

Optimization of Preclinical Profiling Operations in Drug Discovery

By
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Submitted to the MIT Sloan School of Management
and the Department of Chemical Engineering
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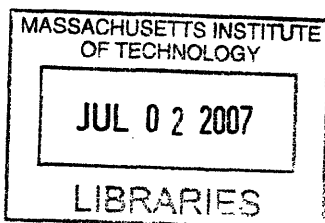
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Abstract

In early-stage drug discovery, thousands of compounds must be tested using in vitro assays to determine their exposure and safety characteristics. This data is used to guide the selection of potential drug candidates and to help chemists in optimize the properties of those compounds. At Novartis, an internal service organization called Preclinical Compound Profiling (PCP) provides these services to the company as a whole. The purpose of this internship was to help PCP make significant improvements in cycle time and cost effectiveness without reducing the quality of information provided to their customers.

The project utilized a series of deterministic and stochastic models to predict the impact of multiple operational changes on cost and cycle time. The data from each model was synthesized to create a unified view allowing combinations of changes to be analyzed together. This data was evaluated in the context of the customer needs and organizational strategy to present recommendations. Changes were implemented that will reduce materials spending by \$500,000 per year while simultaneously increasing capacity, reducing cycle time, and improving customer value. Additional recommendations were developed that will enable further improvements.

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Introduction

1.1 The Pharmaceutical Industry

A major challenge facing the pharmaceutical industry is illustrated in Figure 1. It shows that even with dramatically increasing R&D expenditures, the number of new drugs or New Molecular Entities (NMEs) approved has remained relatively constant.

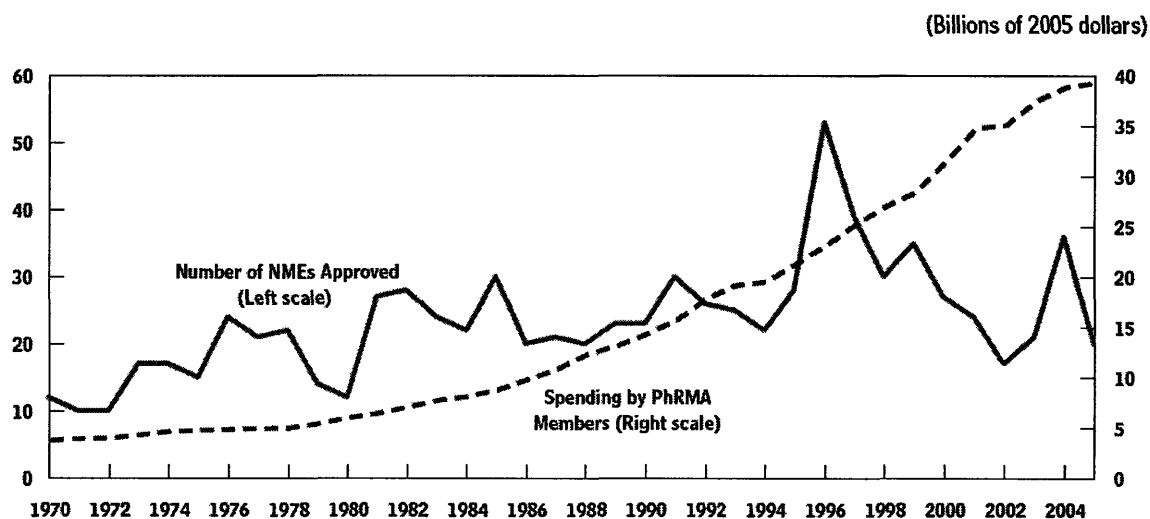


Figure 1 – Pharmaceutical Industry Productivity¹

Since it typically takes 10-15 years to develop a new drug², productivity may increase in future years. However, today the industry faces significant pressure to contain rapidly increasing research costs. The industry is also threatened by increased competition from generic drug manufacturers. The value of drugs that will lose patent protection is forecast to increase significantly in the next few years. In 2005, drugs worth \$12 billion in sales lost patent protection followed by \$23 billion in 2006 and a forecast \$16 billion in 2007.³ The overall pharmaceutical market is forecast to grow at a slower rate of only 4-5% in 2007, significantly slower than the average of 11% experienced between 1970 and 2005.⁴

All of these factors contribute to reduced profitability in the industry as a whole. Figure 2 below shows the overall Return on Assets (ROA) of pharmaceutical companies over the past thirty years. Since 2000, ROA has decreased significantly, creating further pressure on industry executives to improve performance.

¹ Source: Congressional Budget Office. *Research and Development in the Pharmaceutical Industry*. 2006

² Source: Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006*

³ Source: IMS Health. *Changing Market Dynamics in 2007*. December 18th 2006.

<http://pharmalicensing.com/features/disp/1166448792_458698987263a>

⁴ Source: Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2006*

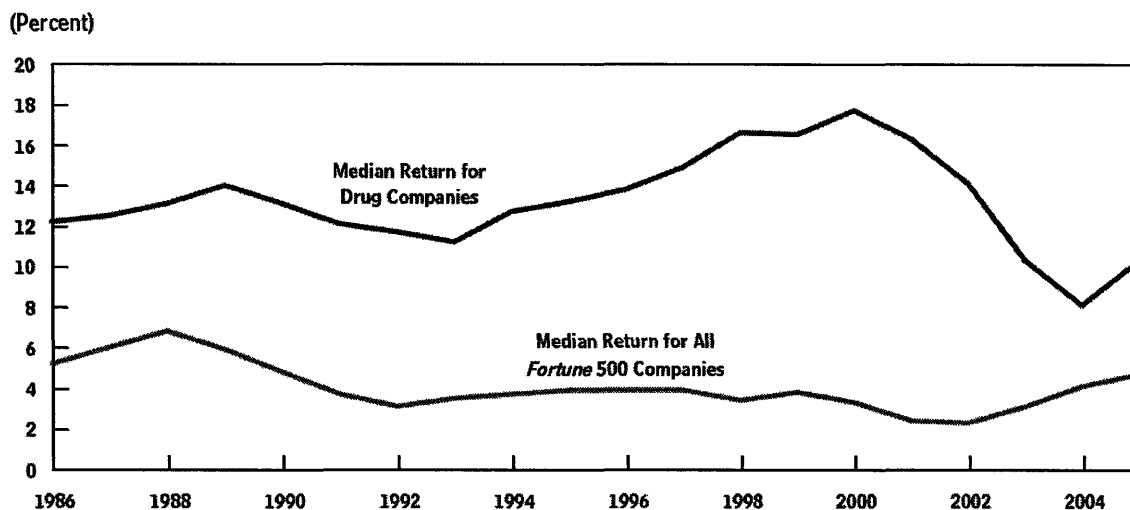


Figure 2 – Median Return for Pharmaceutical Companies⁵

Given this industry situation it is imperative for companies to increase their return on their research and development investments. The purpose of this thesis is to analyze one department at the Novartis Institutes for BioMedical Research, Preclinical Compound Profiling (PCP), and to identify ways to improve their overall cost-effectiveness.

1.2 Novartis and NIBR

Novartis was created as the result of a merger between Ciba-Geigy and Sandoz in 1996.⁶ Both were headquartered in Switzerland and had been in business for more than 100 years. Novartis is the fourth largest pharmaceutical company by market share holding a 5% worldwide market share compared to industry leading Pfizer with a share of 8.7%.⁷ In 2006, the company had sales of over \$37 billion, net income of over \$8 billion and employed more than 100,000 people.⁸

In 2002, Novartis announced the creation of the Novartis Institutes for BioMedical Research (NIBR). This new organization would function as the research arm of Novartis, responsible for the discovery of new medicines. It was also announced that this new organization would move the headquarters to Cambridge, Massachusetts from Basel Switzerland.

Dan Vasella, CEO of Novartis, chose to locate in Cambridge to attract local talent, to be close to leading universities and hospitals, and to have a greater presence in the world's

⁵ Source: Research and Development in the Pharmaceutical Industry. Congress of the United States Congressional Budget Office. 2006

⁶ Source: Novartis A.G. Website, <<http://www.novartis.com>>.

⁷ Source: Global Pharmaceuticals Industry Profile. Datamonitor. December 2006

⁸ Source: Novartis A.G. *Novartis Annual Report 2006*.

<http://www.novartis.com/downloads/investors/reports/AR06_E_web.pdf>

largest pharmaceutical market.⁹ Since then Novartis has won awards in both 2005 and 2006 for having the best pipeline in the pharmaceutical business.¹⁰

1.3 Thesis Outline

This thesis is organized into the following nine chapters.

Chapter 2 provides background information on how Preclinical Compound Profiling (PCP) fits into Novartis' overall drug development process. It also discusses the basic requirements of a successful profiling organization

Chapter 3 discusses the profiling technology and investigates how well the organization has performed on three key metrics: capacity, cycle time, and cost. Also provided is additional information on the cost structure and products offered in Preclinical Compound Profiling.

Chapter 4 presents a typical process flow diagram, showing each step that takes place between the initiation of a customer order and order fulfillment. Based upon that process flow, areas of opportunity will be identified that could significantly reduce the overall cycle time.

Chapter 5 analyzes a proposal to more efficiently allocate capacity by allowing a flexible assay ordering system for the Safety Pharmacology area in PCP. A model will be presented showing the potential costs and benefits. Also discussed is an intermediate proposal to gain some benefits of flexible ordering without the associated investment costs.

Chapter 6 will discuss three proposed changes to the operations of the Safety Pharmacology area: assay run frequency, assay location, and outsourcing. Several simple models will be introduced to evaluate the impact of these changes on cost and cycle time. Results from the models will be synthesized to provide a unified view of how the changes interact and affect the key output parameters.

Chapter 7 investigates the long-term strategy of the PCP organization and provides recommendations on strategies to maximize the long-term value of the group.

Chapter 8 describes the organizational structure of the PCP group and provides recommendations on organizational changes.

Chapter 9 summarizes the recommendations presented in the thesis and general principles that can be applied to similar situations.

⁹ Source: Naik, Gautim. *Vasella Drives Stodgy Novartis into a New Era*. Wall Street Journal. B1. 13 October 2003.

¹⁰ Source: SCRIP Awards Website. 2006. <<http://www.pjbpubs.com/scripawards/index.htm>>

2 The role of Profiling in Drug Discovery

2.1 The Drug Discovery Process at Novartis

The drug discovery process at Novartis is described in Figure 3.

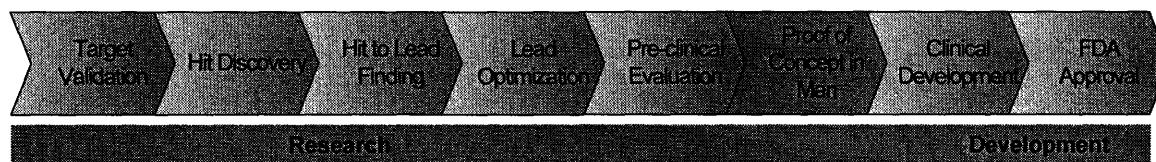


Figure 3 – Novartis Drug Discovery Process¹¹

The process begins with the discovery of the mechanism and pathway of a disease. Researchers identify a specific interaction in the pathway that could be blocked by an antagonist or stimulated by an agonist and then validate the target to ensure that modulating the target causes a measurable response. Once a target is identified and validated, Novartis scientists move on to the next stage where they develop assays that can be used to test potential compounds with broad chemical diversity to see if they will have affinity to the target. When an assay is successfully developed, the program moves to the Hit Discovery stage and performs High-Throughput Screening (HTS). In a typical screen, about a million compounds from the Novartis compound archive are tested to determine if they will successfully bind to the target. Compounds that bind to the target are called “hits.” These hits are evaluated in more detailed screens to determine their potency. Additional tests are developed to validate that these hits actually bind to the desired target rather than degrading the proteins used in the screening assay or binding to multiple sites in addition to the desired receptor.

Once the hits are validated the program moves to the next phase called Hit-to-Lead Finding. The objective of this phase is to further reduce the number of validated chemical structures to those that have good potency, structure-activity-relationship (SAR) at the therapeutic target and reasonable exposure and safety parameters. This stage ends with Lead Nomination. During the following stage, Lead Optimization, lead compounds are modified by medicinal chemists in order to optimize their structure to obtain maximum potency, exposure and safety. Chemists in this phase rely on a variety of *in vitro* and animal studies to gain insights into how their structural changes to the compound affect its properties in a living system.

Promising compounds progress to the Candidate Selection Process (CSP) where they are prepared for a Proof of Concept (PoC) trial. This is a human trial of the drug in a small population that may have the disease of interest or a different disease with a related mechanism. The purpose of the PoC is to validate that the drug has a measurable therapeutic efficacy in humans without major safety problems. Doing a PoC very early in the clinical development is designed to increase the likelihood of success before beginning very expensive and lengthy clinical trials.

¹¹ Source: The Novartis Institutes for BioMedical Research Website, <<http://nibr.novartis.com>>.

If the compound is successful in the PoC, it moves into full clinical development and a series of human trials. If the compound appears to have acceptable an efficacy and safety profile, it is submitted for final approval to the Food and Drug Administration (FDA).

2.2 Preclinical Profiling

2.2.1 The Purpose of Preclinical Profiling

The mission of Preclinical Profiling (PCP) is to “support the needs of drug discovery projects by providing essential information on compound properties to help lead selection and lead optimization.”¹² They accomplish this by analyzing the exposure and toxicity properties and liabilities of compounds with *in vitro* assays. Exposure is the ability of the drug to reach a significant concentration in the body and is also referred to as bioavailability. Toxicity is the ability of the drug to cause damage or unacceptable, undesirable side-effects. The path that oral drugs take through the body is shown in Figure 4 below.

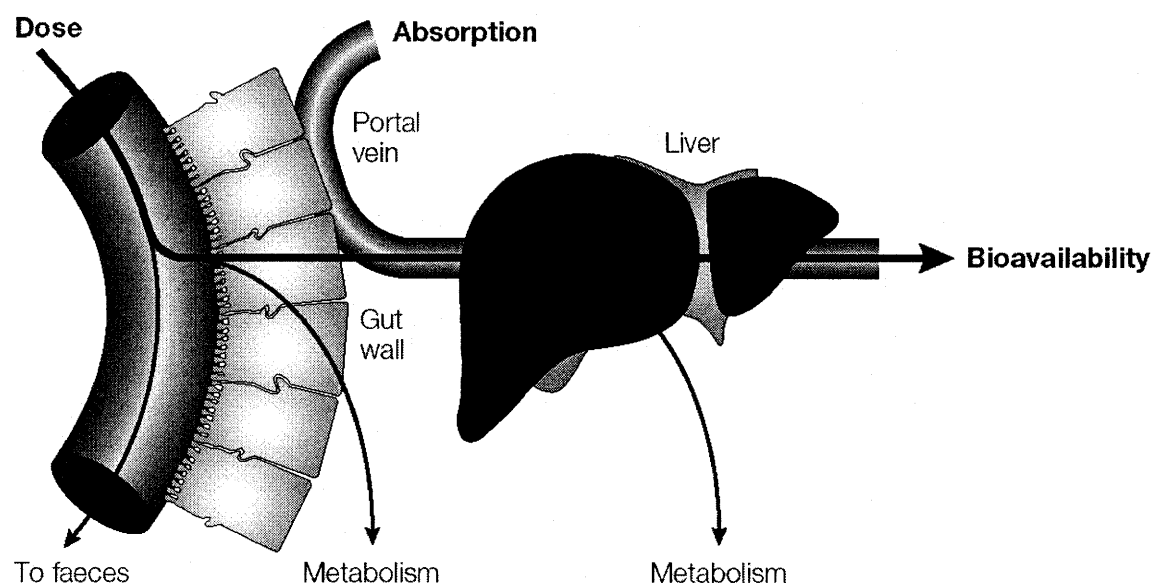


Figure 4 – Pathway to Bioavailability¹³

Orally administered drugs must pass several hurdles before they can become effective in the body. The first obstacle is absorption. Absorption is primarily dependent on two factors: solubility and permeability. To enter the bloodstream the drug must be soluble in the gut environment and must be capable of passing through the cell membrane of the intestinal wall. Some drugs can compensate for low solubility with high permeability and vice-versa, but drugs with low solubility and low permeability are rarely successful.¹⁴

¹² Novartis Internal Website: <http://nibr.novartis.intra/DT/lcd/pcp/index.jsp>

¹³ Suzanne Tilton. Novartis Internal Presentation. *Physicochemical: Pka and Log P/D*. May 11 2006

¹⁴ Source: Lipinski, C.A. et al. *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*. 1997

Once the drug has made it into the cells of the body it faces the second obstacle: metabolism. Blood flows from the intestines to the liver, the primary organ responsible for drug metabolism. In the liver, many different enzymes can act upon drugs to change their functional groups and potentially render them inactive or alternatively unsafe in the body. Drugs that are rapidly metabolized are unlikely to be effective because they will never reach a significant concentration in the body in the form in which they were delivered.¹⁵

The problem of toxicity is the third major obstacle drugs face in becoming effective in a living person. When a drug is present at the required concentration in the bloodstream, it can cause the desired, therapeutic effect or it can cause an undesired, off-target effect. These effects can range from a mild case of nausea to heart failure and death. Almost any drug becomes toxic at high concentrations. The difference between the concentration required to create the therapeutic effect and the concentration required to create a toxic effect is called the therapeutic index. Medicinal chemists always try to maximize the specificity and potency of their drugs at the desired target to make the therapeutic index as large as possible.

