaigns	0	0	0	0	0	0	0	0	0
	Total Campaign Weeks	0	0	0	0	0	0	0	0	0
microbial	Total Campaigns	3	1	2	2	2	3	3	3	4
	Total Campaign Weeks	34	9	21	21	18	28	27	32	40
mAb biosimilars	Total Campaigns	0	0	0	0	0	0	0	0	0
	Total Campaign Weeks	0	0	0	0	0	0	0	0	0
microbial biosimilars	Total Campaigns	1	0	1	0	1	0	0	0	1
	Total Campaign Weeks	10	0	10	2	17	4	5	5	8
Vaccines/ 3rd Party	Total Campaigns	5	5	4	4	4	4	4	4	4
	Total Campaign Weeks	48	50	43	43	38	39	45	46	44

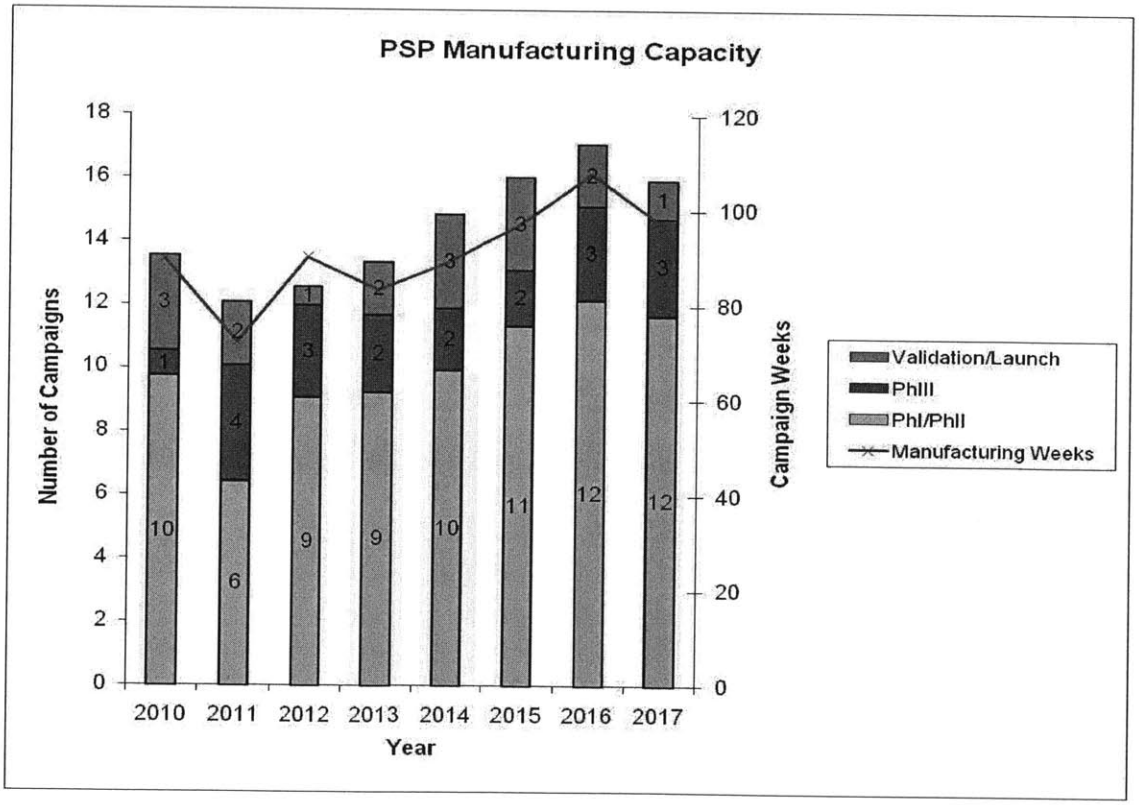
Figure 15 shows a more detailed output for the microbial product family in Kundl. Output tables for Drug Product Campaign Forecasts look very similar.

