Optimization of Chemical Reagent Storage and Distribution at Novartis Institutes for BioMedical Research

by

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Submitted to the Sloan School of Management and the Department of Materials Science and Engineering in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration and
Master of Science in Materials Science and Engineering

In Conjunction with the Leaders for Manufacturing Program at the Massachusetts Institute of Technology
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Abstract

The Novartis Institutes for BioMedical Research is the drug discovery arm of Novartis Pharmaceuticals. Drug discovery is generally considered to be the primary driver for success in the pharmaceutical industry. Success in the early stages of drug discovery relies on dependable, innovative, disease related high-throughput screening of biological compounds and the creation of a screening deck of highly diverse, proprietary chemical compounds. In contrast with many of its peers, Novartis relies strongly on combinatorial chemistry to populate its screening deck. The Chemical Libraries (CLI) group is responsible for this approach at Novartis and delivers more than 100,000 compounds per year to the Novartis Compound Archive. Since the introduction of high-throughput screening and combinatorial chemistry techniques, the bottleneck in many drug discovery processes has shifted to the roles that support these high-volume techniques.

The aim of this thesis is to provide a general collection of short and long-term suggestions for process improvement in the chemical supply process. This process includes compound search and ordering, order fulfillment, and compound delivery, was investigated. The chemical supply process is responsible for delivering compounds to chemists that would otherwise cost hundreds of dollars per compound with a delay of between one and four weeks, or would require a multiple day synthesis procedure. Stockroom automation, content and process scope, and physical layout were all evaluated.

The following major conclusions were developed as a result of the research. First, the procedures for using the compound archives and libraries must be clearly presented to the end user so that s/he is fully able to utilize and contribute to the libraries. Second, compound libraries should be conglomerated into one large library that is also responsible for compound acquisition. Third, compound metering for intermediates does not appear to be an effective use of resources and should be severely restricted following the successful implementation of the SciQuest compound management system. Finally, compound libraries should use automated pick and place systems but metering and dispensing systems should remain manual.

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I am thankful for the advice and directions of my thesis advisors, Charles Cooney and David Simchi-Levi, as well as my thesis readers, Randolph Kirchain and Donald Rosenfield. Their willingness to share their experience and knowledge was invaluable to my learning.

Finally, I would like to thank the Leaders For Manufacturing program for providing me with this internship opportunity. The collective support of my peers, the faculty, and the staff at MITSloan School of Management and the School of Engineering was immeasurable.

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1 Introduction

1.1 Project Motivation

The pharmaceutical industry has entered a more competitive era with higher costs of drug discovery and fewer "blockbuster" drugs. This new environment dictates the need for a more efficient and streamlined discovery process. Efforts to automate and institute high-throughput discovery techniques have pushed the bottleneck in the discovery pipeline upstream, so that it now often resides in supporting resources for these techniques.

Upstream processes are now generally regarded as inhibiting bottlenecks in many drug discovery organizations. Consequently, it is now a high priority to maximize the efficiency of synthetic chemistry processes. A large factor in the ability of chemists to efficiently produce desired compounds is the availability of chemical intermediates or building blocks, chemical precursor compounds that are used in the synthesis of drug candidate compounds. Better availability of commercially available and proprietary compounds will have a direct impact on chemists' efficiency.

This thesis takes a broad look at the system for supplying intermediate and building block compounds to the chemists and attempts to discern a configuration that maximizes responsiveness, accessibility and quality of compounds, while minimizing costs. The libraries that hold these building blocks are an essential component of the synthetic chemistry process. Each archive contains 20 – 30 thousand compounds. Many of these compounds are proprietary and would take, on average, approximately two days of a technician's time to prepare from scratch. The compounds that are commercially available cost hundreds of dollars per order and have lead times from several days to a month. Consequently, optimal functionality of compound libraries saves Novartis thousands of dollars per day and, more importantly, dramatically decreases cycle time for compound production.

1.2 Thesis Overview

This document is organized as described below:

Chapter 1 outlines the general motivation for this project and gives an overview of the thesis.

Chapter 2 provides a brief discussion of Novartis and the Novartis Institutes for BioMedical Research. It also delivers a concise outline of the industry and competitors.

Chapter 3 discusses the evolution and current state of the drug discovery process with special emphasis on medicinal chemistry. This chapter aims to supply an initial understanding of the needs of the customer and the materials properties that are typically desired by the customer.

Chapter 4 introduces the project by discussing the setting and goals of the problem along with the approach that was implemented.

Chapter 5 details the current service offerings that are available, gives a brief overview of the customer locations, and discusses utilization.

Chapter 6 investigates the customer definition of value, customer satisfaction and desires, current ordering procedures, archive workflow and content, and competitor approaches.

Chapter 7 explores the use of automation in the specific archives and discusses the options that are currently on the market.

Chapter 8 describes a suggested future archive, to be implemented as part of the Novartis Campus Project, that implements many of the improvements discussed earlier in the paper.

Chapter 9 summarizes the findings from the research.

2 Industry and Company Background

2.1 Industry Summary

The pharmaceutical industry is highly consolidated with large barriers to entry. The top 10 companies made up almost 50% of sales in 2005. Research and development costs for new compounds are generally extremely high; in 2005, the biopharmaceutical industry spent an estimated USD 51.3 billion on research and development costs[1]. Approval from the Food and Drug Administration (FDA) for a new drug application (NDA) is also an arduous and costly process. Additionally, only one in 5000 compounds makes it to market and only one third of commercial drugs are successful enough to recuperate their own research and development costs. This environment favors large companies that are able to spread risk among many drug candidates. The 10 largest pharmaceutical companies and their 2005 sales are listed in Table 1.

Pfizer	47.6
GlaxoSmithKline	34.7
Sanofi-Aventis	30.0
Novartis	28.5
Johnson & Johnson	25.3
AstraZenica	24.1
Merck	23.5
Roche	19.8
Abbott Labs	15.7
Wyeth	14.7

Table 1 - Leading pharmaceutical companies in 2005 (pharmaceutical sales only)[2]

As noted above, most drug candidates end up being unsuccessful and many of the ones that do make it to market cannot produce enough revenue to justify their costs. On average, it requires about

[1] Source: Pharmaceuical Research and Manufacturers of America. "Pharmaceutical Industry Profile 2006." Washington, DC: PhRMA, March 2006.
[2] Source: Saftlas, Herman., et. Al. "Healthcare: Pharmaceuticals." Standard & Poor's Industry Surveys. May 25, 2006.

USD 800 million and ten to fifteen years to develop a new drug[3]. This leads pharmaceutical manufactures to focus on what are deemed "blockbuster" drugs, compounds that generate more than USD 1 billion for their owner[4]. It is hoped that these "blockbusters" will produce enough revenue to cover the costs of their development as well as the costs of all the failed candidates. The ten leading drugs by sales in the United States are listed in Table 2, below.