2.2.2 Requirements for Successful Preclinical Compound Profiling

Profiling data is primarily used in the Hit to Lead Finding and Lead Optimization stages of drug discovery. In Lead Optimization the process is iterative. Chemists synthesize a compound or group of compounds and then need to test the compound's properties. At each cycle they evaluate the effect of each change to the compound's structure and then devise new modifications to test. At the end of the process they hope to optimize three parameters simultaneously: efficacy, exposure and safety. To support this activity, PCP needs to provide assays that are fast, inexpensive, and predictive.

It is critical that profiling data is provided to chemists quickly so that they can make the best decision on what to do in their next synthetic cycle. If a chemist is missing some useful data she will most likely go ahead and move to the next synthetic cycle based on the information at hand. With incomplete information it is less likely that the chemist will make the best decision. This causes delays, frustration, wasted effort and worst, uneducated decisions. For this reason it is critical that PCP provide data quickly to support chemists in making the best decisions possible.

Chemists in early-stage drug discovery at Novartis produce tens of thousands of new compounds each year in their attempts to create a few promising new drugs. Because the number of compounds is so large it is vital that inexpensive means are employed to measure their properties. PCP needs to operate a high-volume, low cost set of assays to support these requirements.

¹⁵ Source: Pritchard, J.F., et al. *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*. 2003.

The data that PCP generates is used to make key decisions about the direction of drug discovery programs and is often an important factor in the decision to discontinue development of compound scaffolds. The type of assays that PCP chooses to offer must be well correlated with actual effects in living systems. Otherwise the results will be misleading and will lead to poor decisions.

Interestingly, profiling data does not need to be extremely precise or extremely accurate.¹⁶ At this early stage of development it is very important to be able to say that a compound will have high solubility rather than low solubility, but exactly how high or how low isn't as critical until later in the process. It is preferable to have an assay that is always in the correct order of magnitude, than it is to have an assay that is usually within 5% of the true value but 20% of the time it is completely wrong.¹⁷

3 Profiling Technology and Performance Overview

This section will describe the basic principles involved in performing an assay and the technology employed. It will also describe the basic assays that are performed by the preclinical profiling group with specific focus on the safety pharmacology assays. The cost structure and recent performance of the PCP organization will also be discussed.

3.1 Profiling Technology

Preclinical compound profiling must process thousands of compounds every year that are generated in Novartis' labs. Each compound is only available in low milligram quantities, and the cost of specialized proteins, radioligands, and other reagents can be hundreds of dollars per milligram. In this environment it is critical to have technology that will allow the scientists to obtain high quality data on many different compounds using tiny amounts of compounds and reagents. This section will describe the basic technology used to perform the assays.

In Preclinical Compound Profiling, compounds arrive in the form of microtubes that contain up to 500 μ L of a standard 10mM solution of the compound in the solvent DMSO (dimethylsulfoxide). Up to 96 tubes, each containing one compound in solution are arranged together on racks such as the one shown below.

¹⁶ Uusitalo, Jouko. ADME Solutions from Drug Discovery to Lead Optimisation, Candidate Selection and Beyond. 2005.

¹⁷ Based on interviews conducted by the author with multiple NIBR scientists.

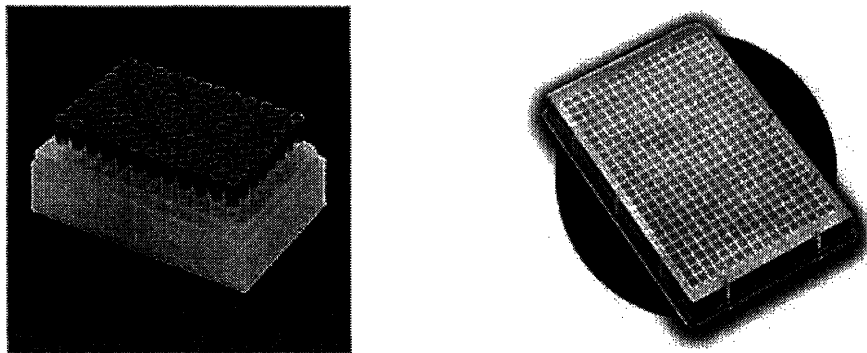


Figure 5 – 96 Tube Rack¹⁸ & 384 well Plate

Automated liquid handling systems, such as the one shown below in Figure 6, can accurately transfer very small amounts (10-100 μ L) of the samples into 96 or 384-well plates (shown in Figure 6 above) for further processing. Each sample is serially diluted to create a series of wells with progressively decreasing concentrations of the compound to be studied. Typical concentration curves go from 30 μ M to 3 nM.

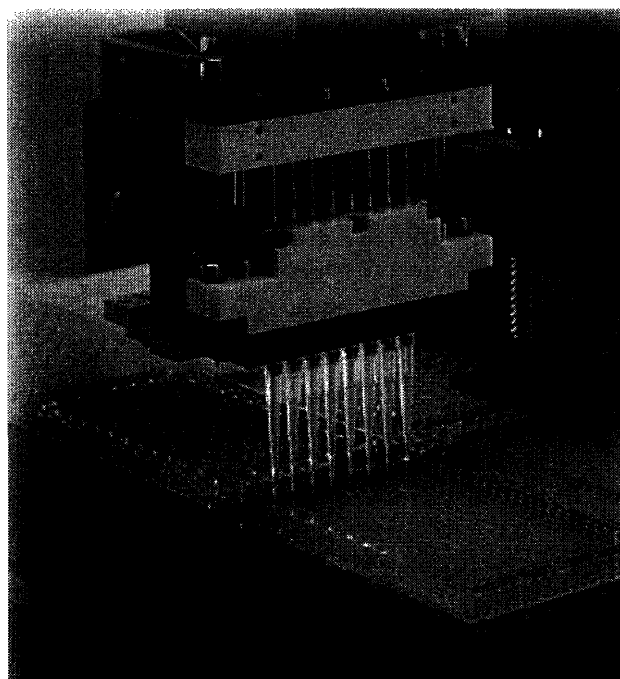


Figure 6 – Automated Liquid Handler¹⁹

The automated liquid handlers are often integrated into a bench scale system that can perform an entire experiment on multiple assay plates. The operator must first setup the equipment and supply all of the necessary reagents and sample plates. Once the setup is

¹⁸ Microtube Rack System. Samin Science Company Website
<http://www.saminsci.com/html/business/general_vails03.htm>

¹⁹ BioTek Company Website. BioTek Precision 2000 Automated Pipetting System.
<http://www.biotek.com/products/tech_res_detail.php?id=114>

complete the system follows a program selected by the operator that performs all of the steps in the assay protocol. Some systems integrate the appropriate reader to perform experimental data collection, while others require separate data acquisition equipment.

3.2 Assays Offered

To provide the information that chemists need in drug development PCP offers a broad selection of major assays. These assays are described in the table below.

Assay Name	Data provided
PAMPA	Permeability
HT-Sol	Solubility
HT pKa	Ionization Constant
Microsomal Stability	Metabolism
CYP 450 IC50	Inhibition of Metabolism (Drug-Drug Interactions)
Caco – 2	Permeability & Efflux
HERG binding	Cardiac Q-T Prolongation
Safety Pharmacology Panel	Side-effects (adverse drug reactions)
Micronucleus	Genotoxicity
Hepatotox	Liver Toxicity

Table 1 – Profiling Assays Performed at Novartis

The Preclinical Compound Profiling department publishes a catalog that contains a list of all available assays, the committed turnaround time for each assay, and an estimate of the cost of each assay. Since individual departments are not billed for the assays they request, this data is provided to help the requestors make reasonable decisions about how many compounds to submit to a single assay.

3.2.1 Scintillation Proximity Assays

This thesis will focus on the Safety Pharmacology area within PCP. Safety Pharmacology uses two primary types of assays: filtration binding assays and scintillation proximity assays (SPA). The SPA format will be described in detail as it is the dominant format employed at Novartis.

Any safety pharmacology assay begins with an identified and purified biological receptor. These are typically protein structures in the body that are known to cause a specific biological response when a ligand that matches the receptor site interacts with the receptor. Drugs often function by inserting themselves into the receptor and preventing the ligand from binding to the receptor and sending the signal which causes the biological response. This behavior is shown in Figure 7 below.

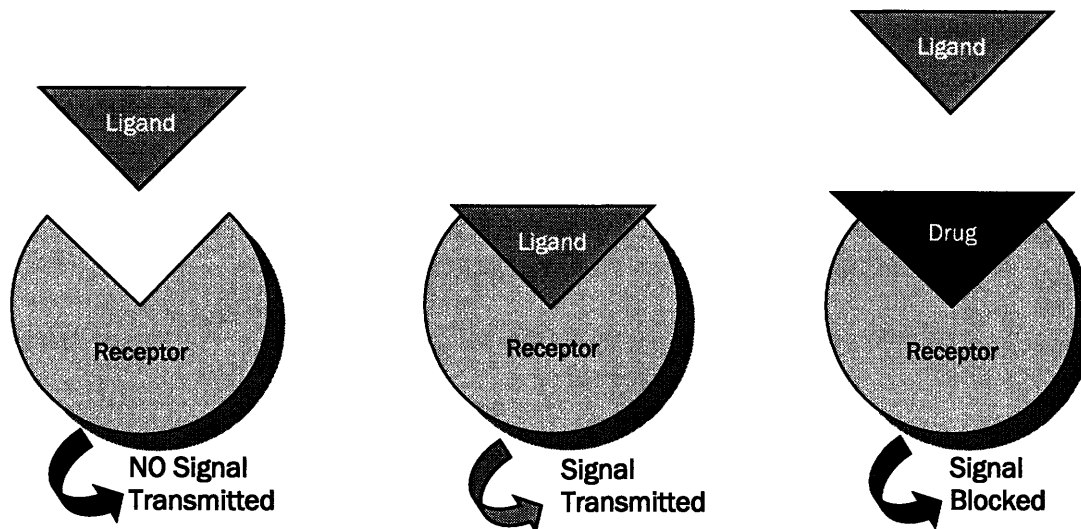


Figure 7 – Receptor Binding Diagram²⁰

In a scintillation proximity assay, radioactive isotopes are attached to the ligands, and scintillation beads are attached to the receptors. The scintillation beads are made from either yttrium silicate or PVT (polyvinyl-toluene). Both compounds emit light in the visible spectrum when exposed to low-energy radiation.

If a radioligand successfully binds to the receptor, the radioactive tag will cause the bead to fluoresce, creating a measurable light emission. This is shown in Figure 8 below. The radioactive isotopes used are typically ^3H and ^{125}I because both emit low energy beta particles that can only travel about 10um in water.

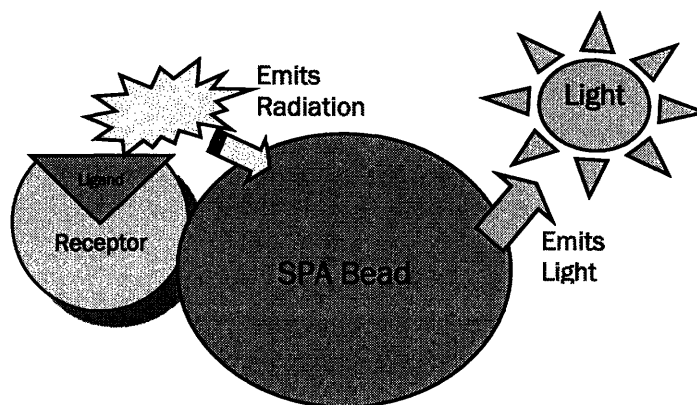


Figure 8 – Scintillation Proximity Assay Diagram ‘On’ State²¹

Ligands that are not bound to a receptor will not be close enough to the scintillation bead to produce a response. This behavior is shown in Figure 9 below. In this case the radiation is absorbed by the water in the solution and will not cause the bead to emit light.

²⁰ Alex Fekete. Novartis Internal Presentation. *In vitro Safety Pharmacology*. May 2006.

²¹ Fekete, Alex. Novartis Internal Presentation. *In vitro Safety Pharmacology*. May 2006.

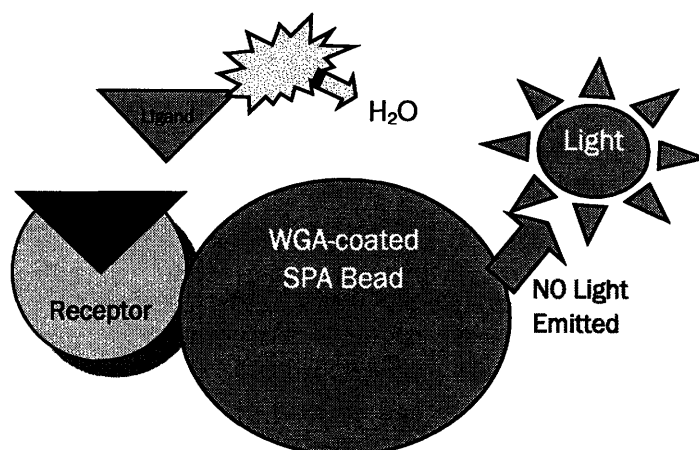


Figure 9 – Scintillation Proximity Assay Diagram “Off” State²²

Scintillation detectors are used to measure the relative amount of light emission and determine to what extent the drug bound to the receptor and blocked the ligand from binding. These detectors will record a value for the intensity of light emission for each well on the microplate. If the drug is very effective at binding to the receptor, then at high concentrations of drug we would expect the light emission to be close to zero. Reference wells without the drug being tested are used to establish the maximum intensity, while other reference wells are populated with a known drug that binds to the receptor establishing the low reference point.

Once all of the data is collected, the data points are fit to a curve in order to determine the IC_{50} , or the concentration at which the compound inhibits 50% of the normal binding of the radioligand. A typical example of a compound that bound to the ligand is shown in Figure 10 below.

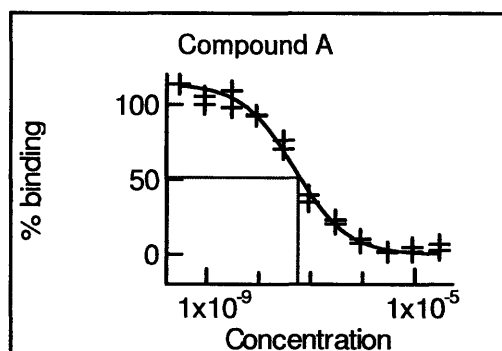


Figure 10 – IC_{50} Determination

In any given assay, most compounds are inactive and show no significant change in binding even at concentrations up to 30uM. This behavior is shown in Figure 11 below. In this case the profiling group reports the IC_{50} as being greater than 30uM.

²² Fekete, Alex. May 2006

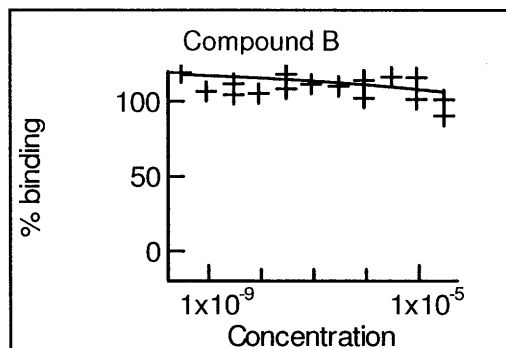


Figure 11 – Inactive Compound

PCP collects this data for each assay and each compound and uploads it to a central database that stores all compound-related information.

3.3 Cost Structure

The largest source of cost in the Cambridge profiling organization is personnel. Entry level associates all have Bachelors or Masters degrees in science and nearly all lab heads or supervisors have Doctorate degrees. The distribution of costs is shown in the figure below.