Figure 15: Drug Substance Campaign Forecasts - Detailed

	Output:	Kundl								
		2010	2011	2012	2013	2014	2015	2016	2017	2018
microbial	Phase I/II Campaigns	1	1	1	1	1	2	2	3	3
	Phase III Campaigns	1	0	0	0	0	0	0	0	0
	Validation/Launch Campaigns	1	0	1	0	0	0	0	0	0
	Total Campaigns	3	1	2	2	2	3	3	3	4
	Phase I/II Campaign Weeks	8	6	11	13	14	21	22	27	34
	Phase III Campaign Weeks	10	2	1	5	4	2	2	3	5
	Validation/Launch DP	16	0	9	3	0	5	3	1	2
	Total Campaign Weeks	34	9	21	21	18	28	27	32	40

Another interesting functionality of the campaign forecasts is comparing the campaign forecasts against manufacturing capability. A discrepancy in manufacturing capacity and projected need merits the investigation into expanding capacity either through new construction, acquisition, or partnership. As described in the pharmaceutical risk hedging section, many pharmaceutical companies enter into relationship with CMO (Contract Manufacturers). Novartis has such a relationship that allows them flexibility in dealing with the inherent uncertainty in drug development. However, many of these contracts are multi-year and signed years in advance so an accurate forecast is paramount to ensure that Novartis is able to fully utilize its own manufacturing capacity while still fulfilling its contractual obligations to the CMO. An example of the PSP organization's manufacturing capacity is shown in Figure 16 below.

Figure 16: PSP Manufacturing Capacity



- **Financial Summary** - Internal and External Costs per site, located in the "Total Costs" and "Materials and Services Costs" worksheets

Financial transparency and granularity was a key model request by Novartis. I worked closely with the unit heads to capture all costs associated with each step of the process. The budgeting process is complex and very time consuming. Initially the model will be used to help the budgeting process start off in the correct ballpark. As management begins gaining confidence in the model, usage of the model has the potential to reduce the time taken for yearly budgeting by 90%.

Figure 17 shows a snapshot of the projected yearly costs of mAb product development in Basel by functional group.

Figure 17: mAb Costs – Basel

		Basel								
In kUSD		2011	2012	2013	2014	2015	2016	2017	2018	2019
mAb	Process Development	$536	$1,205	$1,471	$2,268	$2,739	$2,790	$3,663	$4,134	$4,185
	Analytical Development	$854	$1,139	$1,362	$1,943	$2,331	$2,370	$2,973	$3,380	$3,552
	Quality Control	$223	$269	$166	$257	$226	$221	$289	$299	$320
	Formulation	$779	$717	$774	$921	$1,029	$1,083	$1,258	$1,461	$1,665
	Project Leadership	$569	$768	$593	$721	$733	$778	$944	$999	$1,080
	Production DS	$27,944	$24,065	$27,962	$18,599	$20,575	$21,413	$21,182	$21,123	$20,775
	Production DP	$0	$0	$0	$0	$0	$0	$0	$0	$0
	IBP Cell Culture	$158	$212	$226	$258	$285	$321	$313	$330	$360
	IBP Microbial	$148	$11,766	$10,012	$8,809	$6,864	$16,614	$15,545	$14,230	$18,163
	Toxicology	$33,643	$41,598	$47,253	$31,616	$34,584	$33,080	$30,873	$33,491	$34,597
	Total	$64,854	$81,738	$89,817	$65,392	$69,365	$78,670	$77,039	$79,446	$84,698
	PSP Total	$30,682	$27,893	$32,162	$24,452	$27,407	$28,434	$30,019	$31,096	$31,257

Figure 18 is a compilation of all the costs that hit the Process Science Production (PSP) budget.