Lipitor (Pfizer)	Cholesterol reducer	8.4
Zocor (Merck)	Cholesterol reducer	4.4
Nexium (AstraZenica)	Antiulcer	4.4
Prevacid (TAP Pharma-Abbott)	Antiulcer	3.8
Advair Diskus (GlaxoSmithKline)	Antiasthmatic	3.6
Plavix (Sanofi Pharmaceuticals)	Blood clot inhibitor	3.5
Zoloft (Pfizer)	Antidepressant	3.1
Epogen (Amgen)	Red blood cell stimulant	3.0
Procrit (Johnson & Johnson)	Antianemia	3.0
Aranesp (Amgen)	Antianemia	2.8

Table 2 - Leading US drug sales in 2005[5]

Once a company has successfully developed a novel compound, its research and development investment is protected under patent law. A patent is a legal barrier to entry that prohibits competitors from entering the market for a compound. Patents can be issued based on the drug's chemical structure or on its method of manufacture. The World Trade Organization (WTO) requires all of its member countries to recognize patents and grants protection for 20 years following the date of application. Because it takes a significant amount of time to bring a product from the application stage to the market, the effective length of protection in the market is effectively only eight to 10 years[6].

A drug that has lost its patent protection can be produced by any manufacturer as a generic drug. Additionally, manufacturers can submit their drug in the United States for faster FDA approval under an

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[3] Source: Pharmaceuical Research and Manufacturers of America. "Pharmaceutical Industry Profile 2006." Washington, DC: PhRMA, March 2006.
[4] Generally, blockbuster drugs address afflictions that have large populations of victims. However, this is not a necessary criterion, as notably illustrated by drugs that treat Orphan Diseases, such as Genzyme's Cerezyme (2006 revenues USD 1 billion, with significantly less than 10,000 patients).
[5] Source: Saftlas, Herman., et. Al. "Healthcare: Pharmaceuticals." Standard & Poor's Industry Surveys. May 25, 2006.
[6] Ibid.

expedited abbreviated new drug application (aNDA). Once a drug is in the generic stage, more competitors enter the market and generally erode the profitability of the innovator. The strategy in this more competitive market is somewhat different; manufacturers tend to compete on cost rather than on perceived quality.

Generic drugs are taking on added significance in the contemporary market. In 2006 alone, drugs with a combined USD 21.3 billion market share will lose patent protection. Between 2006 and 2010, 70 or more drugs will lose patent protection. At least 19 of these are considered "blockbuster" drugs. This places additional pressure on those responsible for drug discovery to produce new compounds to replace them.[7]

Many companies are also trying to fight the onslaught of generic competition by forging agreements with generics manufacturers to produce "authorized generics" slightly before patent expiration. This gives the selected generic manufacturer an advantage but discourages additional competition. Other manufacturers, such as Novartis, have decided to produce generics in-house, generally within a separate division. This reduces the required legal and marketing budget that would be squandered defending the labeled drug while allowing the company to maintain market share in the generic drug, which will generally have a leg up on the competition.

Global pharmaceutical sales are still growing faster than the economy in general, but there is expected to be a marked deceleration of growth. The United States is, by far, the largest segment of the market, with 2005 sales of USD 252.2 billion[8]. Figure 1 below shows the global division of sales.

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[7] Ibid.
[8] Ibid.

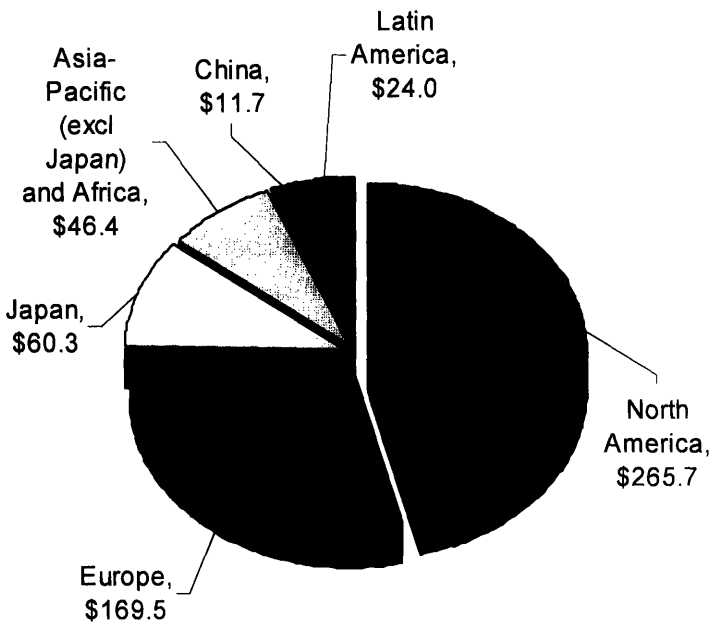

Figure 1 - 2005 Pharmaceutical sales by region in Billion USD[9]

2.2 Novartis AG

Novartis resides in Basel, Switzerland and was formed on March 7, 1996 by the merger of Sandoz and Ciba-Geigy. At the time, this was the largest corporate merger in history. At year-end 2005, Novartis net sales of USD 32,212 MM, providing a 21.4% Return on Sales[10]. The present incarnation of Novartis is a result of a long history of corporate mergers and acquisitions.

Novartis is divided into three divisions, with a fourth pending shareholder approval. Sales for the three pre-existing divisions for calendar year 2005 was USD 20,262M, divided by division as illustrated in Figure 2.

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[9] Ibid.

[10] Source: Novartis Annual Report 2005 < http://www.novartis.com/downloads/2005_annual_results_E.pdf>

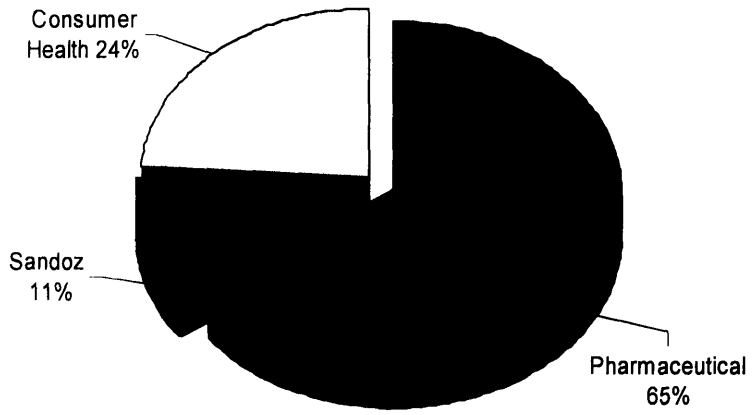

Figure 2 - Novartis sales by division for 2005

The Novartis Pharmaceuticals division is responsible for general and specialty medicines to treat a large range of conditions. The top ten selling Novartis pharmaceuticals for 2005 are listed in Table 3. In recent years the Novartis pipeline has been more successful than the industry average. Novartis contributes a large part of this success to it's unique drug discovery unit's organization and methods.