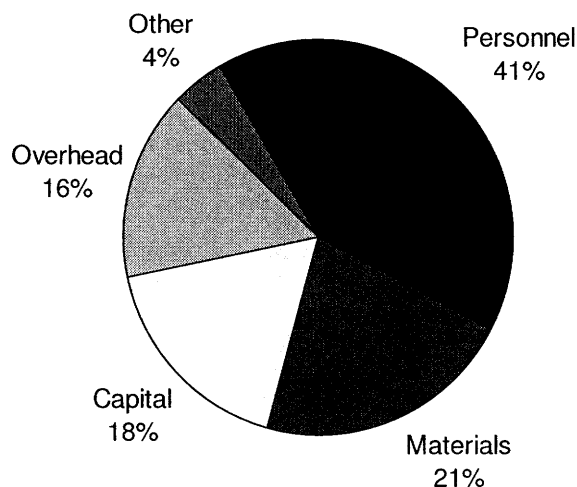


Figure 12 – PCP Expenses by Category

This breakdown allows us to see where the opportunities lie in reducing the cost of the assays on a per-compound basis. Personnel, capital, and overhead are relatively difficult to modify in the current business environment. Also, PCP output is capacity constrained rather than demand constrained for most assays. This leads to the conclusion that the best opportunity for reducing costs per compound is through increasing capacity and utilization of the current resources.

Materials costs are also a significant cost component and are much easier to change through improvement projects. However, these costs are not split evenly between the various types of assays. The Safety Pharmacology group consumes about forty percent of

the total budget and about two-thirds of the materials budget, meaning that some of the best opportunities for savings are in the Safety Pharmacology area. As a result, much of this thesis will focus on potential improvements to the Safety Pharmacology department.

3.4 Performance

The performance of the PCP group is challenged by average demand that is above their stated capacity. They also face high demand variability. Figure 13 below shows a typical demand pattern and capacity level for two assays, Safety Pharmacology and Caco-2 which both experience very heavy demand.

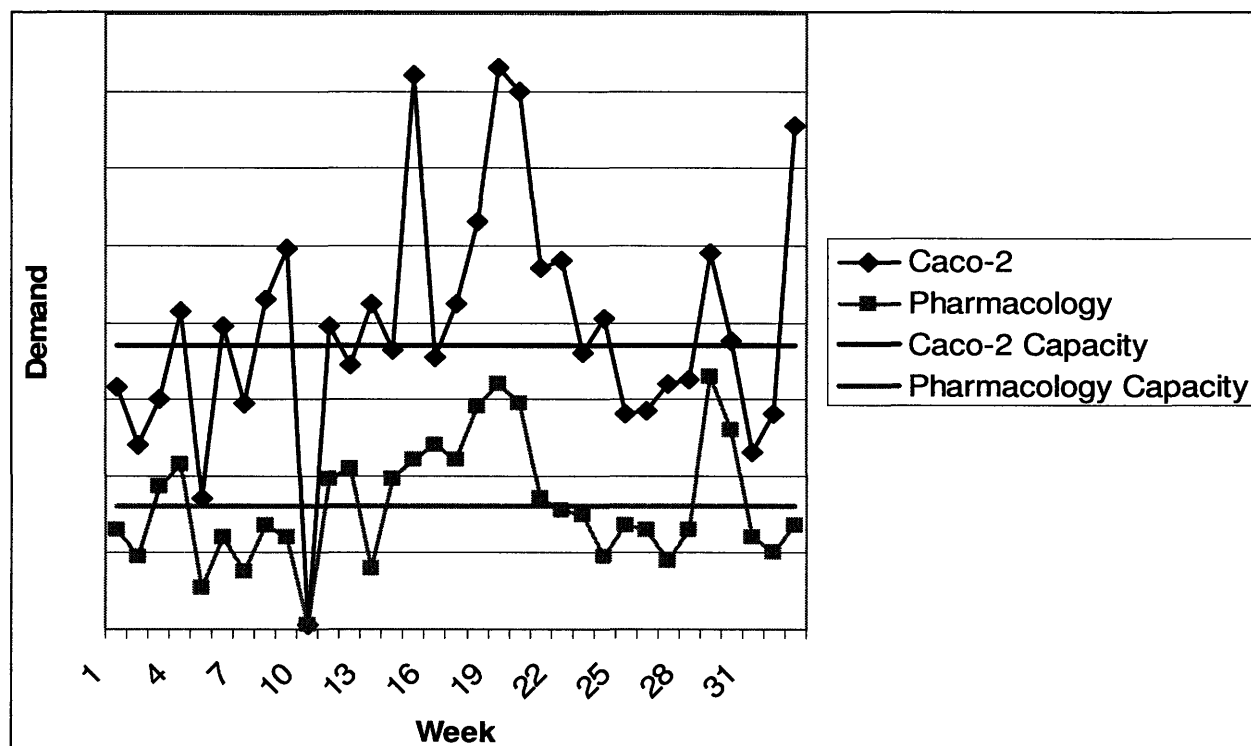


Figure 13 - Weekly Demand Patterns vs. Capacity

Table 2 shows the five major assay groups, the coefficient of variation of demand, and the overall capacity utilization.

Assay Group	CV	Utilization
Solubility & Permeability	0.5	85%
Metabolic Stability	0.5	110%
Caco-2	0.3	150%
hERG channel	0.3	115%
Safety Pharmacology	0.4	158%

Table 2 – Assay Demand Variability and Utilization

Based on this information we can see that variability is significant and that in many cases utilization exceeds 100%. Given this information we would expect nearly infinite queues

for some of these assays. Although several assays experience long queue times, none have showed continuous build-up due to the fact that capacity is somewhat fungible in PCP.

3.4.1 What is Capacity?

As mentioned previously, labor is the most significant component of cost in PCP. Interestingly, it also turns out that labor is the primary system constraint. Equipment is often idle and there are always compounds available for testing. Classic views on dealing with constraints would tell us to subordinate everything in the system to the constraint to maximize the system performance.²³ However, performing the assays is only one piece of the job description of a typical associate working in PCP. They are also responsible for assay improvement projects, new assay development, supporting project teams and many other tasks. The amount of time that they can dedicate to performing the assay is not necessarily fixed from week to week.

Given that the associates' time is the constraint, it is useful to investigate how the capacity is determined. At Novartis the PCP organization publishes a catalog that lists each assay they perform, how many compounds they can process each year, the turnaround time or cycle time for each assay, and how much each assay costs the company on a per-compound basis. The capacities stated in this catalog are typically determined based on an assay schedule chosen by the profiling department. For example, the pharmacology area prefers to run their assay once every two weeks. If their equipment was setup to handle 4 plates per assay and each plate held 10 compounds, they would state their yearly capacity as 1000 compounds (40 compounds per run with 25 runs per year).

In reality, the pharmacology area could process many more compounds than their stated capacity by either increasing the number of compounds per run or by running the assay more frequently. When they increase the time spent on performing the assay they will naturally be forced to spend less time on their other job responsibilities. As is often the case with knowledge workers, it is extremely difficult to precisely determine how much time various projects should take and to quantify how busy or how well utilized a particular worker is. This in turn makes it extremely difficult to determine what the true underlying capacity is.

In the Safety Pharmacology area, the associates have been inserting extra assay runs into their schedule whenever the queue becomes very long. Similar strategies are used by the associates in other areas, explaining how they are able to operate at a utilization of over 100%.

3.4.2 Cycle Time

Before discussing cycle time performance, it is important to understand how cycle time was defined in PCP. For most assays, cycle time began when an associate picked up a

²³ Source: Goldratt, Eliyahu. *The Goal: A Process of Ongoing Improvement*. 1984

compound for analysis and ended when data was uploaded to the database. Based on this criteria, most of the profiling assays met their cycle time goals because the process of performing the assay was consistent and had a relatively stable cycle time.

The critical problem with this metric was that the measured and reported cycle time did not correspond to the cycle time experienced by PCP customers. The metric did not measure the entire process, it only measured the small piece that occurs within PCP. The metric ignored the process of getting compounds to the profiling lab as well as the queue time that compounds experienced waiting for profiling to retrieve them. This process will be discussed in detail in section four.

When we include only queue time before PCP along with process time in PCP, the cycle time picture is not good. Figure 14 below shows the week by week cycle time performance of two selected assays, Safety Pharmacology and hERG.

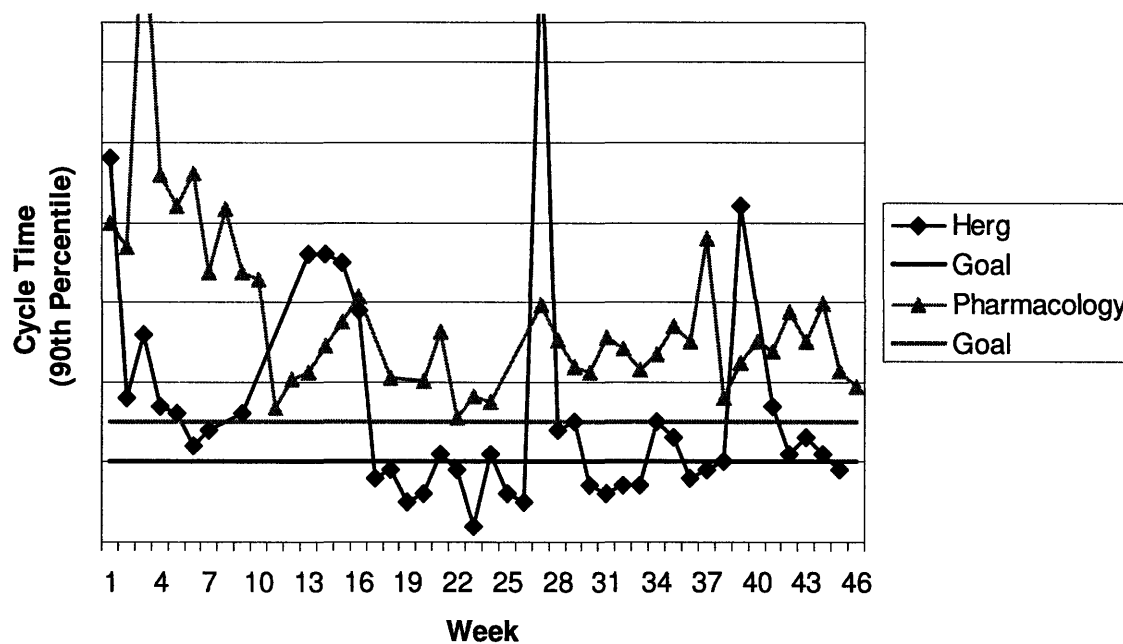


Figure 14 – Cycle Time vs. Goal

As you can see from the chart above, Safety Pharmacology rarely achieved its cycle time goals. The hERG assay performed better but still frequently exceeded its cycle time goals as well. These two assays along with a few others have persistent problems meeting their cycle-time requirements when the length of the entire process flow is considered.

3.4.3 Cost

On a per-compound basis, preclinical profiling is typically cost-competitive versus external vendors, with a few specific exceptions. Table 2 below shows the external cost of several assays compared to the calculated internal costs.

Assay	External Cost
A	281%
B	65%
C	187%
D	70%
E	99%
F	240%
G	204%

Table 3 - External Cost as a Percentage of Internal Cost²⁴

These comparisons were made versus third party vendors that typically perform assays on small numbers of compounds for many different customers. It is reasonable to expect that an internal organization with a stable flow of compounds going to a small, fixed collection of assay formats would be able to outperform these types of vendors. Another interesting comparison is how PCP compares with other profiling organizations that are captive within large pharmaceutical companies. Based on an internal study, NIBR estimated the labor per compound tested for major competitors. This measure is not as complete as total cost, but since labor is a large fraction of overall costs it is a reasonable surrogate. The results for several assay technologies is shown below in Figure 15.

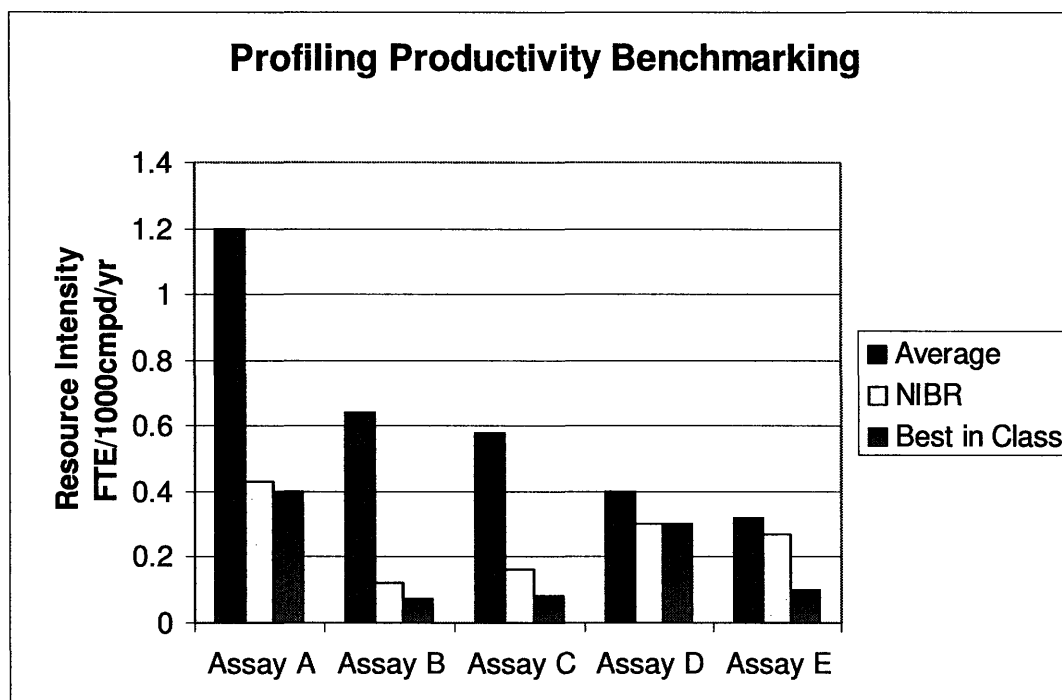


Figure 15 - PCP Productivity Benchmarking²⁵

²⁴ Based on 2006 historical costs and outsourcing quotes from multiple vendors compiled by Melanie Hann

²⁵ Data from NIBR analysis performed by Jianling Wang.

Based on this data the NIBR Profiling group has costs that are significantly below industry average. However, in several assay technologies there is room to improve to match best-in-class performance.

Overall, we can conclude that costs on a per compound basis are not unusual with respect to third party vendors and other pharmaceutical companies. However, these per compound costs for existing assays exclude portions of the overall profiling budget. PCP spends a significant portion of its resources on new assay development. In 2006 this fraction was near 30%. PCP also performs a significant number of secondary assays that account for about 10% of its budget. These are typically more labor intensive, more expensive, and done in very low volumes. Since spending on development activities and secondary assays is not included in the cost per compound calculations for the primary assays shown above, the overall profiling budget is significantly larger than one would estimate based on the primary assays alone. This contributes to the perception by some in the company that PCP is relatively expensive.

4 Process Flow Analysis

4.1 Profiling Process Flow Description

The process of obtaining profiling data on a potential new drug begins and ends with a medicinal chemist. The chemist will synthesize a new compound and decide to submit that compound for testing. To do this they must first fill out an electronic request in the Test Request Tool (TRT). This is the first step in the process flow diagram shown below. The diagram is color coded showing the currently accepted areas of responsibility for each section of the process flow. Green corresponds to the requesting chemist, orange to the Compound Management Unit (CMU), and blue to Preclinical Profiling. The average duration of each process step in the case of the Safety Pharmacology assay panel is also indicated in units of business days.

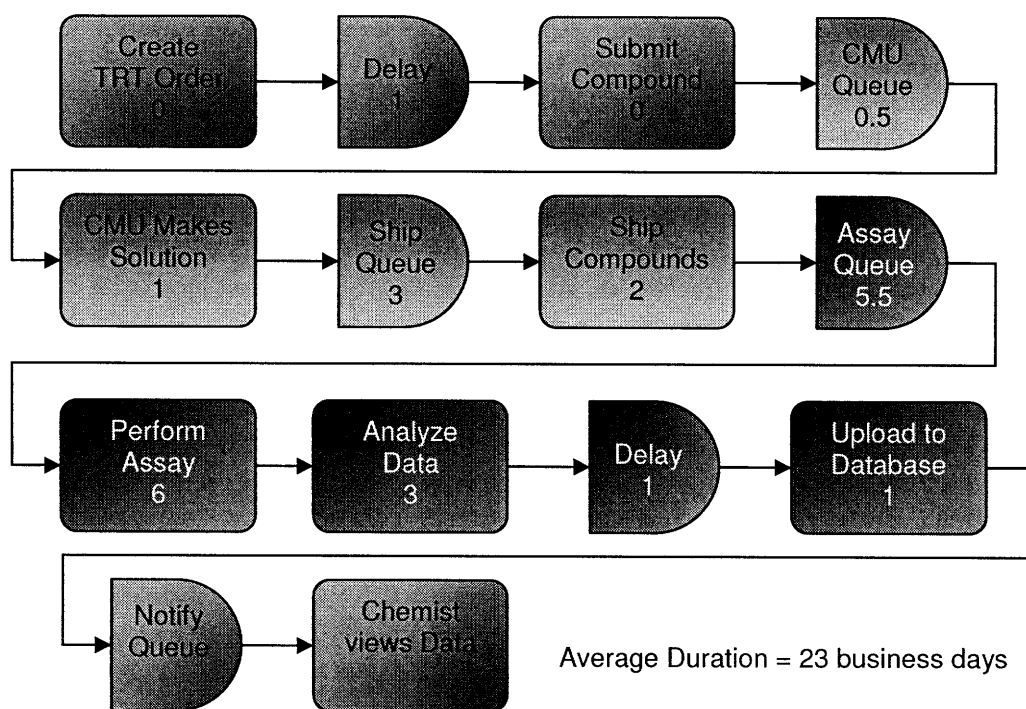


Figure 16 – PCP Process Flow Diagram

After submitting the electronic request they must physically deliver the compound and its associated documentation to the Compound Management Unit (CMU). This is done by physically walking to the location or by interoffice mail depending on the location of the chemist. Once the compound is dropped off at CMU it goes into a queue for processing. Compounds are typically processed the day after they arrive. CMU will register the dry compound and create a 10mM standard solution in DMSO (dimethylsulfoxide). They will then take aliquots from this standard solution to create individual samples for each assay package that was requested by the chemist. These samples are then delivered to a cold storage area where they wait to be retrieved by PCP associates.