Figure 18: Total Costs – PSP Budget

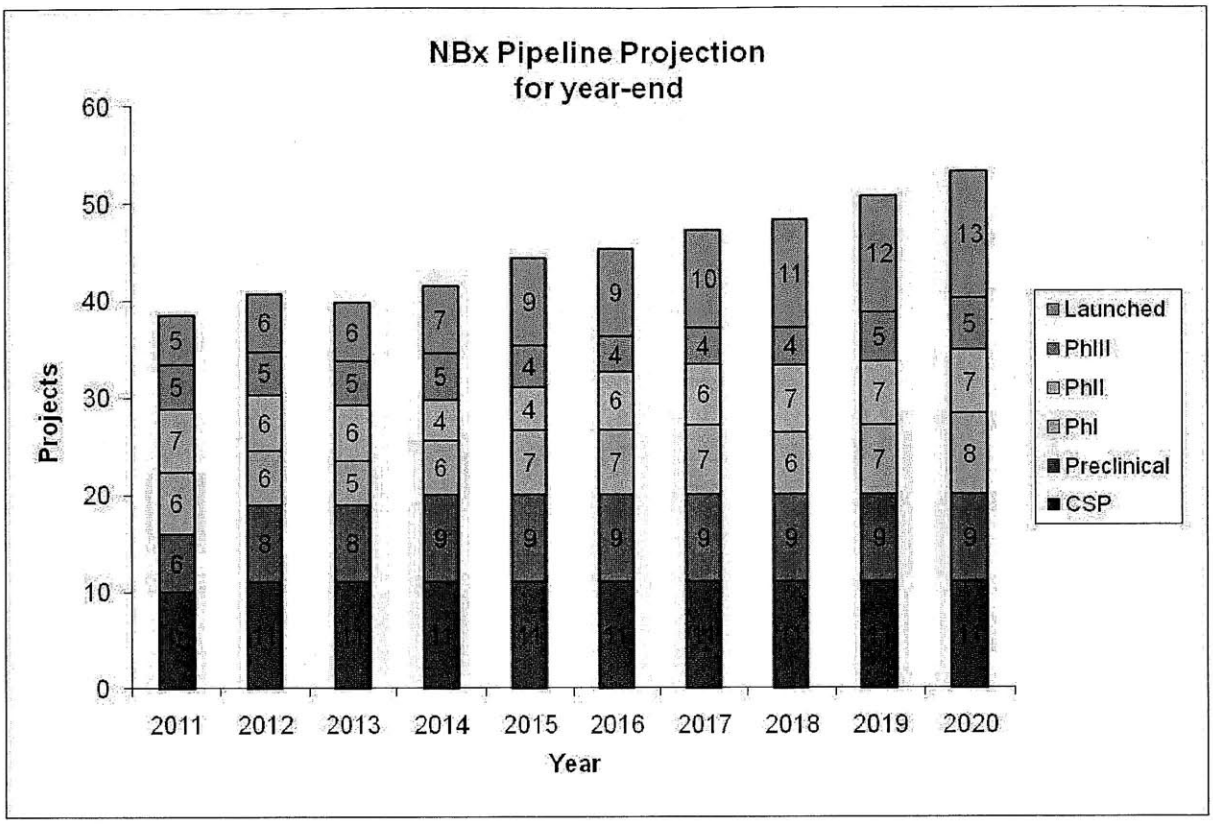
		PSP Budget Only								
In kUSD		2010	2011	2012	2013	2014	2015	2016	2017	2018
mAb	PSP Total	$35,912	$54,722	$56,374	$47,587	$46,059	$65,586	$64,981	$63,606	$72,798
microbial	PSP Total	$25,223	$14,521	$18,269	$26,119	$26,309	$30,356	$33,528	$41,074	$49,836
mAb	PSP Total	$18,173	$20,663	$23,647	$23,872	$26,605	$26,986	$26,207	$27,752	$32,062
microbial	PSP Total	$12,819	$1,966	$10,886	$2,429	$4,677	$3,842	$5,575	$5,749	$5,938
Vaccines/3rd	PSP Total	$0	$0	$0	$0	$0	$0	$0	$0	$0
External	PSP Total	$39,550	$29,278	$35,319	$40,656	$42,892	$40,413	$44,729	$46,247	$48,077
Non Generic	PSP Total	$2,231	$1,291	$1,291	$1,143	$1,143	$1,143	$1,143	$1,143	$1,143
Enabling	PSP Total	$2,388	$2,891	$3,520	$3,771	$4,095	$4,067	$4,211	$4,619	$5,039

- **Projects per year** - matrices and charts describing the number of projects per development year projected for the upcoming ten years, located by division in the "NBx PSP" and "BPO" worksheets

The most visible output of the model is the projects per year. A project portfolio matrix is calculated for each one of these project types and is easily used to create charts showing the forecasted project pipeline.

An example pipeline chart is shown below in Figure 19. The pipeline charts are often used in meetings to upper management.

Figure 19: Novartis Biologics Pipeline Projection



- **Assumptions Summary** - printable report of key assumptions, located in "NBx Assumptions Summary" and "BPO Assumptions Summary" worksheets

The assumption summaries are broken down by division, Novartis Biologics and Biologic Process Organization (BPO). Each summary details out headcount, pipeline, and development stage assumptions. These assumption reports are meant to be a simple way to explain the logic of the model to new users or management.