Diovan	1,551	2,125	3,676	1	hypertension
Glivec	524	1,646	2,170	1	Chronic Myeloid Leukemia and Gastrointestinal Stromal Tumors
Zometa	704	520	1,224	1	bone metastasis and a variety of tumors
Lamisil Group	538	595	1,133	1	antifungal agent
Lotrel	1,075	0	1,075	1	hypertension
Neoral/Sandimmun	150	803	953	3	immunosupressive agent for transplantations
Sandostatin/LAR	376	520	896	1	reduce blood levels of growth hormone and IGF-I in acromegaly patients
Lescol Group	257	510	767	8	atherosclerosis
Voltaren	5	684	689	3	Nonsteroidalanti-inflammatory, antirheumatic agent
Trileptal	462	153	615	7	epilipsy

Table 3 - Top 10 Novartis pharmaceutical compounds for 2005[11]

Following the acquisitions of Hexal and Ion Labs, the Sandoz division is the world's second largest supplier of generic pharmaceuticals. Novartis is the only company that can claim a position as one

[11] Ibid.

of the top five producers of both branded and generic drugs[12]. Sandoz has an entirely separate supply chain from the Pharmaceuticals division and is generally viewed internally as competition. However, Novartis is actively working to institute a process of allowing Sandoz early access to Novartis patents setting the groundwork for early launch to gain larger amounts of generic market share. It is hoped that as a result of this handoff, the loss to the Pharmaceuticals division due to cannibalism will be more than accounted for by the increased sales in generics and the reduced marketing and legal expenses of protecting the name brand drug.

The Novartis Consumer Health division produces Over the Counter drugs, animal health products, Gerber baby products, and CIBA vision products. Similar to Sandoz, OTC drug sales can gain a synergistic advantage with the Pharmaceuticals division by working to reformulate prescription drugs and brand names into OTC dosages as patents expire. In December 2006, Novartis sold its medical nutrition products group to Nestlé SA, for USD 2.2 billion, in an attempt to focus more on pharmaceuticals[13].

The new Vaccines and Diagnostics division will consist of the Chiron Corporation's diagnostics and vaccines businesses. It is the world's fifth-largest vaccine maker and the second-largest manufacturer of flu vaccines.[14] The Vaccines and Diagnostics division is headquartered in Emeryville, CA.

2.3 Novartis Institutes for BioMedical Research (NIBR)

The Novartis Institutes for BioMedical Research (NIBR), organized in May 2002, is the global research organization of Novartis. NIBR currently has seven locations, illustrated in Figure 3, with an eighth USD 100 Million facility slated for construction in July 2007 in China[15]. The world headquarters is located in the Cambridge, MA location but the largest facility is located in Basel, Switzerland with approximately 1600 employees.

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[12] Source: Whalen, Jeanne. "Betting $10 Billion on Generics, Novartis Seeks to Inject Growth." The Wall Street Journal. A1, May 4, 2006.
[13] Source: Ball, Deborah and Jeanne Whalen. "Nestlé Buys Novartis Nutrition Unit." The Wall Street Journal. A10, December 15, 2006.
[14] Source: <http://www.novartisvaccines.com/>
[15] Source: Zamiska, Nicholas. "Novartis to Establish Drug R&D Center in China." The Wall Street Journal. A3, November 6, 2006.

NIBR is sub-divided into ten Disease Areas[16], which focus on major areas of human affliction. Additionally, NIBR contains eight Expertise Platforms[17], which work in parallel to the Disease Areas and provide understanding of particular research technologies.

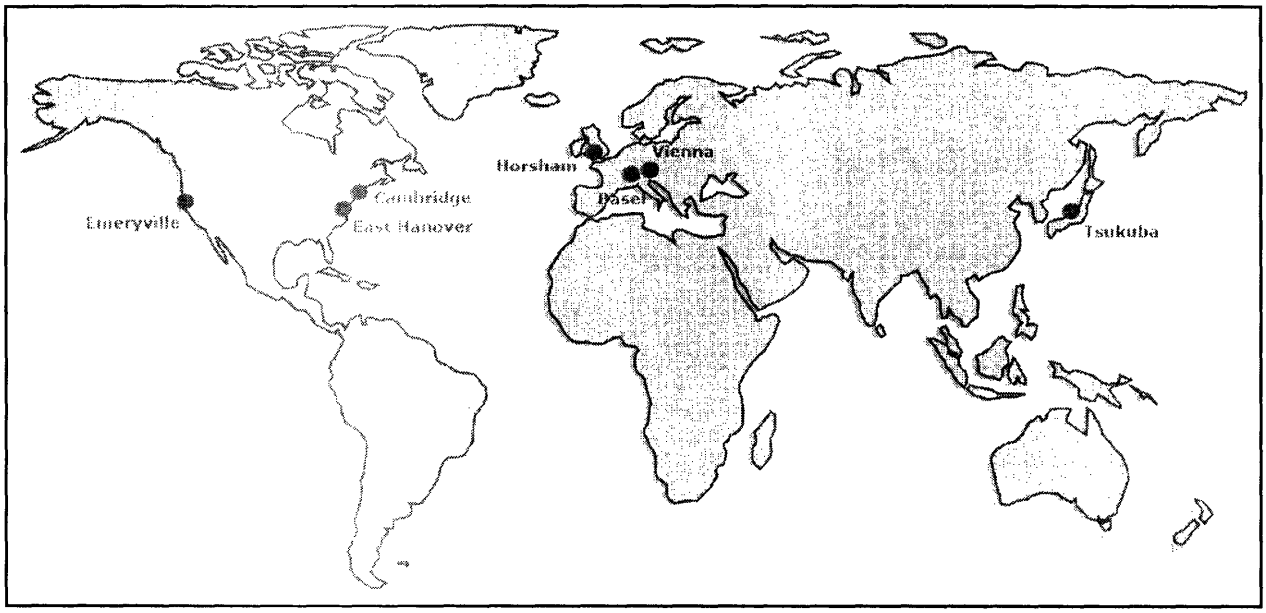

Figure 3 - NIBR Locations[18]

Following is a brief description of drug discovery methodology that is typical of the Novartis approach for small molecule drugs with a specific focus on the US market. The approach for other pharmaceutical companies and, to a lesser extent, biotechnology firms is similar.