The PCP associates will retrieve the samples from the cold storage area just prior to beginning their assay. They will use the solutions to create an assay plate in the configuration required by their assay. They will then process the assay plates on their automated equipment. The data collection process for each assay varies. Some assays require the use of mass spectrometer equipment that resides in the Central Technologies (CT) department. For these assays the samples must be delivered to CT who then send the data when the measurements are complete. For the remaining assays the detection equipment is present in PCP.

Once the necessary data is collected the associates must retrieve and analyze the data. Typically this is accomplished in Excel templates. They check the data quality to ensure the assays were performed properly. Occasionally the data will indicate problems with the assay and the assay has to be repeated.

When the data analysis is complete the data must be properly formatted and uploaded to the centralized compound data repository. Once the data is uploaded chemists can view the data using a variety of programs and queries. Currently, there is no automatic notification system to inform chemists when new data is available. Because of this, the profiling department typically summarizes the data from all compounds in a batch and sends out an email to all of the requestors informing them of the results.

4.2 Process Flow Cycle Time Analysis

To gain some insight into how long each process step takes I chose to examine just one assay, the Safety Pharmacology assay, which typically has the worst cycle time performance. Figure 16 above shows the average cycle times for each step in performing the Safety Pharmacology assay.

Looking at the Process Flow Diagram we can see that there are several opportunities to improve cycle time. The first in is the assay queue. The length of this queue is primarily dependent upon the schedule chosen for the assay itself. In the case of the Safety Pharmacology assay, the biweekly schedule forces an average queue time of 5.5 business days with a maximum queue time of 10 days. If the assay could be performed more often, e.g. once per week, this queue time would be reduced from 5.5 days to 3 days.

The second opportunity is the process time of the assay itself. The physical process of performing the assay, analyzing the data, and uploading the data can be done in 5 days, however since the assay is only performed every two weeks, the data is frequently not reported until the end of the 10-day cycle. Each day saved in the assay process time results in the same savings in the overall process length.

A third opportunity exists in the shipping queue and shipping time. Since shipments are made only once per week, the average queue time is 3 days with a maximum of 5 days. If shipments could be eliminated or made more frequently we could realize significant time savings.

These three opportunities will be analyzed in the context of specific change proposals discussed in section 6.

5 Evaluating the Benefits of Flexibility

5.1 Why Individual Assay Ordering?

The 80-assay Safety Pharmacology Panel is used for three different purposes: defining the promiscuity of a compound (the extent to which it is likely to cause diverse side effects in the body), defining the therapeutic index (the difference between the dose needed for a therapeutic effect and the dose that will cause significant off-target effects), and defining the relationship between the chemical structure and specific off-target activity. This is also referred to as the structure-activity relationship or SAR.

The structure of the panel, a single package in which all assays are performed together, is well suited to defining the promiscuity of a compound. However, since so many assays must be performed it is expensive to process any single compound. This restricts the number of compounds that can be run in a given year so that each program may only submit a few compounds for testing in the Safety Pharmacology panel. This serves the needs of development programs that are only interested in determining promiscuity, however, this limitation makes it extremely difficult to develop structure-activity relationships for individual targets (SARs).

Some programs are working on compounds that do not have promiscuity problems, but have a specific and strong off-target effect that they would like to eliminate. In this case it would be helpful to process many compounds with different structural modifications through a single assay or a small group of assays. In this way they could determine the SAR, or portion of the chemical structure is responsible for the off-target activity in a specific assay.

To serve these types of customers, the profiling group developed the concept of Individual Assay Ordering so that a customer could either order the standard panel or order a customized a panel of assays to serve their specific needs. This system would give the customers complete flexibility to order whatever is most appropriate for their specific program and compounds.

The individual ordering structure also has the potential to enhance the allocation of pharmacology resources. Customers would be able to use their expertise to select the assays that provide the most useful and relevant information, rather than being forced into a strict panel. More compounds could be processed in fewer assays, providing more useful information for the same cost.

5.2 Costs and Challenges

The current system is not capable of allocating different compounds to different assays within the panel. Today, all of the compounds requested for Safety Pharmacology profiling are arranged in dilution curves on a set of 384-well master plates at relatively high concentration. These master plates are copied directly by taking a tiny amount of liquid from each well of the master plate, placing it into the matching well on the daughter plate, and diluting it to the appropriate concentration. This procedure is performed by an automated liquid handler with a 384-tip head that can transfer material from every well on the plate in a single motion. In this process an identical set of plates can be created for each of the assays in the Safety Pharmacology panel. However, there is no clear way to produce different arrangements of compounds on the daughter plates.

In an individual ordering scenario it is possible that each assay will require a unique combination of compounds and that each set of plates for each assay will be unique. Managing this process by hand is not feasible, so an automated system must be created to manage the process.

The automated system would need to gather data from the order database and inventory database in order to match the right compounds with the right customer orders. Once it understood which compounds would be required in which assays it would need to create the appropriate assay plates for each of the assays.

This type of system would require new liquid handling hardware as well as software to automate the complex compound-to-assay matching. It would also have to interface with the data analysis system to ensure that the data from each plate could be matched with the proper compound and assay protocol. After discussions with vendors in the industry we determined that such system could be created using currently available products. Some amount of software customization would be required, but nothing that is unusual with respect to existing compound and assay managements systems in the industry.

5.3 Modeling the Impact of Individual Ordering

The aim of the modeling exercise was to determine how individual ordering would affect the overall cost of running the P5 panel. Since compounds are processed in batches on sample plates, the labor and materials required to perform the assay are primarily dependent on the number of plates required rather than on the number of compounds directly. For example, if an assay uses a plate format with a capacity of 16 compounds per plate and we have 48 compounds to process, then we must use 3 plates and each plate will be completely full. If we only have 33 compounds we still need to use 3 plates, but the third plate will only have one compound present.

Historical Demand for the P5 Package shows a pattern of high variability with a coefficient of variation of 0.4. Given this scenario we chose to model the impact of Individual Ordering with a Monte-Carlo simulation. A Monte-Carlo simulation will allow us to gain an understanding of the distribution of possible outcomes and make an objective analysis based on more than assumptions about the average case.²⁶

The model required an assumption regarding how to distribute orders for individual assays among the entire assay panel. After interviews with customers and discussions with senior individuals in PCP we chose to assume that orders for individual assays would create an exponential distribution among the assay set. In any given week we predicted that a few assays would be popular and requested often, a few more would have a moderate level of requests, and that most assays would not receive any orders at all. The reason behind this is that most programs submit compounds in groups. If a particular program wanted individual ordering they would most likely submit a large number of compounds for the same assay or group of assays. With several programs doing this each week and with certain assays being much more common problems than others we predicted that orders would be distributed among the assays in a pattern similar to the one shown below.

²⁶ Source: Ragsdale, Cliff. *Spreadsheet Modling and Decision Analysis*. 2004

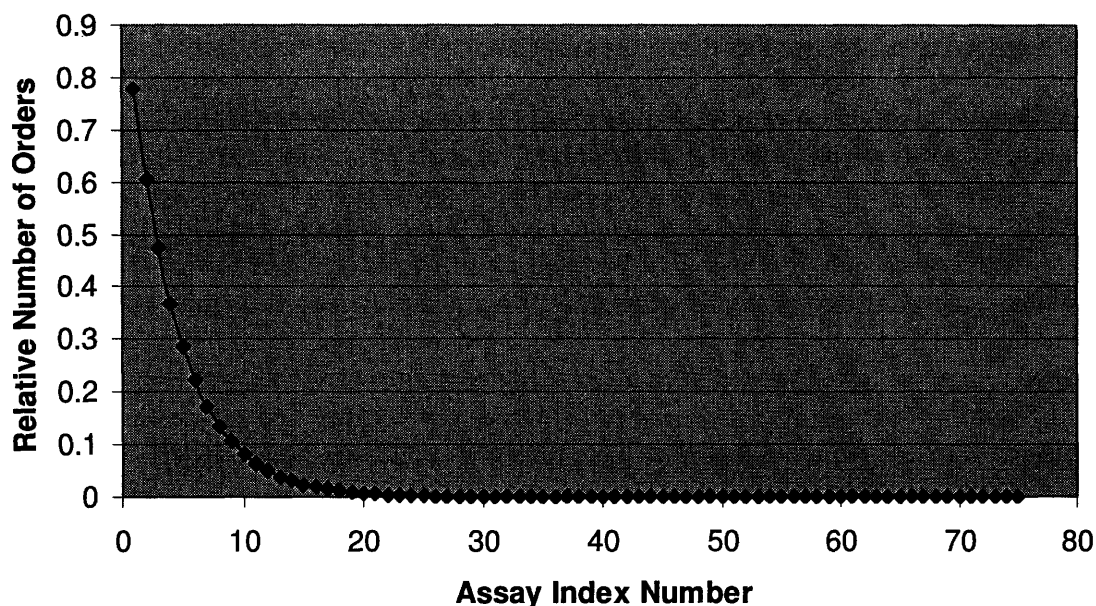


Figure 17 – Assumed Distribution of Orders by Assay

This chart above was created using the following expression:

$$W_i = \left(\frac{1}{\beta} e^{-\frac{\alpha i}{\beta}} \right), i \geq 0$$

Where “*i*” is the index number of the assay, W_i is the relative weight for assay *i*, and “ α ” and “ β ” are scale parameters to allow us to adjust the shape of the curve. Based on interviews with customers and safety pharmacology experts we chose values for α and β as 0.25 and 1 respectively. This provides for a relatively steep slope and a starting point of about 0.8, consistent with our assumption that a small number of assays will be ordered and that there will be significant overlap in the assays ordered by each customer.

Given this assumption the number of plates required for a specific assay “*i*” can be expressed as the following:

$$Plates_i = \frac{W_i \cdot D \cdot f_{ind} + D \cdot (1 - f_{ind})}{Cp_i}$$

Where

- W_i = Assay Weight for assay “*i*”
- D = Demand in number of compounds
- f_{ind} = Fraction of orders for individual assays
- Cp_i = Compounds per plate for assay “*i*” from lookup table

The total number of plates needed for a complete run could then be found as :

For $i = 1 \dots n$ where $n =$ number of assays

$$\text{Total Plates} = \sum_{i=1}^n \frac{W_i \cdot D \cdot f_{ind} + D \cdot (1 - f_{ind})}{Cp_i}$$

In the Monte-Carlo simulation, a normal distribution was used for the parameter “ D ” based on the mean and standard deviation of historical data. We also had to assume an Individual Order Fraction (f_{ind}), the fraction of total orders that were for individual assays or small groups of assays as opposed to the entire panel. A single simulation creates results like those in the figure below, showing the distribution of total plates required under a single set of assumptions for demand (D) and Individual Order Fraction (f_{ind}).

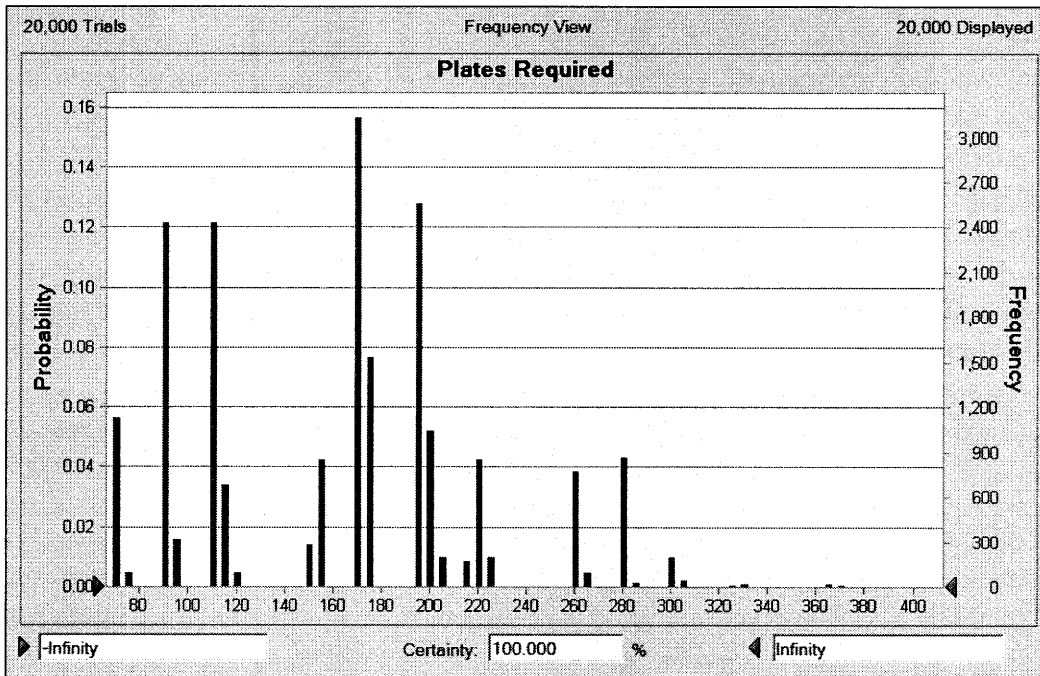


Figure 18 – Monte-Carlo Simulation of Plates Required per run

While the simulation is running we also collect data on how many plates would have been required if individual ordering was not enabled. Combining this information with the materials cost of running one plate allows us to calculate the total savings due to individual ordering in any specific run. An example of the simulation output is shown below in Figure 19.

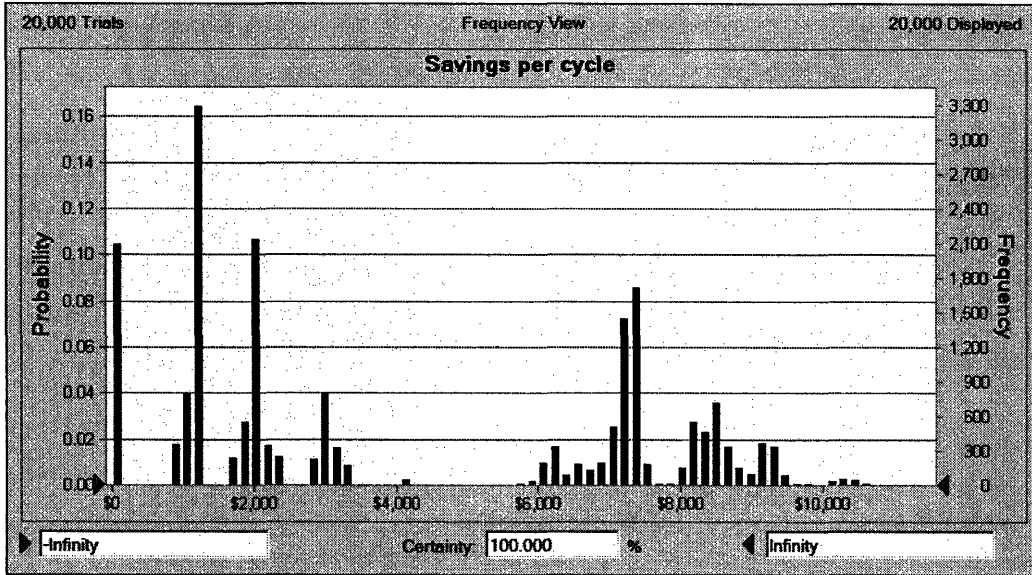


Figure 19 – Savings per Run When Using Individual Ordering

Once again we notice the discrete nature of the results. We can also see that in this set of assumptions there is a high probability of moderate savings of \$1000-\$3000 per run and then a moderate probability of a high savings of \$6000-\$10,000 per run. Since we know the distribution of savings likely in any one cycle and that there are 26 runs in a given year we can then determine the distribution of the likely savings that will accrue in any single year as shown below.