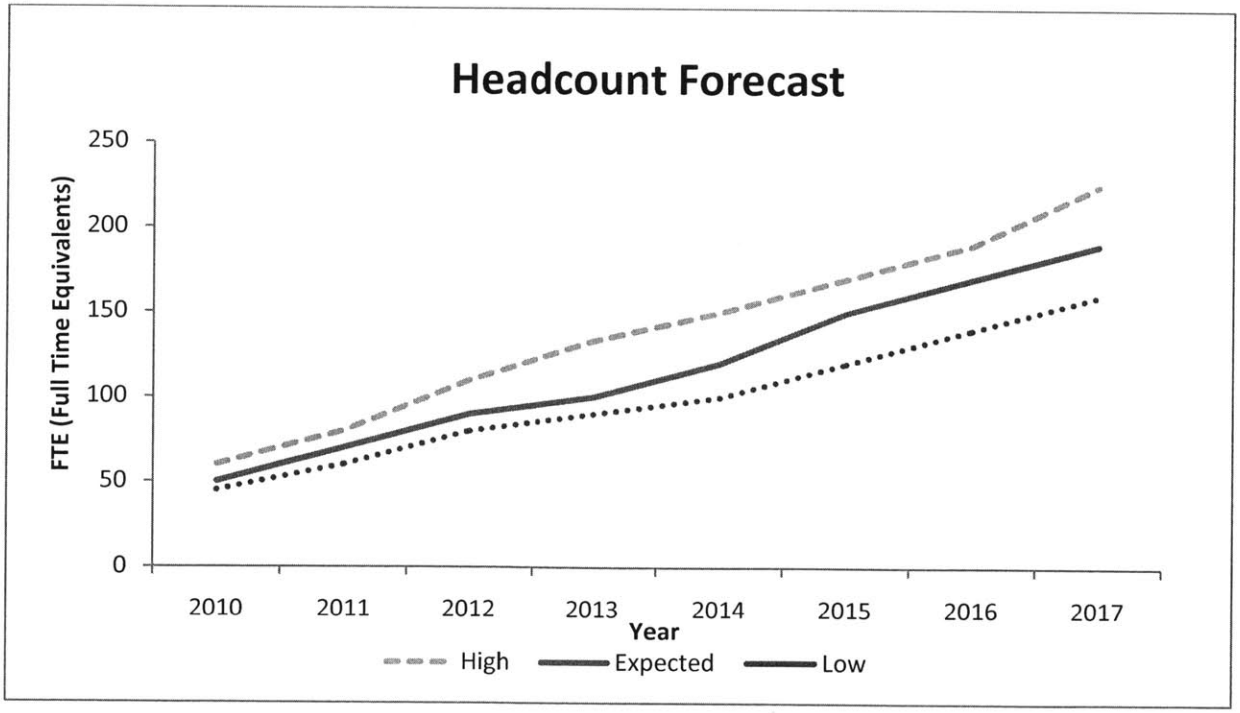
4.7 Uncertainty

This model uses a simulation tool to forecast a project portfolio matrix, and calculate the resources required based on that matrix. However, most of the model inputs and even many of the fixed assumptions carry an amount of uncertainty. For example, the future projects are listed up to ten

years in the future. To combat this uncertainty while still allowing users to make long-term strategic decisions based on model predictions, a Crystal Ball Monte Carlo simulation is incorporated into the model. Crystal Ball is a software program from Oracle that has the ability to simulate a large number of scenarios [7]. It accomplishes this by populating cells with randomly generated numbers based off of user defined probability distributions. In this model, the simulation is run 1000 times and the resource requirement outcomes are saved. These outcomes can be graphed and statistically evaluated. This allows the user to understand the probability that a specific number of resources are required and evaluate the sensitivity of assumptions.

Figure 20 below shows the model's predicted headcount forecast with a Monte Carlo simulation. 1000 trial simulations were run and both a high and low scenario was generated. The dashed lines represent the number of FTEs needed in a 10% and 90% scenario.

Figure 20: Headcount Forecast



4.8 Validation

Since any model is only as useful as it is accurate, testing is imperative. A forecasting model is challenging to test since stakeholders do not want to wait to determine how close a model predicted a future event. Instead, I chose to use historical data to back validate. Unfortunately Novartis Biologics is a new organization and data is only available for 2008 and beyond.

To back validate, I entered in the current list of projects for 2008 and their corresponding development stage. To replicate the pipeline projection at that point in time, I combed through management presentations to determine what they intended for the pipeline to look like ten years out. I also adjusted the structure of the model to replicate the manufacturing sites available and their respective capabilities in 2008.