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[16] The ten Disease Areas are Autoimmunity & Transplantation, Cardiovascular, Diabetes & Metabolism, Gastrointestinal, Ophthalmology, Infectious Diseases, Musculoskeletal, Neuroscience, Respiratory Diseases, and Oncology

[17] The eight Expertise Platforms are the NIBR Biologics Center, Developmental & Molecular Pathways, Discovery Technologies, Center for Proteomic Chemistry, Epigenetics, Genome & Proteome Sciences, Global Discovery Chemistry, and Models of Disease

[18] Source: NIBR Web site <http://nibr.novartis.com/Downloads/About/NIBR_printable_map.pdf>

3 The Process of Drug Discovery

3.1 Introduction

For millennia, man has harnessed the medicinal properties of naturally occurring drugs, initially utilizing plant sources. The practice of analytical chemistry became relevant to medicine in the 19th century when, in 1815 Sertürner was able to isolate morphine from opium[19]. In 1938, Chain and Florey made the fortunate decision to further study Fleming's penicillin. The immense success of penicillin provided an impetus for general research on antibiotics[19]. The 1950's saw the beginning of isolating natural products used as leads and random screening in animals. This early mechanism of drug discovery was a serial process in which the isolated natural compounds were then sent off to be tested in simple biological screens and rodents. The results of the screens were then used to chemically modify the compound and the feedback loop was repeated until a satisfactory result was produced. The next steps were animal testing and clinical trials, followed by FDA approval and production.

At this early stage, the animal testing process was the primary bottleneck in the discovery pipeline. However, in the 1970's molecular modeling and *in vitro* experimentation became available to filter compounds. This allowed for more intelligent and selective animal testing and shifted the bottleneck to the lead-optimization stage. Then, in the 1980's computer aided modeling and structure-based design tools, such as NMR were added to the drug discovery toolbox, further refining the number and quality of compounds escaping the discovery process.[20]

The lead-optimization bottleneck in the pipeline prohibited the pharmaceutical industry from developing new drugs at a pace that satisfied corporate investors. Following the introduction of high-throughput screening (HTS) between 1989 - 1991, companies achieved the ability to screen millions of compounds in high-capacity biological assays, thus pushing the bottleneck from screening to medicinal chemistry[21] and *in silico* drug design.

Focus on eliminating the new constraints, led to the development of the techniques of combinatorial chemistry and parallel chemistry. Success of these techniques requires several significant supporting resources including insightful design, automation and robotics, and, notably for this thesis, a diverse, unique and readily available supply of precursors.

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[19] Source: Drews, J. "Drug discovery: A historical perspective." Science. 287, 2000, 1960 - 1964.
[20] Much of the general information for this section is taken from Ali, Mohammad Farat et. Al. Handbook of Industrial Chemistry: Organic Chemicals. New York: McGraw-Hill, 2005, 337-347.
[21] Source: Edwards, Paul J. "The Impact of Parallel Chemistry in Drug Discovery." IDrugs. 9, 2006, 347-353.

Of course, in addition to focusing on the throughput rate of the drug development pipeline, it is equally important to focus on the quality of the product from each step in the process. The early efforts of combinatorial chemistry were more like a "shotgun approach" designed to maximize primarily the quantity of compounds produced, yielding large but generally low quality libraries. This initial foray led to the conclusion that the two primary indicators of success are quality and diversity. The former refers to both purity of the compounds and the defensibility of their intellectual property. It is improved by more efficient purification techniques and the use of more novel, proprietary intermediate sources. The latter is a result of scaffold and building block selection, which is limited by the available supply to the chemists.

Many pharmaceutical manufacturers became frustrated with the lack of return on combinatorial drug design methods and abandoned the concept almost entirely. However, others, including Novartis, began an emphasis on parallel synthesis, a derivative of combinatorial chemistry that addresses the problems discussed above. Parallel synthesis is thought to add value in all stages of drug development form hit finding to lead optimization.

Parallel synthesis relies highly on a readily available, high quality selection of proprietary and commercial compounds. The focus of this thesis is to evaluate the functionality of the reagent and chemical intermediate supply and storage for chemical synthesis, in order to enable a faster and more effective collection, distribution and storage of commercial and proprietary building blocks and reagents.

Currently, about 1 out of 10,000 compounds that are prepared in the optimization process eventually becomes a new drug. Better filtering in the early stages of development helps to alleviate exponentially greater per compound costs at the later stage, leaving resources for focusing on the truly promising leads. However, Research and Development expenditures for BioPharmaceutical companies reached an estimated USD 51.3 Billion in 2005[22]. Figure 4 illustrates growing cost of Research and Development as a function of sales. The research and development path is illustrated generally in Figure 6 and more specifically for Novartis in Figure 5. It typically takes 10 – 15 years to go from initial discovery to FDA approval[23].

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[22] Source: Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2006.* Washington, DC: PhRMA, 2006, 47.
[23] Ibid.

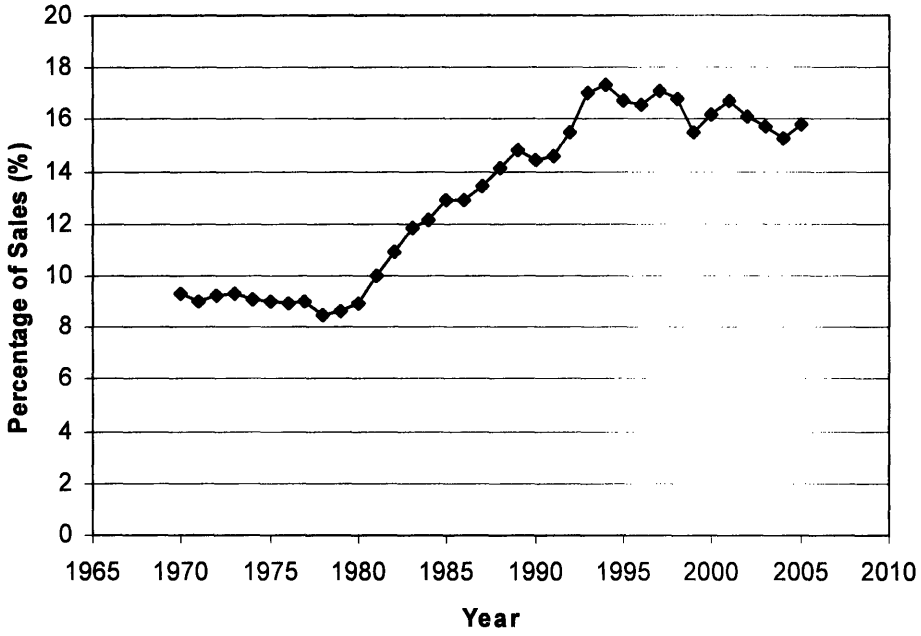

Figure 4 - R&D costs for PhRMA Member Companies[24]