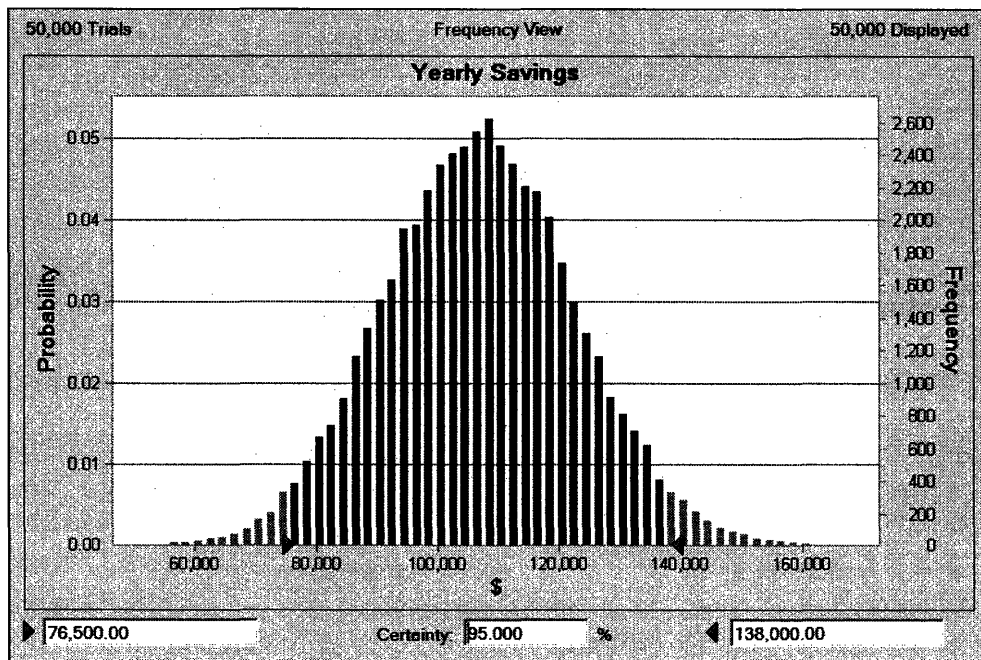


Figure 20 – Distribution of Yearly Savings

5.3.1 Sensitivity Analysis

These examples only show the expected distribution under a single set of assumptions for overall demand and for the individual order fraction. Since both of these parameters are uncertain, we need to perform a sensitivity analysis to show how the results change as both of these parameters vary. We performed an array of Monte Carlo simulations using different assumptions for demand and for individual order fraction and then calculated the average weekly cost. The results are shown in the figure below with the actual figures disguised.

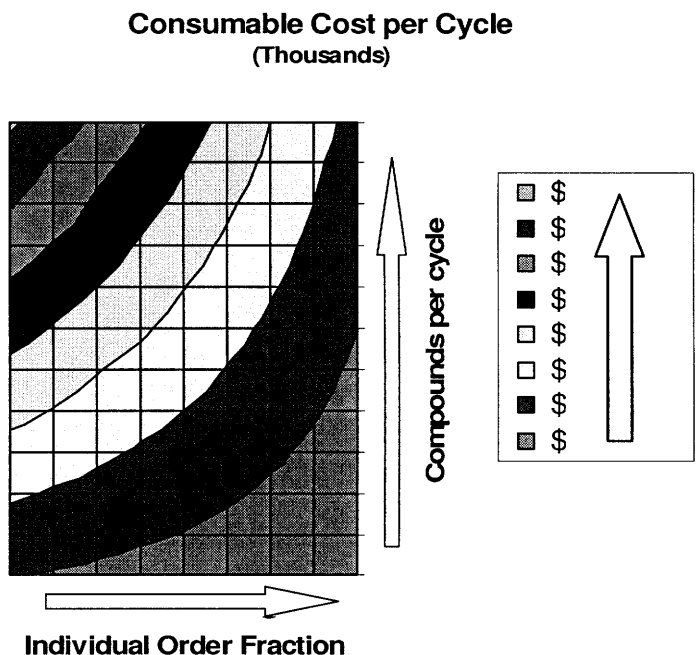


Figure 21 – Sensitivity Analysis of Demand and Individual Order Fraction

The lines on the contour plot are iso-cost curves that show different options for utilizing individual ordering. We could enable individual ordering while holding the capacity steady, allowing for cost savings. Alternatively we could hold cost steady and climb up the iso-cost curve, allowing us to run many more compounds at the same price.

5.3.2 Key Assumptions

All Compounds Processed Each Cycle

The model assumes that all compounds requested in a given cycle will be processed. No compounds will wait and carry over to the next cycle. This assumption is valid so long as the Safety Pharmacology area holds to their cycle time commitments. Past performance shows that this is not always the case, however, recent improvements have increased run capacity such that this assumption is likely to hold. There is the potential that deliberately delaying some compounds could increase plate utilization and reduce costs. However, since speed is so critical in drug discovery, the cost savings due to waiting and filling up plates is unlikely to offset the cost of the delay.

Exponential Demand for Individual Assays

Our assumption of exponentially distributed assay demand is based on customer interviews. Most indicated that if they were submitting a compound for individual ordering that they would request between 1 and 5 assays for that compound. Though we cannot verify this assumption with actual data it is highly unlikely that the distribution will be dramatically different. A distribution that is slightly more likely is still exponential in its overall shape, but instead with large stair-steps that reflect the fact that most orders will arrive in bundles, a few compounds for assay A & B, a few more for Assays B&C, etc. However, our exponential distribution is a good approximation for this type of stair-step pattern.

Normally Distributed, Constant Demand

The analysis also assumes that demand will remain constant throughout the year and that it will be normally distributed. Figure 22 below shows that the assumption of normally distributed demand is not grossly inaccurate. However, a log normal distribution may be a little closer to the underlying historical data.

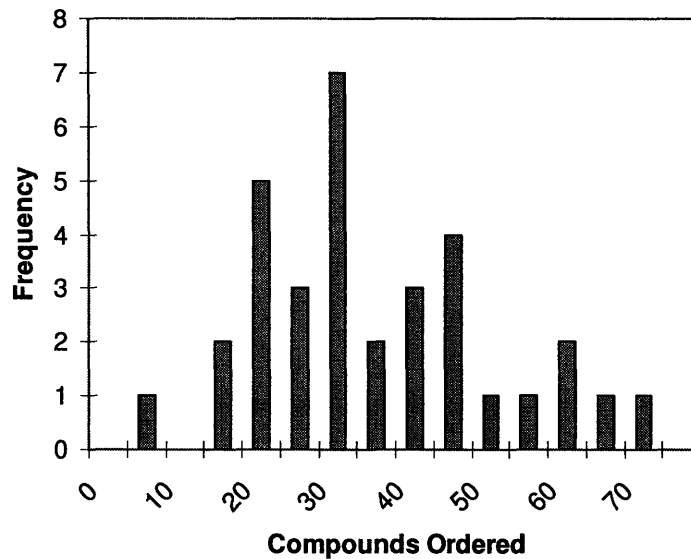


Figure 22 – Histogram of Weekly Demand

The assumption of constant demand is less likely to be true over the long term. Demand for Safety Pharmacology has been increasing along with continued expansion in NIBR’s research efforts. However, the sensitivity chart shows how the results will change as demand changes.

5.3.3 Results

Our results showed that for the most likely scenario we could save less than \$200,000 per year in materials costs through individual ordering, and the 95% confidence interval was between \$160,000 and \$240,000. Alternatively we could keep costs steady and increase capacity by about 50%. We estimated the total capital cost of installing the system at \$2 million based on discussions with vendors. Given the high investment required and the

relatively modest savings, individual ordering will not pay for itself based on cost savings in Safety Pharmacology alone.

As this analysis was ongoing it became evident that there are other areas within Novartis that could benefit from the hardware and software necessary to do individual ordering. Quantifying the benefit to these outside departments was determined to be outside of the scope of this project, but it is still being evaluated by the compound management group at NIBR.

5.4 An Alternative to Individual Ordering

Due to the high capital cost of installing an individual ordering system, other alternatives were explored to determine if a lower cost option could capture some of the benefits. The most common use of the Safety Pharmacology Panel is to screen for compound promiscuity, i.e. how likely it is to affect other targets in the body besides the primary target. One could probably accomplish this goal without using the entire panel of 80 assays. One proposal was to split the panel in two parts, running a reduced panel for most compounds and only running the entire panel at selected decision points in the drug discovery process. This scenario does not require significant additional investment and it only requires a small amount of additional labor to perform. Also, if we could reduce the size of the primary panel by 50% we estimated we could save approximately \$500,000 per year in materials costs. The primary question then becomes which assays to place in which panel.

Three important characteristics of the panel aid in this analysis: assay hit rate, assay to assay correlation, and assay to side-effect correlation.

5.4.1 Assay Hit Rate

Based on historical data, certain assays are much more likely to show activity than others. Currently, all compounds are screened in all assays at the same frequency. A more cost-effective solution would be to screen compounds in the higher hit-rate assays more frequently and check the lower hit-rate assays on a less frequent basis. Figure 23 below shows the relative hit rate of many of the assays in the Safety Pharmacology panel.

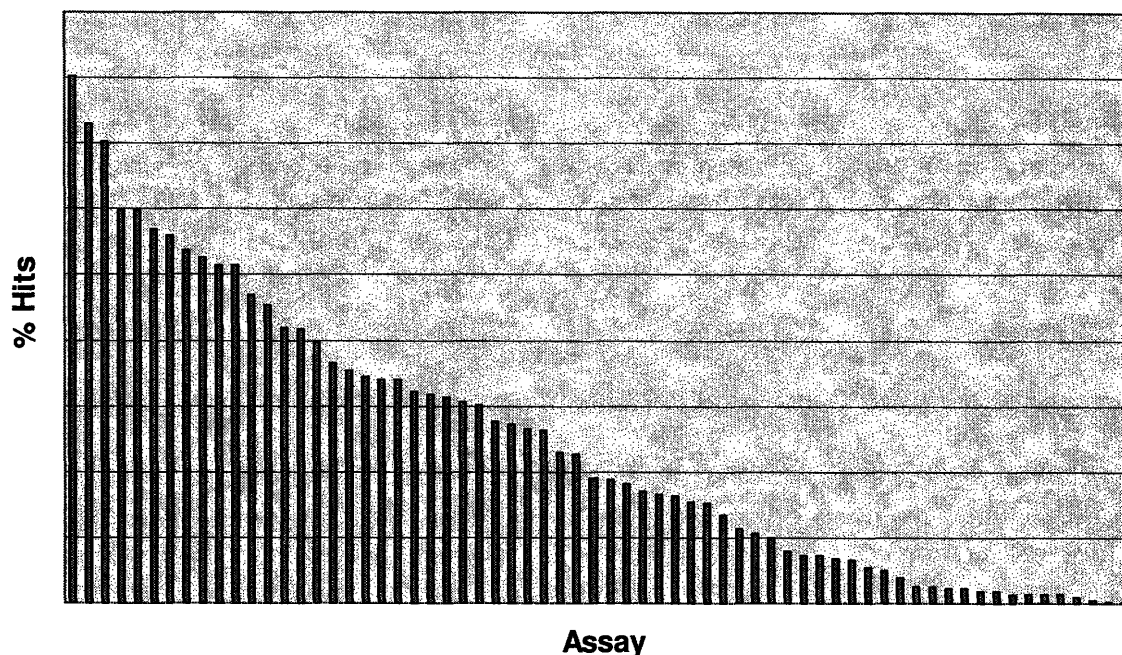


Figure 23 – Pharmacology Assay Hit Rate Pareto

Based on this information we can see that there are a significant number of assays with very low hit rates. If we assume that future compounds will have a similar safety profile as past compounds, it becomes relatively easy to identify some assays that could be performed less frequently.

5.4.2 Assay to Assay Correlation

The Safety Pharmacology panel contains multiple assays from a single receptor family. For example, there are three primary types of histamine receptors and each receptor has its own assay. Each receptor is responsible for regulating different types of biological responses including heart rate, bronchoconstriction, and gastric acid secretion.²⁷ However, each receptor has a similar chemical structure so compounds that bind to one of the receptors are likely to bind to the others.

Andreas Bender and Jeremy Jenkins at Novartis have used historical data on many pharmacology targets to produce a matrix which shows how well correlated various receptors are to one another (See Figure 24 below). Unsurprisingly, families of receptors are often well correlated and show up as blocks of red along the diagonal. However, there are many off-diagonal correlations as well, meaning that there are significant correlations between different families.

²⁷ Source: Foye, W.O. *Principles of Medicinal Chemistry*. 1995.

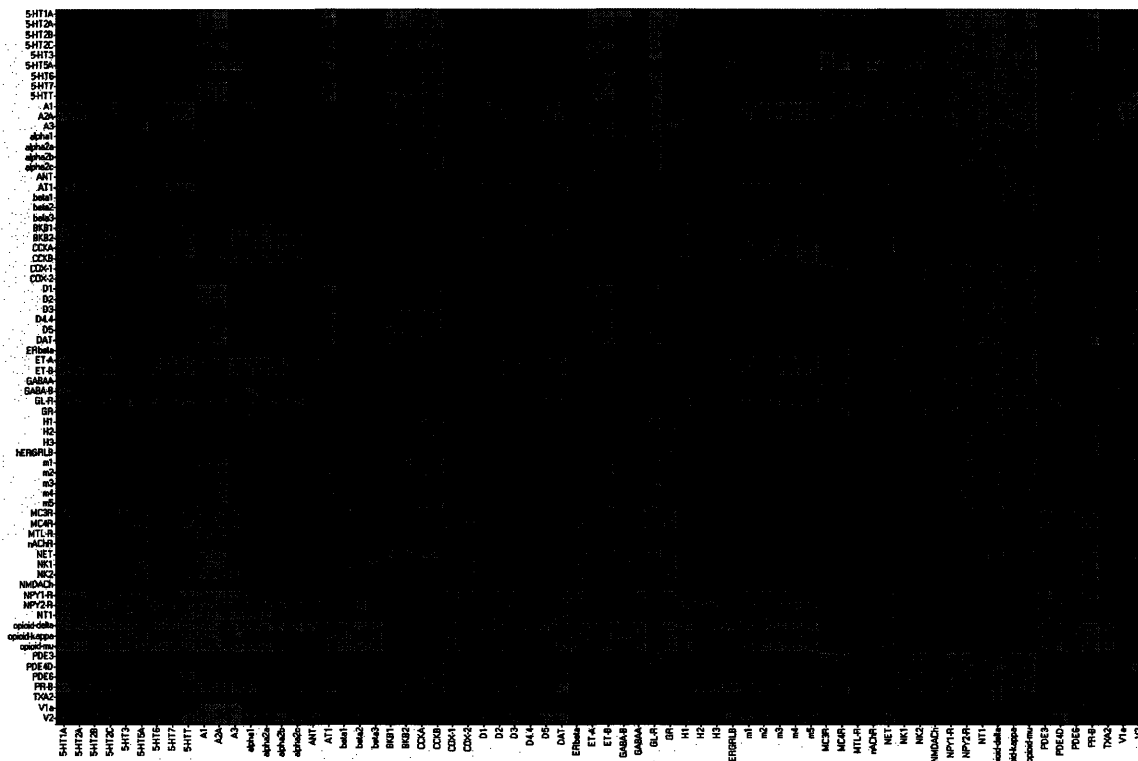


Figure 24 – Correlation Matrix of Safety Pharmacology Receptors²⁸

The optimum panel would have a low inter-assay correlation to maximize the likelihood of identifying potential problems.

5.4.3 Assay to Side Effect Correlation

Another important dimension to consider is the predictive capability of an assay and the seriousness of the associated side effect. If a drug tests positive in one of the assays, the probability of that drug causing a side effect when given to a real person is not known. However, continuing research provides some insights into the predictive ability of these preclinical assays. An optimized panel would include only assays that have significant correlation to side effects in real people.

Also, some assays are known to be associated with very severe side effects while others may cause little more than mild stomach discomfort. An optimized panel would weight assays that predict serious side effects more strongly than those that predict minor irritations.

5.4.4 Selecting an optimized panel

Quantifying the optimum level of hit-rate, assay-to-assay correlation, and assay-to-side-effect correlation is challenging. It becomes particularly difficult when attempting to

²⁸ Andreas Bender, et. al. Prediction of Adverse Drug Reactions and Off-target effects from chemical structure based on Pharmacology Data.

combine the three parameters together because it is unclear how heavily various components of the analysis should be weighted. A detailed analysis of this problem was determined to be outside the scope of this project, however, a simplified analysis was used as a first attempt to create a reduced primary panel of assays.