The resulting FTE, financial, and resource requirements and project pipeline for 2010 were then compared to the actual. These figures ranged from 10 – 25% off of target. By reviewing the discrepancies, I ascertained that the drug development timeline was longer in practice than in the model. This meant that a project started in the beginning of 2008 that should have progressed to development year 2.5 by the middle of 2010 was in reality only at development year 2.0. The difference in the overall eight-year development process was approximately 1.5 years. This discrepancy is not surprising since Novartis is still learning the biologics industry. Altering the structure of the model to account for the new timeline led to a much tighter adherence. The extended product development timeline resulted in a 2 - 9% match between historical projections and actual data. Using historical data to back validate the model was repeated using 2009 inputs. The resulting forecasts from the 2009 for the year 2010 matched 2010 actual data within 4 – 8%. Though there are obviously limitations to using historical data for validation, the results of the validation tests were important to iteratively improve the model and ultimately prove its accuracy.

5 Recommendations and Conclusions

5.1 Conclusions

During validation runs, the model demonstrated accuracy of greater than 90% when compared against historical data for headcount, number of campaigns, costs, and projects per year. In addition, the model's Monte Carlo simulation capabilities allow users to forecast variability and test the sensitivity of the results. This proves the model can be confidently used by project management, operations, and finance to predict their respective future resource needs.

5.2 Recommendations

In order for any model to have long-term success, it must remain accurate, respected, relevant, and easily usable. I would like to address each one of these challenges separately below.

1) Accuracy

   Novartis Biologics is an organization in flux. While I was on my internship, the organization went through several different rounds of structural change. Each round of changes had some impact on the model. Even in a stagnant organization, processes are updated and ownership changes hands. Since much of the model is structured to fit the context of the current organization, future organizational changes will merit substantial model updates. In order to address these concerns, I recommend reviewing the model each time structural changes are made in addition to implementing a well-defined model review process. In addition, it would be helpful to pull data in from SUCEED for short-term planning and more frequent updates than the yearly meetings.

2) Respected

Model credibility and correspondingly respect was a key issue I encountered during my six months in Basel. There is a certain uneasiness by most people to the unknown. So much of the work of the model is done outside the view of the end-user. Model owners need to work with end-users to ensure understanding and agreement with the core assumptions. In addition, visual upper management support is crucial to credibility.

3) Relevancy

The ultimate goal of the model output reports, charts, and tables is to present the data that is most helpful to key decision makers to aid them in strategic planning. In order to do this, the model owners must foster close dialog with upper management and other key decision makers to understand their needs, gain support, and increase the usefulness and thus value of the model. Keeping the model relevant will also help it remain respected.

4) Easily Usable

The model is complex. It involves two different Excel files that must be used in conjunction and a Crystal Ball Monte Carlo simulation if the user wants to incorporate variability and test the sensitivity of analysis. At present, there are a handful of users who are model experts and a few more who are able to use the model to generate charts and figures for presentations. Some stakeholders mentioned wanting a robust model in a non-Excel program. Though I investigated this option and Novartis' internal software building capabilities, I ultimately ruled it out because the learning curve for a new software would be too great for the casual user. In addition, the model complexity may become a hindrance to its expansion into other applications. The volume of data and calculations in the current model was sufficient enough to necessitate two partner files.

From an overall perspective, I recommend implementing a well-defined model review process to review input data and key assumptions. This could take the form of an annual data review by the model owners, unit heads, and other key stakeholders to ensure accuracy. By implementing a review process and taking strides to address the key issues previously described of accuracy, respected, relevant, and easily usable, the model will be able to assist Novartis Biologics in long-term resource planning and allocation for the foreseeable future.

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Appendices

GLOSSARY

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

EMEA (European Medicines Evaluation Agency): the European regulatory agency established to regulate the release of new foods and health-related products

FDA (United States Food and Drug Administration): the federal agency in the Department of Health and Human Services established to regulate the release of new foods and health-related products

FTE (Full Time Equivalent): amount of work equal to one full time employee

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

mAb (Monoclonal Antibody): complex protein-based molecules produced in mammalian cell culture, a type of biologic therapeutic

NBx (Novartis Biologics Group): formed in 2007, housed within Novartis Pharmaceuticals

NME (New Molecular Entity): compound or molecule that is patent protected

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