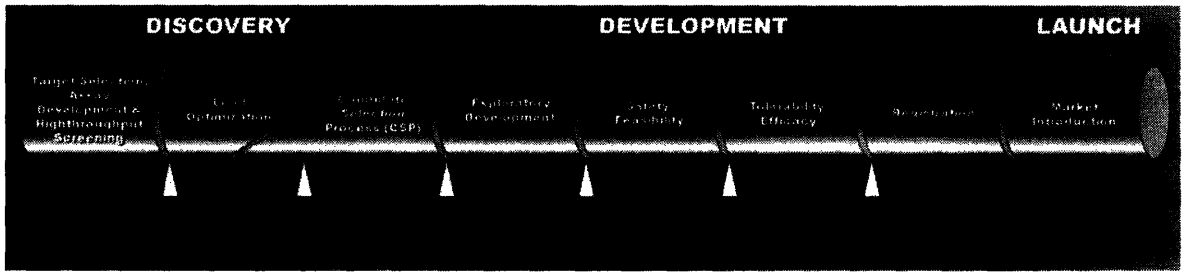

Figure 5 - Drug Discovery and Development process at Novartis[25]

[24] Ibid.
[25] Source: Novartis NIBR web site < http://nibr.novartis.com/OurScience/drug_discovery.shtml>

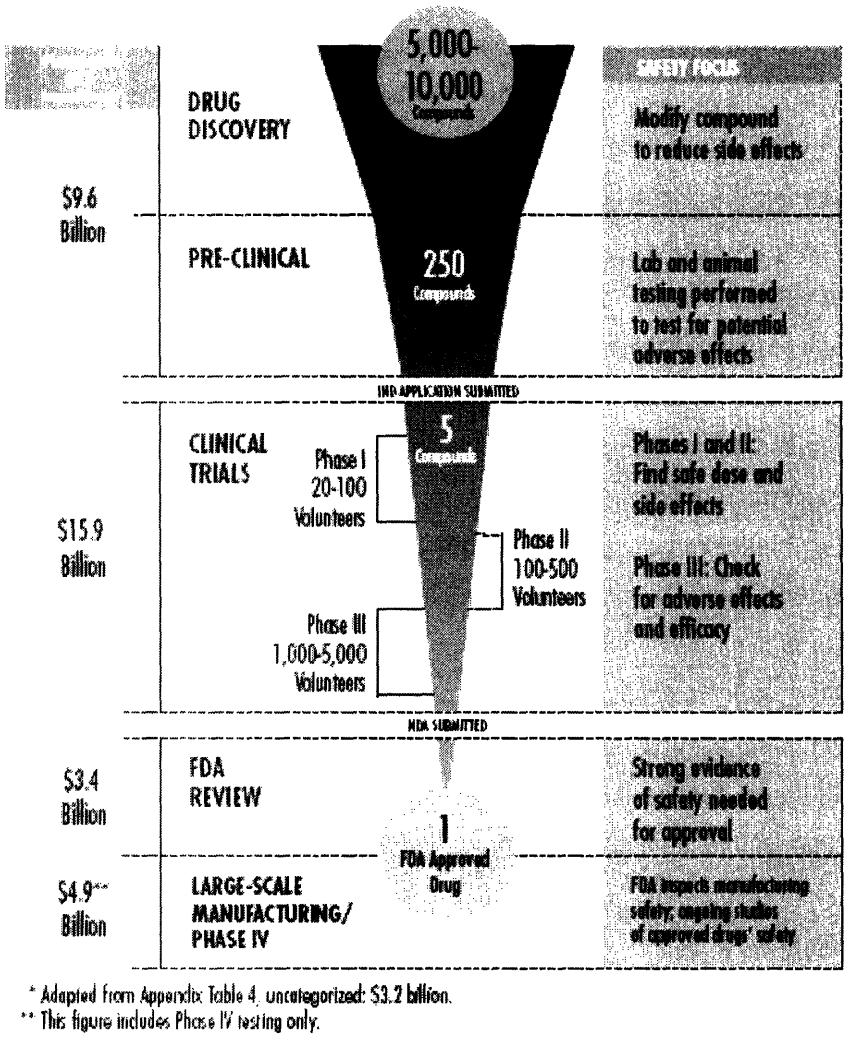

Figure 6 - The journey from hit to drug[26]

3.2 Target Selection

The first step on the path of the classical, bottom-up approach to drug discovery and development is target identification and selection. A target is generally described as a therapeutic area for an affliction that currently does not have a satisfactory remedy. The four types of targets for small molecule therapeutic agents are proteins, polysaccharides, lipids and nucleic acids. Figure 7 depicts the most common targets for small molecule orally administered drugs. The most common target, an enzyme, is a protein that acts as a highly specific catalyst in cell metabolism. More recently pharmaceutical companies

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[26] Source: Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2006.* Washington, DC: PhRMA, 2006, 47.

have begun to target kinases. Novartis has done groundbreaking work in this field, culminating in the discovery of Gleevec. The second most common target, G-protein coupled receptors (GPCRs), sit on the cell wall and allow information from outside the cell to be transported into the cell. Typically, a ligand attaches to the receptor cite external to the cell, causing a change in physical conformation of the GPCR. This leads to a release of a G-protein on the inside of the cell. Most drugs that target GPCRs act to either inhibit or stimulate the receptor.

There are two minimally necessary requirements for classification as a target; (1) it must be druggable and (2) it must be linked to a disease. Drugability is the term coined for a target that can be modulated by a ligand that has the appropriate bio-physico-chemical properties and bioavailability for development into an effective drug[27].

A recent study illustrated that of the 30,000 genes in the human genome, approximately 3,000 might be druggable and about 3,000 are disease modifying. However, the overlap of these properties is expected to yield only between 600 and 1,500 targets.[28] In fact, it is estimated that all drugs currently on the market target less than 500 biomolecules[29].

The typical large pharmaceutical company generally focuses on between 30 and 50 targets at a time. As shown in Figure 8, target selection is considered from many angles, including business strategy, research strategy and patient demand[30]. The Novartis Institutes for BioMedical Research takes the following approach to target selection, which highlights the importance of understanding the mechanism of a disease and therapy:

> "We determine which diseases to focus our research efforts on based on two questions: Do we have or can we gain significant understanding of the cause or "mechanism" underlying the disease, and does this disease represent a significant unmet medical need in human well-being?"[31]

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[27] Source: Bleicher, Konrad H. et al. "Hit and Lead Generation: Beyond High-throughput Screening." Nature Reviews – Drug Discovery. 2, May 2003, 369-378.
[28] Source: Hopkins, Andrew and Colin Groom. "The druggable genome." Nature Reviews – Drug Discovery. 1, September 2002, 727-730.
[29] Source: Drews, J. "Drug discovery: A historical perspective." Science. 287, 2000, 1960 - 1964.
[30] Much of the general information for this section is taken from Knowles, Jonathan and Gianni Gromo. "Target Selection in Drug Discovery." Nature Reviews – Drug Discovery. 2, Jan 2003, 63-69.
[31] Source: NIBR web site < http://nibr.novartis.com/OurScience/drug_discovery.shtml>