The simplified analysis took the form of three screens used in an iterative process. First we filtered out assays with very low hit rates; second we looked at the receptor families with multiple, well-correlated assays and removed the assays with the lowest hit rates and least importance for safety; third we reviewed the entire list and removed those assays identified in the literature as having low predictive value or predicted only minor side effects. This analysis was performed by the pharmacology lab heads based on their decades of experience in the field.

5.4.5 Split Panel Results

After the analysis of the existing assays, Preclinical Profiling at NIBR decided to create two different Safety Pharmacology Panels. The primary panel, consisting of 40 assays, will be used on all compounds submitted for Safety Pharmacology testing. The secondary panel of 30 assays will be run upon request and at certain major decision points in discovery process. The remaining 10 assays were dropped entirely from the in-house panel.

The new process was reviewed and implemented and should result in materials cost savings of \$500,000 per year on an ongoing basis. In addition, as part of this change the process time for the primary panel will be reduced by five days. With the panel split in two pieces and with the reduced overall workload, the department is able to finish the primary panel and report results in a single week instead of two weeks.

6 Safety Pharmacology Operational Improvements

6.1 Improvement Options

In our assessment of Safety Pharmacology Operations we identified many change proposals to study. This section will describe three key changes in detail. They include the following: changing the assay run frequency, changing the assay location, and outsourcing portions of the assay.

6.1.1 Assay Run Frequency

The Safety Pharmacology Panel is processed as a batch in order to simplify the process of creating the plates needed to perform the assay. As mentioned previously, increasing the run frequency would significantly reduce both the queue time and process time for incoming compounds. Discussions with the Safety Pharmacology department revealed that a weekly assay schedule is feasible, though it would increase the labor requirements due to the large setup times required to perform the assay. Other schedules of less than one week or between one and two weeks were deemed either beyond the equipment

capability or unwieldy for the operators. This left two primary options for consideration, the existing biweekly schedule or a weekly schedule.

In addition, we also proposed a hybrid schedule in response to the Split Panel described previously. In this scenario the assay would still be performed on a biweekly schedule, but the primary assay would be completed by the end of the first week. This reduces cycle time by five days but does not provide a queue time reduction. This scenario provides more modest cycle-time benefits but does so with little change in the amount of labor required.

6.1.2 Assay Location

The assays in the Safety Pharmacology department are either performed at the Basel site or at the Cambridge site, but not both. When a compound destined for Safety Pharmacology arrives for processing at CMU it must be split into two solutions; one for the local site and the other for the remote site. Cambridge only performs SPA assays while Basel performs both Filtration and SPA assays. About 60% of the assays are performed in Basel with the remainder in Cambridge.

Considering potential alternatives to this structure it is obvious that we could consolidate all activities to a single site in either Basel or Cambridge, or expand each site so that it could process the entire assay panel. A single site would have lower capital and labor requirements, and two independent sites would have faster cycle times by avoiding shipments. The current structure gains neither benefit. It requires all the overhead of two sites, but gains none of the cycle time benefits because all compounds must be shipped and processed at both sites.

6.1.3 Outsourcing the Secondary Panel

The split panel described above makes outsourcing an interesting alternative. Our customer surveys indicate the requests for the secondary panel are likely to be less than 20% of total requests. Given this information it may be more cost effective to have a third party perform these low-volume assays in the panel. The decrease in materials costs and increase in capacity may be more valuable than the outsourcing fees.

Several external vendors already perform assays for NIBR and are capable of performing all of the assays currently specified in the secondary panel. They typically guarantee results within two weeks of receipt of the samples.

6.2 Evaluating the Options

In order to choose the combination of options that is best for the company, it is necessary to understand the impact of each combination on the following criteria:

- Materials Costs
- Labor Costs

- Capital Costs
- Cycle Time
- Intangible factors

The following sections will describe how each of these elements were modeled and then how the results of those models were synthesized to gain a more complete understanding of total impact of each permutation of the three changes identified earlier.

6.3 Materials Costs

Materials costs were estimated using a cost model created in Excel. The estimates were made taking a top down approach starting with the overall materials usage of the entire department. Based upon past expenditures and the volume of requests it was trivial to calculate the average materials usage per assay by the department. We then adjusted this amount for various internal factors such as expenditure on exploratory projects and other non-assay related expenses. If we assume that all assays cost approximately the same amount of money, we can readily calculate the overall materials costs for performing an assay at a given rate of demand.

However, to determine the impact of changes in schedule, outsourcing, and location we need to adjust the assay materials cost appropriately. A key parameter in this analysis is the amount of material that is required for setup, regardless of the number of compounds analyzed. This primary source of material waste is dead volume in the vials and microplates. This is liquid required to wet the tube or vial that cannot be extracted by the pipettes when transferring liquid from one tube to another. This amount was estimated at 20% by the department.

With this information it is relatively simple to estimate materials costs based on assay run frequency, location, and outsourcing. An example is shown in Appendix 1.

This analysis ignores inventory carrying costs. Since each of these change options should reduce inventories, this will cause a slight bias towards underestimating total savings. The model also makes the aggressive assumption that the average cost of all assays within the Safety Pharmacology Panel are equal. If the actual average cost of assays in the secondary panel is significantly different from the average cost of assays in the primary panel this could cause significant errors in the estimates. However, since the number of assays in each group is relatively large, any specific effects from differences in assay costs are averaged over many assays and are unlikely to cause large discrepancies in our estimates. Also, the overall ratio of more expensive filtration assays to less expensive SPA assays is roughly constant, so effects from changes in the assay mix are unlikely to be significant.

6.4 Labor Requirements and Costs

In order to understand the impact of operational changes on labor requirements, a basic labor model was created. The model assumes that labor can be divided into three types: Setup time, run time, and site support. Setup time is the time required to prepare reagents and equipment prior to the start of an experiment. It is modulated by the number and type

of assays that need to be performed, not by the number of compounds in a particular run. Run time is the amount of time that the associate spends attending equipment and plates during a particular experimental run and analyzing data for each compound. Run time is primarily affected by the number of compounds or plates in an experiment. Site support time is the time spent on inventory ordering, lab maintenance, and other activities that is not dependent on the number of assays or the number of compounds being tested.

There are two types of assays in the Safety Pharmacology Panel: Scintillation Proximity Assays (SPA) and filtration-binding assays. In the model, each assay type is assigned a fraction that represents how much of the total time required to perform the assay is setup time versus run time. For SPA assays we used a value of 80% and for Filtration assays a value of 65%. We also chose a value for the number of assays of each type that one person could successfully complete in one week's time. This number assumes that the associate has a multitude of other tasks to complete such as assay development, supporting project teams, and other activities that would keep him or her away from the lab. The numbers we chose were 4 filtration assays and 8 SPA assays at a base level of 1800 compounds per year. We also assigned a value to site support activities of 0.5 FTE (Full-time equivalents). Given these assumptions, we can find the total labor requirements for any given number of assays per week and number of compounds per assay. This model allows us to evaluate the impact of changes in the run frequency, assay location, and outsourcing on the labor requirements.

- N_F = Number of Filtration Assays per week
- N_S = Number of SPA Assays per week
- N_{Site} = Number of Sites
- S_F = Setup Fraction Filtration
- S_S = Setup Fraction SPA
- L_F = Filtration Assays per week per unit of labor
- L_S = SPA Assays per week per unit of labor
- L_{Site} = Site Support Labor
- D = Demand in compounds per year
- D_B = Base Level of Demand

$$Labor = \frac{N_F}{L_F} \cdot \left[S_F + (1 - S_F) \cdot \left(1 + \frac{D - D_B}{D_B} \right) \right] + \frac{N_S}{L_S} \cdot \left[S_S + (1 - S_S) \cdot \left(1 + \frac{D - D_B}{D_B} \right) \right] + N_{Site} \cdot L_{site}$$

6.4.1 Validating the model

This model does not take a detailed bottom-up approach in determining labor requirements, so it is difficult to measure the actual labor requirements directly versus those predicted by the model. However, historical data exists allowing comparisons between past scenarios and the model's predictions for those scenarios. Table 4 below shows the model predictions versus actual amounts for three distinct historical periods.

This analysis assumes that headcount was not over or under-utilized during this period, and that no significant changes in labor productivity occurred.

Scenario	Prediction Error
A	-4.2%
B	-10%
C	+8%
Average	7.4%

Table 4 – Labor Model Error

As we can see the model performed relatively well against historical data giving us confidence that the predictions made by the model will be reasonably accurate.

6.4.2 Observations from the model

Using the model it becomes clear that the total demand has a relatively small impact on the labor requirements. Increasing the number of compounds by 100% only causes a 20% increase in labor. This is not surprising given that the setup fractions are very high. This also has implications for running all assays at both sites. Since most of the work occurs in setting up the assay, setting up all of the assays at both sites and running half the compounds will require almost double the work of just running all assays at a single site. The same can be said for running the assays weekly instead of biweekly. Doubling the number of setups will come close to doubling the amount of labor required.

6.4.3 Model Considerations and Assumptions

This simplified model makes several strong assumptions that limit the utility of the model.

Productivity is Constant

The model assumes that labor productivity is constant. This assumption is likely to become inaccurate as the organization acquires additional capital and changes assay procedures. However, the model can easily be adjusted with new setup fractions and labor constants that reflect the impact of the operational changes.

Productivity is Equal

The capital equipment, procedures, and personnel in Basel and Cambridge are not the same. This will likely cause differences in the productivity of each site. These differences are not accounted for in the model.

All Assays are Equal

The model assumes that the amount of work required to perform a particular assay type is always the same. This assumption is not strictly true. In reality there are multiple sub-types of filtration and SPA assays that have slightly different procedures. In addition, certain assays are less likely to yield good results, causing different rework rates. These considerations are also missing from the model.

Labor Changes Linearly

The model adjusts the amount of labor required linearly based on the number of assays and the number of compounds. This is a relatively good assumption for small changes, but as the changes from the baseline become large it is likely that the relationship will cease to be linear.

Though the model has significant limitations, it functions well for its designed use – to provide a rough estimate of how labor requirements will change as we change the operational parameters of the assay.

6.4.4 Modeling labor costs

When comparing investment proposals Novartis uses a standard value for the cost of one full-time worker, also known in the company as an FTE (Full-time equivalent). For the purposes of discussion, assume this value is \$250,000. This number is determined by adding up all of the costs allocated to a department and then dividing by the number of people in the department. These costs include everything from salaries to building rent to IT support to direct materials purchased.

However, when evaluating the impact of changes to the operational structure, this FTE cost value can be misleading. For example, if a department is contemplating a change that would save \$250,000 in materials and free up one FTE they might compute their total savings as \$500,000. However, since the FTE component already includes materials cost, they are double-counting some of the materials savings. The actual savings may be only \$450,000. Labor costs are convoluted with all other costs, leading to some confusion when attempting to estimate the real impact of change proposals.

In the cost model that we created to evaluate our change proposals we separated costs that were directly related to headcount from costs that are related to other factors. We performed this separation for each individual cost category used by the department. We assumed that infrastructure, IT, salaries, benefits, and travel were headcount related. However, depreciation and materials costs were independent of the number of employees in the department. This allowed us to determine a new average value of the cost of one FTE in both Basel and Cambridge that is not convoluted with other factors.

By combining this updated cost information with the labor model discussed below, we were able to estimate the true cost or savings associated with changes in labor requirements with greater accuracy. If we had used the standard value for labor costs, our estimates would have double-counted savings resulting in estimation errors of up to 25%.

6.5 Capital Costs

Some of the change options being considered require capital cost investments. Specifically, performing all assays in both locations would require Cambridge to purchase additional capital equipment for performing filtration assays that it does not currently have the capability to do. The other major potential source of capital investment is the software and hardware to enable individual compound ordering. To estimate these

costs we contacted appropriate hardware and software vendors, described our requirements, and received estimates for the capital cost outlay that would be required.

These capital costs were incorporated into the NPV calculation as a cash outflow in year zero with cash inflows in the form of tax benefits from depreciation allowances in years 1-5. We assumed a straight-line depreciation over 5 years with a 30% tax rate.

One capital-related item missing from the model is the impact of site consolidation on capital costs. Currently the model does not allocate any ongoing savings or costs related to the disposition of equipment that will be made redundant by the consolidation activities. This will likely understate the potential savings of consolidating to a single site. In addition, future expenses and upgrades will now only need to be made at a single site, which will likely provide more ongoing savings that are not accounted for in the model.

6.6 Cycle Time

In order to examine the impact of changes to the process I created a simple simulation of the Safety Pharmacology process using the parameters shown above in the process flow diagram. The model makes another key assumption, that capacity is infinite. This assumption was chosen because recent modifications to the Pharmacology area have increased the capacity of a single run so that the likelihood of submissions exceeding capacity in any given week is less than 3%.

Also, the model does not use a strictly normal distribution for calculating turnaround times. Since the area operates on a daily schedule, if an activity is accomplished a few hours early it has no impact as long as the material is ready for the processing step that will take place in the following day. Because of this I used discrete time periods with a minimum unit of 1 day. For example, when modeling shipping I used a discrete custom distribution in which there is a 20% chance of waiting for 1 day, a 20% chance of waiting for 2 days, a 20% chance of waiting for 3 days, etc. Similarly, for compound management I assumed that 50% of the time the compounds will be completed in one day, but 50% of the time it will take two days. Additional details can be seen in Appendix 2 below.

When the simulation is complete it allows us to estimate average, median and 90th percentile cycle times for multiple scenarios. In particular I modeled the current situation in which the assay package is run once every two weeks, the future planned situation in which the assay is run every two weeks, but the data is reported at the end of the first week, and the potential option of running the entire assay every week. The results are shown in the table below.

Scenario	Average	Median	90th Percentile	% < 20 days
Biweekly Runs	21.5	21	26	40%
Biweekly, data in first week	16.5	16	21	87%
Weekly Runs	14	14	17	100%

Table 5 – Cycle Time Model Results

6.7 Intangibles

Each option carries with it not only significant labor, material, and capital changes but also other impacts that are not directly accounted for in the model. Some of the considerations that fall outside the model are described below for each of the major change options.

Assay Run Frequency

The primary intangible effect in changing the assay run frequency is the impact on the personnel. The associates fear that increasing the run frequency will force them to spend all of their time simply running the assay and leave them little time left for their other duties. The labor model projects significantly higher labor demands for higher run frequencies, so this concern can be alleviated if additional resources are provided as suggested by the model.

Outsourcing

One significant concern with outsourcing is data quality and consistency. Due to differences in assay formats, IC_{50} 's from vendors will likely be based on a smaller number of data points, slightly reducing the accuracy of the IC_{50} data and making direct comparisons to previous internal data a bit more difficult. Another concern is the impact of changes in demand. In a typical contract NIBR must guarantee a certain volume of orders to obtain preferential pricing. Should NIBR's needs be less than forecast, they will be forced to pay extra costs. Outsourcing in this case takes what are now variable costs and transforms them into fixed costs, increasing the sensitivity to demand shortfalls. In the case of excess demand, NIBR will be forced to either exceed its budget or ration assay capacity.

Assay Location

The location chosen to perform the assays is potentially disruptive to the personnel affected. Certain employees would be forced to either move or find new jobs within the company. Also, there are some concerns that consolidating to a single site reduces the accessibility of safety pharmacology expertise in the company. Chemists at the site that is closed would not have local access to subject matter experts and would have to rely on a remote site when they have questions. Further, consolidating to a single site could reduce the amount of time available for development and optimization activities.

6.8 Synthesizing the Model Output

The purpose of creating basic models for materials, labor, capital, and cycle time was to synthesize a complete picture of how different operations changes would affect the total costs and cycle time of the process. As mentioned previously we decided to focus on three change options that were closely tied together: the assay run frequency, the assay location, and whether or not to outsource the secondary panel. With three variables, two having two levels and one having four levels, the total possible number of combinations is sixteen. We also have four different outputs to measure: materials, labor, capital, and cycle time. To simplify the output we compressed materials, labor and capital into a

single quantity of dollars and calculated the 5-year Net-Present Value or NPV of choosing that option compared to doing nothing. This leaves us with a more manageable two outputs of NPV and cycle time. When we plot each of the possible options on those two measures we create the following chart below.