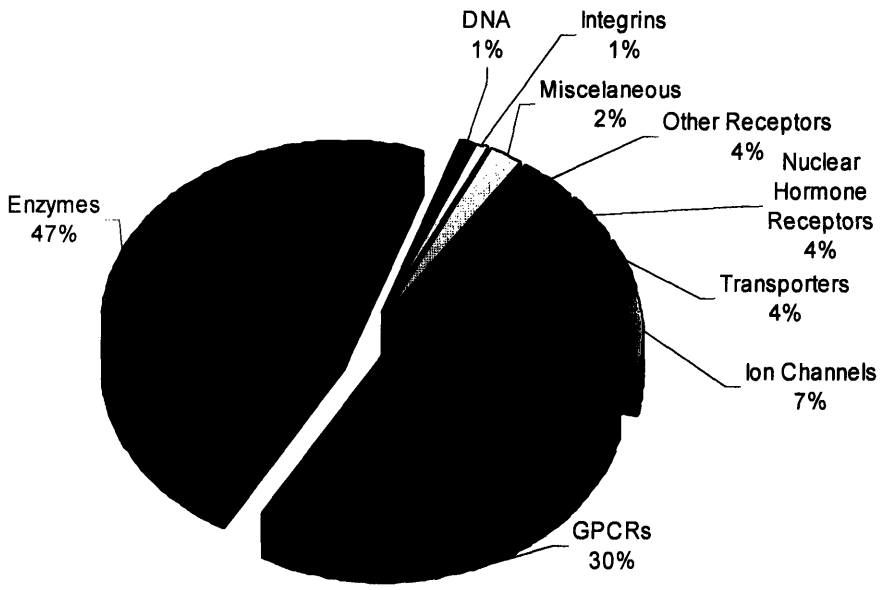

Figure 7 - Drug Targets[32]

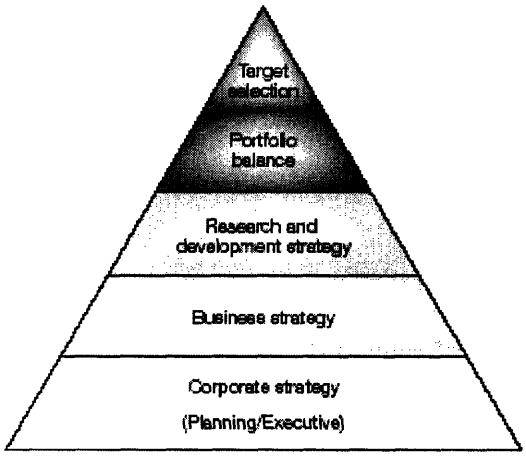

Figure 8 - Considerations for target selection[33]

3.3 Hit Finding and Optimization

A hit is defined as a compound that has been filtered for consideration in a biological assay by showing significant and selective activity against a target and is believed by experts to show potential for

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[32] Source: Hopkins, Andrew and Colin Groom. "The druggable genome." Nature Reviews – Drug Discovery. 1, September 2002, 727-730.

[33] Knowles, Jonathan and Gianni Gromo. "Target Selection in Drug Discovery." Nature Reviews – Drug Discovery. 2, Jan 2003, 63-69.

becoming a drug. Given an indicative biological assay, the principal method of finding and optimizing hits utilizes high-throughput screening (HTS). An initial screen for hits, compounds that are found to be active and selective beyond a predetermined threshold against the target, is generally run. Leads are selected from the lists of hits and are further modified and retested until they exhibit the appropriate behavior. Leads can also be inspired by natural products or result as the product of a molecular modeling effort.

3.3.1 Bioavailability and ADME

Bioavailability is a term that describes the percentage of an administered dose of a drug that reaches the target. To measure absolute bioavailability (F), one first plots blood plasma concentration versus time for a dose of the drug taken both via the preferred method and intravenously, where intravenous introduction is, by definition, perfect bioavailability. The ratio of the area under these curves (AUC), scaled to the dosage size, is the absolute bioavailability of the drug administered by the tested method.

$$F = \frac{AUC}{AUC_{IV}} * \frac{dose_{IV}}{dose}$$

When considering drug potency it is important to consider the shape of the plasma concentration versus time curve rather as well as the area of the curve. Typically, an effective drug will have a curve that peaks fairly quickly, and has mostly dissipated within 24 hours. This allows a drug to be amenable to a daily dosage regimen and reduces the potential for overdose.

ADME is the process of absorption, distribution, metabolism and excretion of a pharmaceutical compound within the body.

Absorption is a measure of the uptake of the drug into the bloodstream and can be predicted by several physical and chemical properties, including aqueous solubility, ionizability, and lipophilicity. *In vitro* tools such as the CaCO-2 assay, which measures the drug permeation through cells that simulate the gut wall, are also often used[34]. Often absorption is the rate limiting step for bioavailability.

Distribution is a measure of transfer through the bloodstream and into the tissue and organs.

Metabolism is the transformation of the drug compound, generally in the liver. Typically, metabolites are produced by oxidation, hydrolysis and conjucation. The metabolites may or may not be pharmacologically active. Though some limited success can be had predicting metabolism from chemical

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[34] Source: Guttendorf, Robert J. "The Emerging Role of A.D.M.E. in Optimizing Drug Discovery and Design." <http://www.netsci.org/Science/Special/feature06.html>

structure, most assessments of metabolism are made using *in vivo* experimentation such as tests using liver redox enzymes, called cytochromes P450.[35]

Excretion is the removal of compounds from the body, generally in urine or feces. Incomplete excretion can cause accumulation of foreign substances, which can hinder metabolism.

During the hit to lead process and further drug development, ADME, and consequently bioavailability, must be optimized. First, sample libraries can be filtered using derivative rules of thumb, such as the "Rule of 5" and "Rule of 3" described below.

3.3.2 Drug-like and Lead-like

The terms drug-like and lead-like describe critical attributes such as selectivity, activity and ADME. Drug-like compounds resemble a potential final product, while lead-like compounds are candidates for further optimization. It is generally agreed that optimization is a net additive process that results in larger, more lipophilic compounds. Drugability is often estimated using the "Rule of 5" championed by Christopher Lipinski, formerly of Pfizer Inc[36]. This set of guidelines received its name from the observation that all of the criteria are set at multiples of five. The "Rule of 5" predicts poor absorption and, consequently, poor oral availability. The "Rule of 3" is an extension of the "Rule of 5" that is used as a guideline to filter non-lead-like compounds. It essentially provides a stricter filter to allow for manipulation during lead optimization. The exclusion criteria for both sets of guidelines are listed in Table 4.

[redacted]		
clogP	≥ 5	≥ 3
Number of Hydrogen bond donors	≥ 5	≥ 3
Number of Hydrogen bond acceptors	≥ 10	≥ 3
Molecular Weight	≥ 500	≥ 300

Table 4 – "Rule of 5" and "Rule of 3" exclusion criteria

In the table above, "clogP" is the calculated value for the log of P, the partition coefficient. P is the ratio of the concentration of the un-ionized compound in a non-polar organic phase, typically 1-octanol, to the concentration in an (polar) aqueous phase. The logP is generally calculated because it is an inexpensive, quick and relatively reliable way to obtain the value for a large number of compounds. If the compound is highly ionizable than it is necessary to use D, the distribution coefficient, rather than P, for

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[35] Ibid.

[36] Source: Lipinski, Christopher A., et Al. "Experimental and computational approaches to estimate solubility and permeability in drug discover and development settings." Advanced Drug Delivery Reviews. 46, 2001, 3-26.

evaluation. D is the ratio of the concentration of the compound in the organic phase, to that of a buffer solution of the ionized and un-ionized drug. This test is dependent on the pH of the buffer so it is not easy to compare logD values across experimental teams that do not follow the same procedures.

1-Octanol is used in calculating logP because it resembles the lipids that form mammalian cell membranes, which contain a polar head group and a non-polar tail. In the cell, the pair of non-polar tails on the lipid are attracted to each other and to the pairs of non-polar tails on other molecules. Similarly, the polar heads are also attracted to each other, creating a lipid bi-layer around the cell as illustrated below. If the logP is too high, then the drug will not be soluble in an aqueous solution and will not be able to pass through the lipid bi-layer in the gut. However, it should also be noted that if the logP is too low, than the drug will not be lipid soluble and will be unable to pass through the bi-layer.

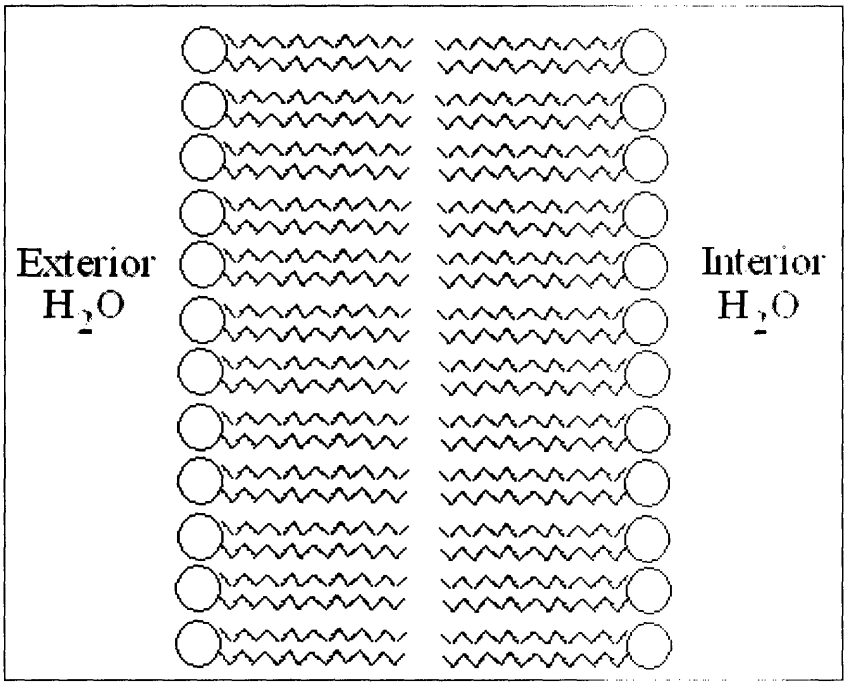

Figure 9 - lipid bi-layer

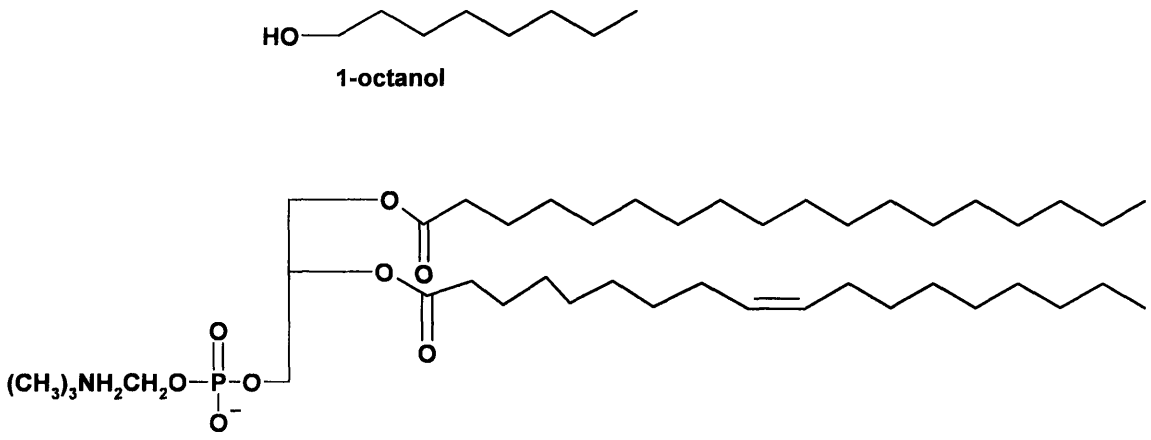

Figure 10 - 1-Octinol is similar to a mammalian cell membrane lipid

3.3.3 Combinatorial and Parallel Chemistry

Combinatorial chemistry is typically used as a high-throughput technique for producing a large set of compounds for screening. The fundamental principal of combinatorial chemistry is the geometric combination of various analogs of starting materials. If it is assumed that Material A has three analogs and Material B has three analogs, then the combination of Material A and Material B will lead to nine possible combinations.

A1 + B1 → X1	A1 + B2 → X2	A1 + B3 → X3
A2 + B1 → X4	A2 + B2 → X5	A2 + B3 → X6
A3 + B1 → X4	A3 + B2 → X5	A3 + B3 → X6

Early combinatorial chemistry technique involved synthesizing and testing large mixtures of unpurified compounds. However, this technique often led to false positive and negative results. Additionally, upon discovery of a hit, researchers were faced with the troubling task of discerning the active compound in the mixture. After purification these compounds were often found to have lost their activity.[37] The need to correct this shortcoming led to the advent of parallel chemistry, also know as high-throughput chemistry (HTC).

A hit that has been uncovered through HTS, drug design, or some other method rarely has exactly the desired properties for drug candidacy. Consequently, its properties are refined and optimized, often using the techniques of parallel chemistry. Drug candidates can be simply described as comprised of a backbone scaffold that supports one or more active functional groups, often called residues. Parallel

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[37] Source: Edwards, Paul J. "The Impact of Parallel Chemistry in Drug Discovery." IDrugs. 9, 2006, 347-353.

chemistry is a general description of the techniques used to produce large numbers of backbone and residue combinations. Parallel chemistry involves creating large numbers of structurally related, but physically isolated, compounds. Often, Structure-Activity Relationships (SAR) and target knowledge of the target are used for smarter design, resulting in smaller and smarter libraries as shown in Table 5.