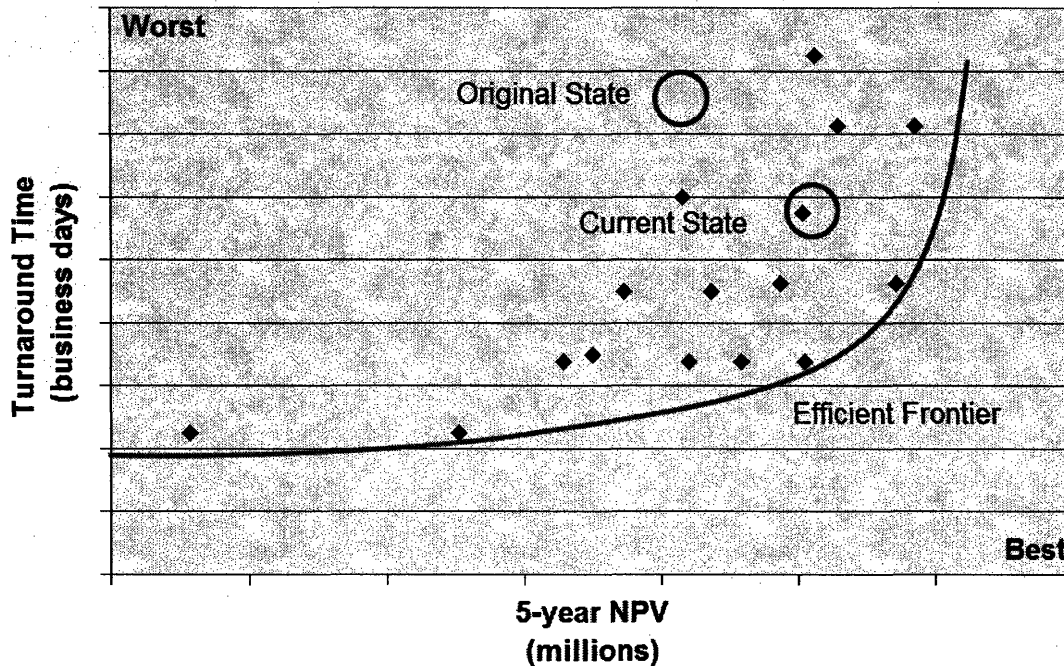


Figure 25 – P5 Options, NPV and Cycle Time

This view allows us to compare the NPV and cycle time of all sixteen options in a single view. Certain options maximize NPV at a given turnaround time, these options could be said to lay on the efficient frontier. We can also see the tradeoff between NPV and cycle time. Depending on the relative importance of cycle time and NPV, we can choose to operate at any point on that efficient frontier.

It is also helpful to have some insight into the source of the difference in NPV. In order to separate the benefit from a direct cost standpoint vis-à-vis a labor standpoint we created the following bubble chart that shows labor impact on the y-axis, NPV not including labor on the X-axis, with the size of the bubble showing the average turnaround time. This is shown in the figure below.

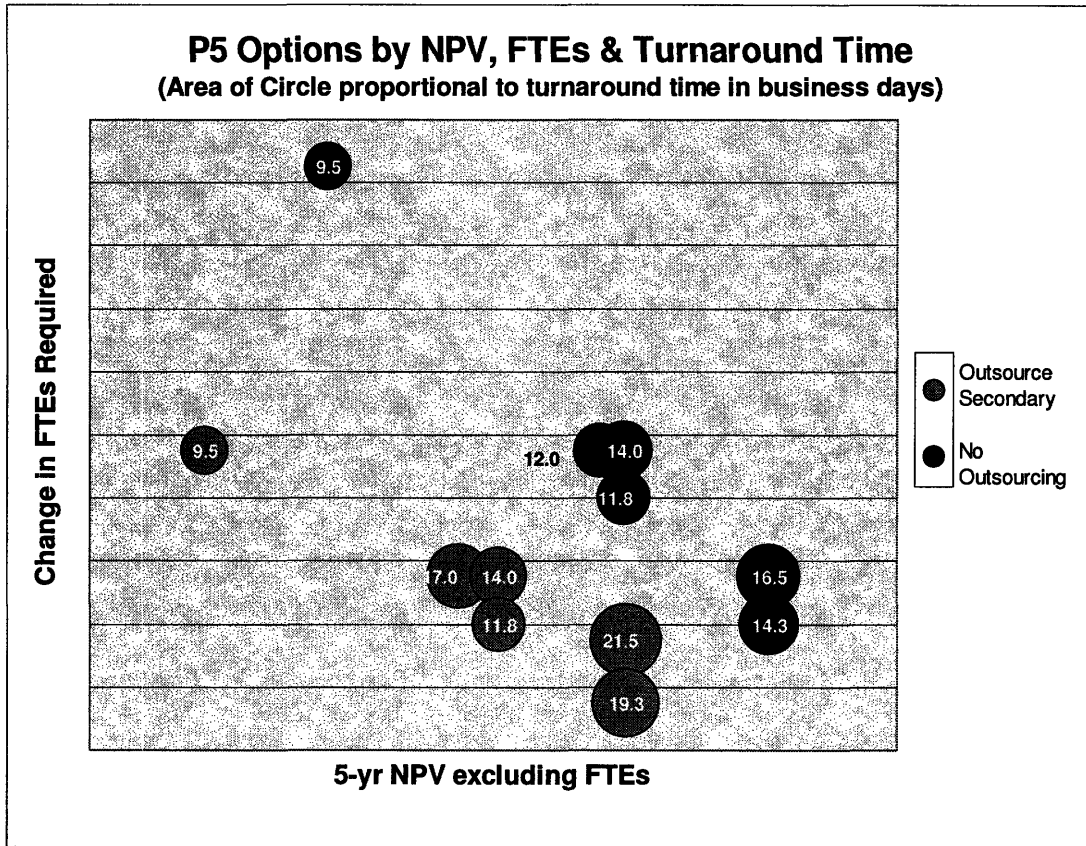


Figure 26 – Options by NPV, FTE’s & Cycle Time

This type of analysis is important to consider because labor savings in the model are unlikely to be realized by reducing headcount. Instead, the “savings” are more likely to be realized in the form of additional projects that can now be accomplished by the department. How the company views the benefit of this additional employee bandwidth may cause them to place a different value on these labor savings.

6.9 Recommendations

Given the results of the analysis above, two options present the best overall performance. The first is consolidating operations to a single site and running the assay biweekly without outsourcing the secondary panel. The second option is to consolidate operations, outsource the secondary panel, and run the primary panel weekly. The first option provides a 5-year NPV that is over \$1 million higher than option 2, however it provides a 90th percentile cycle time of nearly three weeks. Option two is more expensive, but reduces the 90th percentile cycle time to less than 12 business days.

In every case, consolidating operations to a single site was more cost-effective than maintaining two sites each performing part of the assay. We also determined that in general it is preferable to choose to outsource when running on a weekly schedule in order to avoid large increases in the labor requirements. When choosing a biweekly schedule, however, the savings due to outsourcing are not significant.

7 Long Term Strategy

The analysis presented in sections five and six needs to be evaluated within the context of the strategy of the organization. Many external firms specialize in doing the type of compound profiling that Novartis is doing in house. Novartis uses some of these firms to supplement their internal profiling activities. A critical question for Novartis is, “What is the strategy of their internal profiling group”? The internal organization has two primary options, they can either choose to be the low-cost provider or choose to offer a higher quality product than their external competitors are capable of.²⁹

The source of a sustainable, long-term competitive advantage can be derived from a firm’s unique capabilities or position.³⁰ As an internal organization, PCP has a unique position that comes with significant advantages and disadvantages. PCP has a built-in advantage in turnaround time and in potential for collaboration with internal colleagues. However, the internal group also has a distinct disadvantage due to their high fixed costs associated with operating in a high-cost area like Cambridge.

7.1 Two Strategic Options

The PCP group has two primary choices when evaluating the structure of the product they offer to their internal customers. They can either choose to offer a custom structure or a generic structure. The custom option is essentially the individual ordering system described previously. In this scenario, PCP allows the customers to pick which assays to perform on which compounds without any restriction. Chemists would be free to choose the assays that best suit their needs. This option assumes that each discovery program has different needs and that those needs cannot be effectively met by a standardized screening mechanism

The generic structure option assumes the opposite, that most discovery programs are essentially the same and that a well designed package of standard screens will satisfy all of the critical demands of the company. In this scenario, ordering is greatly simplified. PCP would only offer a limited menu of assay packages designed to capture the most common problems that development programs face.

PCP also faces a choice in the type of product to offer to their customers. Currently profiling is a data provider. Customers ask for the solubility of several compounds and in return they receive several numbers. However, PCP also has the ability to provide analysis, rather than data alone. The Cambridge organization has been experimenting with placing profiling associates on the drug development teams. These individuals are the primary contact for answering profiling related questions. Since the associates are scientists in their own right with bachelors and masters degrees they are capable of providing much more. PCP could provide analysis of multiple compounds in multiple

²⁹ Source: Saloner, Garth, et al. *Strategic Management*. 2001

³⁰ Source: Saloner, Garth, et al. *Strategic Management*. 2001

assays to create an integrated risk assessment and suggestions to the drug discovery program. They could be an integral part of helping the chemists to select the appropriate assays for the appropriate compounds and in helping them to understand the meaning of all of the data as it is provided.

7.2 Evaluating the Options

This leaves PCP with a matrix of options. They can choose to provide a general or a custom structure with either data or analysis as their primary product. The four possible options are shown in the table below.

		Custom	General
Product	Analysis	Analysis/Custom support each other. New business model for Profiling.	Limited ability to respond to the analysis with targeted assay selection
	Data	Profiling expertise must reside in each project team to take advantage of custom structure	Lowest cost option for general screening. Limited future in-house.

Figure 27 – PCP Strategic Options

As shown on the figure, the upper-right quadrant and the lower-left quadrant both have problems with strategic fit. If PCP offered detailed analysis with a general structure, they are quite limited in how they can help the development teams. They may be able to help with the meaning of results, but when it comes to next steps and follow up assays to perform, their expertise is wasted because they can only recommend one of the obvious choices on the menu.

If a custom structure is paired with providing only data, the project teams are required to have the expertise to not only interpret that data, but also make decisions on future profiling direction based on the data they received. In addition, every development team at Novartis will need a deep level of expertise in profiling for the company to take advantage of the investment in a custom profiling structure.

Clearly, the best options lie in either providing a custom structure with analysis or a general structure with just the data. Currently, PCP sits in the middle. They offer some assays individually, while others are in packages. They offer just data to most customers, but are starting to offer more analysis to others. To be successful in the long run, the organization needs to commit to a strategy and embrace it wholeheartedly to gain all of the potential advantages. To embrace either option would require significant changes in their organization and their operations.

If PCP chose to offer the general structure and provide only the data, they would be in a position to offer low costs. However, it is questionable how long that advantage would last since they are confined to operating in a high cost location. Over time it is likely that external vendors, operating in low cost areas, could replicate the capabilities of the Novartis Profiling group and offer those services at a lower cost. Novartis already compares its internal assay cost with the cost of outsourcing. For certain assays, external vendors already offer prices that are slightly below the internal cost.

8 Organizational Considerations

8.1 Strategic Design Factors

8.1.1 PCP Organizational Structure

The PCP organization is divided along functional lines. There are separate groups for each major assay class such as absorption, cellular toxicity, and safety pharmacology. Each group is lead by a lab head who has 1-3 direct reports. Lab Heads are almost always Ph.D.'s. Each associate who works for the lab head is typically responsible for a specific assay and often works individually rather than as part of a team. The Associates typically have Bachelors or Masters degrees in a science major like biology or chemistry. Though some associates know how to perform multiple assays, most are only comfortable with their own primary assay.

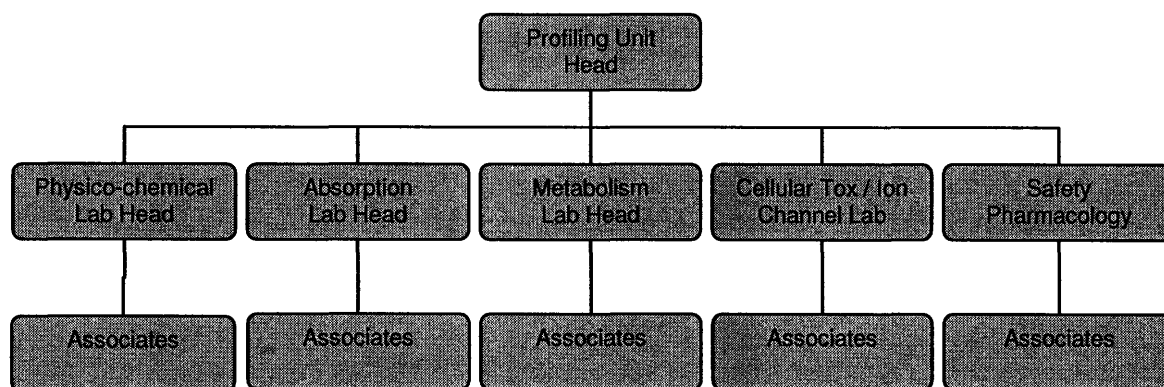


Figure 28 – US PCP Organizational Chart

The profiling group in Cambridge has a companion group in Basel that performs many of the same functions. Some assays are performed at both locations while others are performed only in Cambridge. At a global level the head of profiling for both Basel and Cambridge report to the local head of Discovery Technologies (DT). The local heads of DT then report in to global head of DT. The US head of DT is also designated as the Global Head of Profiling, so the Basel head of profiling has a dotted-line reporting relationship to the US head of DT.

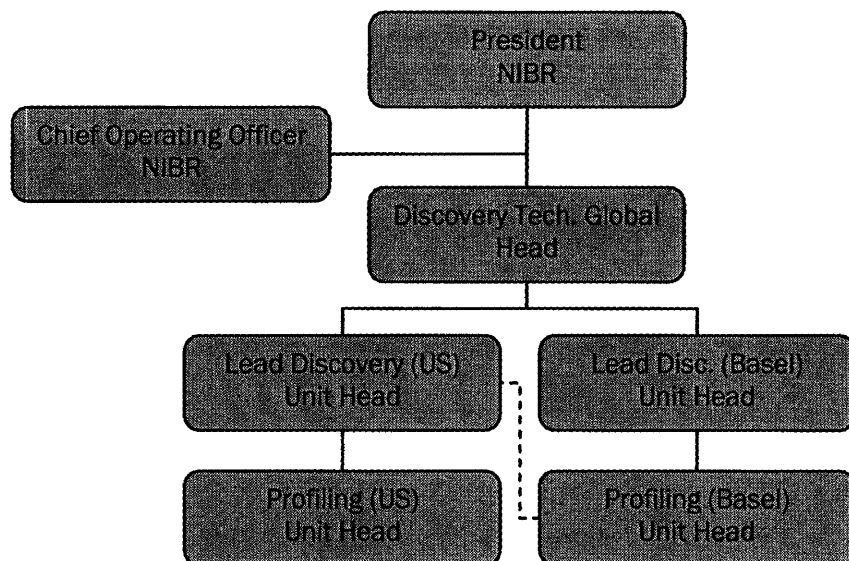


Figure 29 – Global Reporting Structure for Profiling

8.1.2 Implications of the Organizational Structure:

The Basel and Cambridge organizations do not share a common direct manager until one step below the President of NIBR. This makes synchronization and agreement between Basel and Cambridge more difficult than it might be if all of Profiling reported to a single manager who could set direction for the entire organization. There are established lines of communication between the lab heads at each site which help with coordination, but these connections do not extend down to the level of the associates. Also, since the customers of PCP services are in a completely separate organization, evaluating the needs of the customers is more difficult and can be a point of disagreement.

8.2 Organizational Recommendations

8.2.1 Reorganize Departmental Structure

In the current organizational structure, associates are under a glass ceiling. Since lab heads are culturally required to have PhD's to confer necessary legitimacy, associates have very few options in establishing a career path within the company. Also, the structure of the organization focuses on developing assays in each functional department rather than focusing on daily operations. Further, associates are required to perform a lot of manual, repetitive tasks that are required to keep running the assays. These problems are difficult to address without redefining the structure and relationships within the department. A proposed alternative structure is shown below in Figure 30.

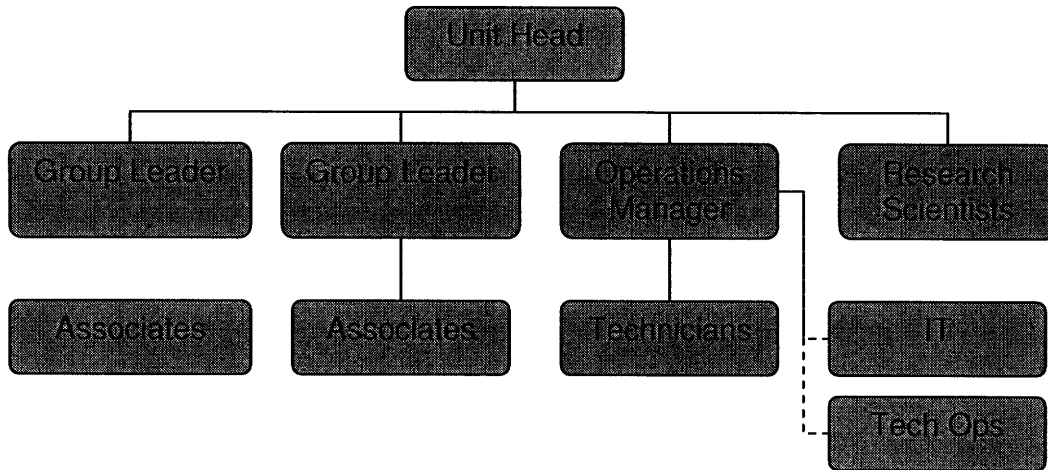


Figure 30 - Proposed Organizational Structure³²

This structure creates several new roles. At the bottom of the organization it creates a layer of technicians. These technicians would be responsible for the daily manual tasks associated with handling samples, setting up the assays, and performing the assays themselves. Supervising these technicians would be an Operations Manager whose primary task is making sure the daily operations run smoothly. This manager would track cycle time and cost performance and ensure that materials flows through the group smoothly.

Associates would work closely with the technicians and would retain responsibility for assay procedures and quality. In effect they would serve an engineering function and would be freed from the repetitive tasks of physically performing their assay. The associates would report to Group Leaders whose primary responsibility would be management of the associates. Each Group Leader would have six or more associates instead of the 1-3 that each Lab Head is responsible for today. Group Leaders would also do project management tasks and coordinate with the Operations Manager to ensure Operations received the support it requires.

Research Scientists would focus on assay and technology development activities. They would be the technical experts in the department and would be assisted by the associates on certain projects, especially as assays were getting ready to transition to full production.

This new structure provides an appropriate career path for all members of the organization. They can progress on either an individual contributor or management career path as shown in Figure 31.

³² Developed in association with Rebecca Roberts, LFM Class of 2007

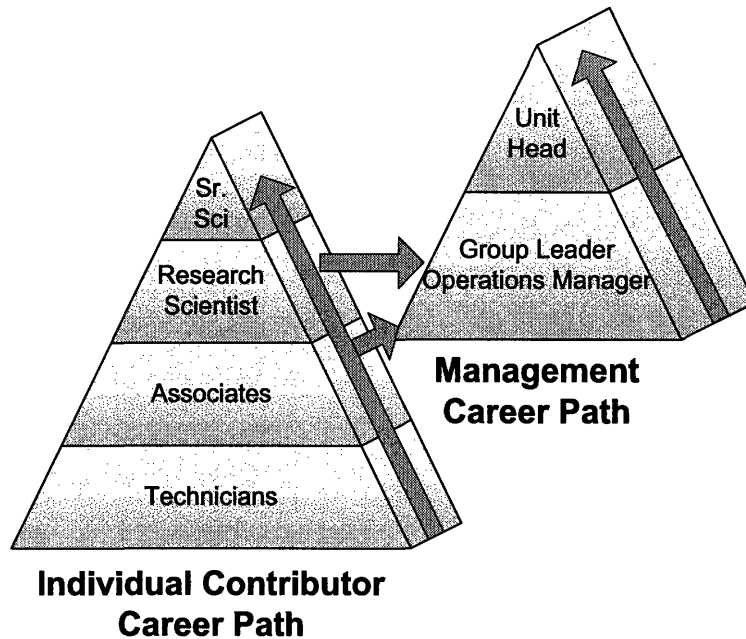


Figure 31 - Career Paths in New Organization³³

Associates in the new organization have more freedom to do interesting work, Operational focus is built into the organization with the Operations Manager role, and researchers can devote their full time to research instead of being saddled with management and daily operational activities.

8.2.2 Change Management Reporting Structure

The split management structure in PCP can lead to difficulties in creating a shared vision and challenges in getting the two sites to work together as an integrated team. A more direct reporting relationship would simplify the process of creating a common strategy, common metrics, and common goals. The head of profiling at each site should have a solid-line reporting relationship to a single individual.

8.2.3 Use Balanced Scorecards as Management Tool

NIBR uses a Balanced Scorecard methodology to do its individual performance reviews.³⁴ However, these Balanced Scorecards are not typically used in the normal course of business in the Discovery Technologies group. In group meetings it is rare to see any mention of specific group goals and current performance relative to those goals. Since the group has already invested in the creation of Balanced Scorecards, they should use them more aggressively to help manage their performance on an ongoing basis.

³³ Developed by Rebecca Roberts, LFM Class of 2007

³⁴ Source: Kaplan, Robert S. and David P. Norton, "The Balanced Scorecard: Translating Strategy into Action."

9 Conclusions

Based upon the analysis presented earlier the NIBR Profiling group should adopt the following recommendations:

- Create a split panel structure for Safety Pharmacology (complete)
- Consolidate all Safety Pharmacology activity to a single site
- Outsource the secondary panel when moving to weekly run schedule
- Adopt a custom/analysis strategy to maximize long-term value
- Update the organizational structure to improve operational focus

This package of changes will enhance the cost-effectiveness of the PCP organization. Resources will be better allocated, cycle times will be reduced, and costs will decrease. Over the long term, the strategic and organizational changes will enable PCP to continue to improve and be competitive.

In addition to some specific recommendations, throughout this project the following principles emerged that are generally applicable.

The Importance of Analyzing the Entire Process Flow

One of the critical failings in the Profiling department was considering only the activities and impact of changes within the department itself. For example, when measuring cycle time, internal metrics indicated performance was good, but looking at the entire process flow showed cycle time performance was extremely poor. The decisions of any one piece of the process inevitably affect the steps before and after. Metrics and change proposals need to include the impact on the entire system rather than just the local department.

Tools of Operational Analysis are Broadly Applicable

The types of tools used in this analysis such as process flow mapping, cost modeling, monte-carlo simulations, etc. are common practice in manufacturing companies. This thesis as well as previous Leaders for Manufacturing Theses^{35,36} have shown that these tools are broadly applicable, even in unlikely areas such as early-stage drug discovery research. Any activity that is repeated or follows a process can be analyzed and improved using these types of tools.

Combining simple models together can provide an integrated view of interacting change proposals

Multiple change proposals in a single department must be evaluated in concert to avoid selecting a sub-optimal combination of options. In these situations, simple models can be combined together to give an understanding of how the proposals interact along multiple

³⁵ Source: Vokoun, Matthew, *Operations Capability Improvement of a Molecular Biology Laboratory in a High Throughput Genome Sequencing Center*. 2005.

³⁶ Source: Penake, David A. *Enabling Sample Tracking in and Reducing Variability in DNA Library Construction*. 2006.

dimensions. Based upon this type of analysis, options that maximize two or more desired outputs can be identified and implemented.

Internal service organizations must develop a long-term strategy to add value

Captive internal service organizations have significant positional advantages and disadvantages with respect to third party vendors. In order to survive they must identify and implement a strategic vision that will exploit those advantages and provide superior long-term performance. Without a coherent, long-term strategy that takes advantage of internal relationships and interests, these organizations will be replaced through outsourcing.

10 Future Opportunities

In addition to the recommendations in this thesis, there are many other opportunities for improvement in the Profiling organization. Some of these include redesigning for continuous flow, implementing ideas from lean manufacturing, and using statistical process control to improve assay quality.

Redesign for Continuous Flow

The increasing miniaturization in the pharmaceutical industry has the effect of driving ever-increasing batch sizes in PCP. The smallest element in an experiment is the microplate. These plates have become more and more dense moving from 96-well to 384-well to 1536-well plates. The automation systems are designed to handle a full plate at a time. Running a partially filled plate typically wastes reagents. This system works relatively well for high-throughput screening in which the compounds to be tested already exist in inventory in a library. In PCP, the compounds are novel and are produced in as a steady stream. Creating full plates requires ever larger batches of compounds and hence ever increasing queue-times. The automation systems for Profiling could be completely redesigned and reconceived to enable samples to be processed one at a time or just a few at time. The actual process time for any assay is often 1-2 days. With a continuous flow system queue time could approach zero and overall cycle time for any assay could be reduced to just a few days, a dramatic improvement from the 1-4 weeks that is common today.

Implement Lean Laboratory Practices

The laboratories at NIBR could benefit from employing the basic concepts of Lean Manufacturing. Successful implementation of these principles has been done previously in a similar environment at the Broad Institute.³⁷ At NIBR, procedures lack standardization and documentation, labs are typically messy and full of equipment, consumable inventory is piled up all over, and metrics are not easily accessible. The basic techniques of 5S, standardized work, kanbans, and continuous improvement could significantly improve performance in the area.³⁸

³⁷ Source: Vokoun, Matthew, "Operations Capability Improvement of a Molecular Biology Laboratory in a High Throughput Genome Sequencing Center."

³⁸ Source: Dennis, Pascal. *Lean Production Simplified*. 2002

Implement Statistical Process Control

Currently there are no metrics to track the performance of key assay parameters on a run to run basis. Many of the assays have built in quality checks that are used as lower limits to determine if an assay must be repeated. However these quality indicators are not systematically tracked or used over time. Employing control charts and statistical process control techniques could significantly increase quality and reduce the occurrence of rework. Assays with marginal performance could be easily identified and improved by optimizing the assay run protocols. Problems with reagents or equipment could be more quickly and more easily identified. Creating a system and a culture of quality performance tracking would be challenging but could yield significant long-term results.

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12 Appendix A – Materials Cost Modeling

This is an example of the cost modeling for the Safety Pharmacology options analysis using fictional numbers. The first table shows the assumptions made and the second how the calculations were performed.

Assumptions	Value	Comments
Labor & Materials		
Cambridge FTE cost/yr	\$120,000	
Basel FTE cost/yr	\$100,000	
Base Materials Cost	\$1,000,000	
R&D materials cost percentage	10%	Non-production costs
Dead Volume	20%	
Outsourcing		
Compound demand/yr for secondary assay	500	
Outsourcing cost/well	\$25	
% Hits in outsourced assays	20%	
		= cost/well*(2) + (hit%) * (cost/well)*6 (assumes single concentration in duplicate with 6pt IC50 follow-up)
Outsourcing cost/cmpd/assay	\$80.00	
Capital Expenditures		
Materials Savings due to Individual Ordering	25%	
Capital for Ind. Ordering on 2 sites	\$1,000,000	
Capital for Ind. Ordering on 1 site	\$500,000	
Capital for All assays at both sites	\$250,000	
Tax Rate	30%	
Equipment Lifetime (for dep. Schedule)	5	
Cost of Capital	15%	

Table 6 - Assumptions used in Safety Pharmacology Cost Model

Ln	Item	Value	Comments
1	Individual Ordering	Yes	Choose Yes or No
2	Primary Assays	40	Choose value
3	Secondary Assays	30	Choose Value
4	Outsource Secondary?	No	Choose Yes or No
5	Assay Frequency	25	Choose 25 or 50 runs per year
6	Location	Both	Choose Both, All, Basel, Cambridge
7	Capital Cost	\$1,000,000	estimate from assumptions (# of Secondary Assays)*Outsourcing cost/cmp/assay * demand for secondary assays
8	Outsourcing Cost	\$0	
9	Base cost for primary assays	\$533,333	number of primary assays/Base # of assays * base materials cost

10	Materials increase due to run frequency	\$0	Dead volume fraction*(base cost for primary assays)*(new runs/yr - old runs/yr) / (old runs/yr)
11	Savings from individual ordering	(\$106,667)	(Ind. Ordering savings rate)*(1-dead volume fraction)*(materials cost subtotal)
12	<u>Materials Cost Subtotal</u>	<u>\$426,667</u>	sum of previous 3 items
13	Secondary Assay Materials	\$151,111	if outsource=no then (secondary cmpds/Base demand)*(Cost subtotal for Base demand cmpds)* (number secondary assays/number of primary assays)*(1-dead volume fraction)+ dead volume fraction*(number secondary assays/number primary assays)*base materials cost for primary assays
14	Adjustment for # of sites	\$0	if Location=all then (dead volume fraction)*base cost for primary assays + materials increase due to run frequency
15	<u>Materials Difference from base</u>	<u>(\$422,222)</u>	Base Materials Cost - Materials Cost subtotal - Secondary Assay Materials - Adjustment for # of sites
16	Net Change in Cash Expenditure/yr	(\$422,222)	Sum of Materials difference from base and Outsourcing Cost
17	Basel FTE Impact	-1	estimate of labor changes from labor model
18	Cambridge FTE Impact	-0.5	estimate of labor changes from labor model
19	Total Labor Change	-1.5	Sum of previous 2 items
20	Labor Cost	(\$160,000)	Basel FTE Impact* Basel FTE cost + Cambridge FTE Impact * Cambridge FTE cost
21	Depreciation Tax Benefit (Straight line)	(\$60,000)	tax rate * (capital investment/ years depreciated)
22	<u>Other Annual Costs</u>		any other manual adjustments
23	5-Year NPV w/o Labor	\$616,484	5-year NPV not including labor cost savings
24	<u>5-year NPV</u>	<u>\$1,152,828</u>	5-year NPV

Table 7 - Calculations from Safety Pharmacology Cost Model

13 Appendix B – Cycle Time Modeling

Following is an example of the type of cycle time assumptions made in the cycle time model. Also shown is an example output of the expected distribution of the cycle time of compounds going through the system.

Step	Time (business days)	Probability
1 - Compound Submission	0	20%
	1	70%
	2	10%
2 - CMU Processing	1	50%
	2	50%

3 - Shipping Required?	0	50%
	1	50%
4 - Shipping Delay	1	20%
	2	20%
	3	20%
	4	20%
	5	20%
5 - Shipping Time	1	20%
	2	60%
	3	20%
6 - Assay Queue	1	10%
	2	10%
	3	10%
	4	10%
	5	10%
	6	10%
	7	10%
	8	10%
	9	10%
	10	10%
7 - Assay Processing	8	5%
	9	10%
	10	70%
	11	10%
	12	5%

$$\text{Total Time} = \text{Step 1} + \text{Step 2} + \text{Step 3} * (\text{Step 4} + \text{Step 5}) + \text{Step 6} + \text{Step 7}$$

Table 8 - Sample Assumptions for Cycle Time Model

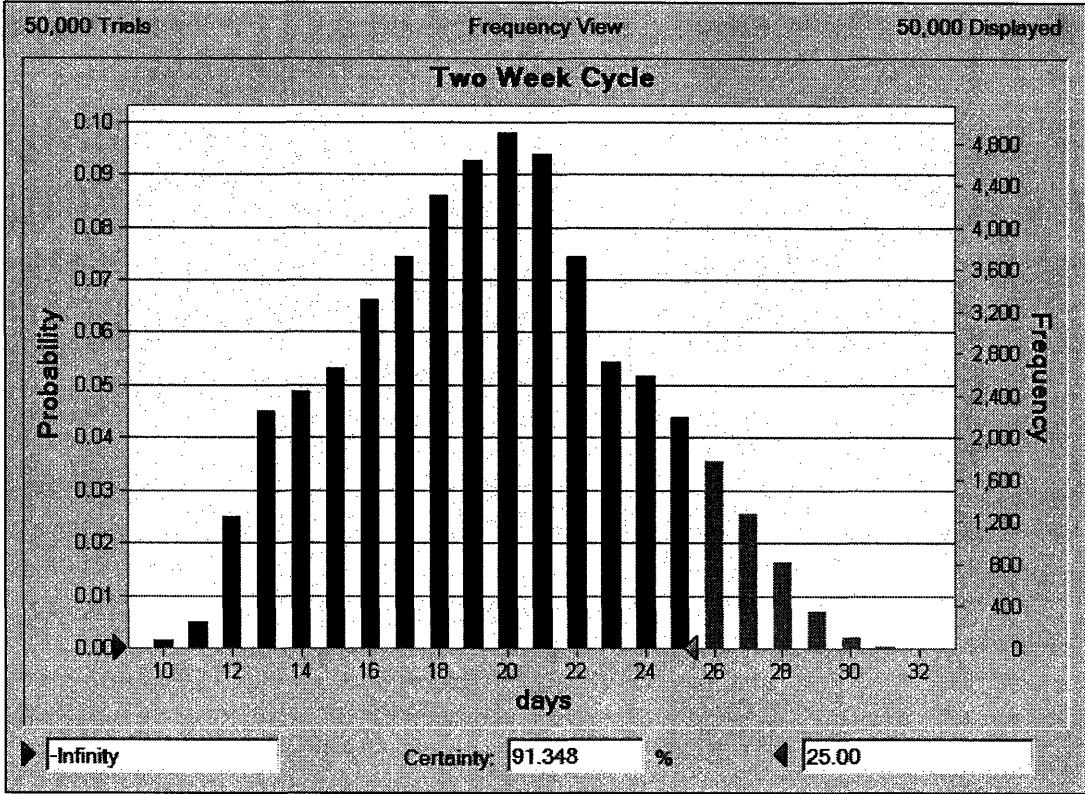


Table 9 - Output of Cycle Time Simulation