Large Pharmaceutical	173	28,400
Medium-sized Pharmaceutical	104	4,100

Table 5 - Pharmaceutical Library Size[38]

3.3.4 High-throughput Screening

High-throughput screening (HTS) and ultra high-throughput screening (uHTS) are methods for *in vitro* testing of large numbers of compounds in solution to find activity against and selectivity for a specific target. Some assays also check for bio-availability and toxicity. HTS consists of highly automated assays that typically perform simultaneous checks. Contemporary formats typically use 96, 384, and 1536 well plates.

The compounds for the initial hit-finding screen are generally taken from a large screening deck of several hundred thousand compounds. Modern compound libraries, such as the Pfizer collection, can contain up to five million compounds from both commercial and, preferably, proprietary sources. In the early days of HTS, the goal of the administrators was generally to maximize the number and diversity of compounds in the archive. However, this tended to provide a significant number of hits that were doomed from the beginning because of one of a number of quality problems such as low purity or insufficient uniqueness for intellectual property protection. General problems, such as molecular weight drift, also tended to occur within the libraries, causing a general tendency for the compounds in the libraries to lack oral availability, as predicted by the "Rule of 5".

When early HTS yielded sub-standard results, focus was changed to maximizing the drug-like and lead-like features of the compounds in the library. Administrators of the libraries began instituting specific rules for entry that barred compounds with specific types of functional groups, high molecular weight, or other filtering criteria. Novartis, for example, requires all candidate compounds to pass a set of

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[38] Source: Kuhl, Philips L. "Best Practices in High-Throughput Chemistry." C.H.A. Pathways. 4, 2004.

three exclusion principals[39]. Internally synthesized compounds only need pass the first two, while purchased compounds must pass all three. The principals are the following:

- Substructure filters for non-drug-like properties or other undesirable properties
- Compounds that are not stable in solution with DMSO or water
- Compounds with sub-structures that are abundant in the library or commercial catalogues

3.3.5 Rational Drug Design

As an alternative or supplement to high-throughput screening, leads can sometimes be developed through statistical or mechanical inference. This is the case when the function and structure of a target are understood in detail. This method generally uses computational chemistry and molecular modeling along with biological, chemical and structural data to model small molecule interactions with targets *in silico*, meaning with a computer. Computer Aided Drug Design (CADD) is used in many phases of drug design. In target selection, CADD can help assess drugability, and modelers can help to understand and interpret the detailed results from in vivo pharmacology. Most of these predictions are verified using Quantitative Structure Activity Relationships (QSAR).[40]

QSAR makes the fundamental initial assumption that compound activity is a function of a combination of physiochemical properties and structural properties. Hence, similar molecules will display similar activities. QSAR predictions are generally made either by mining existing data to make an prediction of behavior for an untested compound. A historical example of this technique was the prediction of the boiling point for alkanes in the late 1800's based on the makeup of their carbon chains.

3.4 Pre-Clinical Testing and Drug Application

Eventually, if a viable compound has been produced, it will go through a multi-year series of pre-clinical trials where the acute and long-term toxicity of a drug is tested. Formulation studies are initiated and analytical and chemical development is started. In parallel, animal tested is initiated in rodents and other species. One out of every fifty compounds that enter pre-clinical trials is successful[41]. For the ones that do, an investigational new drug (IND) application must be submitted to the FDA for approval before clinical trials can begin.

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[39] Source: Schopfer, U. et al. "The Novartis Compound Archive – From Concept to Reality." Combinatorial Chemistry & Hight Throughput Screening, 8, 2005, 513-519.
[40] Source: "What do those modelers do?". <http://nibr.novartis.intra/news/2006/09-26_cadd.jsp>
[41] Source: Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2006.* Washington, DC: PhRMA, 2006, 47.

3.5 Clinical Trials

Finally, the compound enters three phases of clinical trials. The overall time a compound spends in clinical trials before becoming a drug is now an average of 8.6 years[42]. Phase I trials are generally performed on 20 to 100 healthy patients to verify the safety of the drug. Phase II trials are performed on about 100 to 500 patients that are afflicted with the target disease to examine effectiveness. Finally, Phase III trials are performed on a large-scale set of 1000 to 5000 subjects and are used to check for unwanted side effects and verify efficacy and dosage levels. Even after passing all the previous tests, one half of all drugs that reach Phase III compounds eventually fail[43]. Success in the trials leads to the quest for FDA approval, after which the drug can be manufactured and sold.

3.6 Conclusion

It is generally recognized that the cost of drug development increases significantly with each step in the drug development pipeline, as illustrated in Figure 11. Additionally, discovering a false lead early eliminates the cumulative costs of all the successive stages of development. Consequently, it is extremely valuable to drug developers to optimize the upstream processes to deliver the maximum number of drug candidates while successfully filtering as many false leads as possible.

The following chapter discusses the approach taken in the research leading to this thesis, the methodology used, and the metrics for success.

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[42] Ibid.
[43] Ibid.

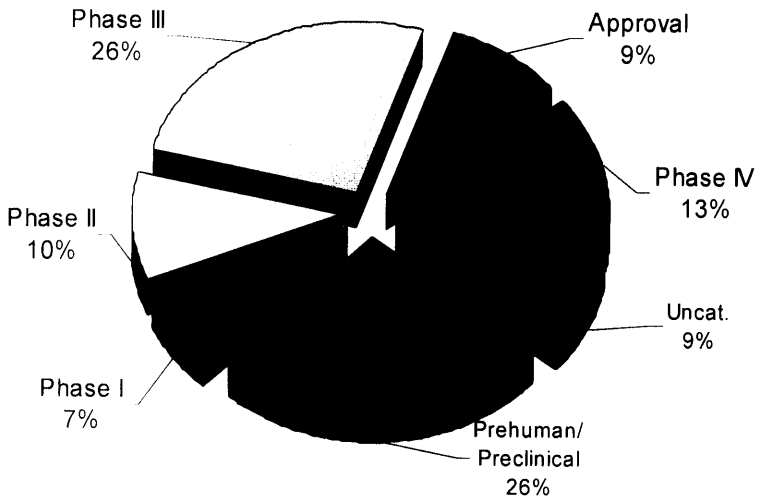

Figure 11 - Typical Drug Development Costs[44]

[44] Ibid.

4 Project Scope and Approach

4.1 Project Setting

The research for this thesis took place within the Chemical Libraries (CLI) team in the Lead Synthesis and Chemogenetics (LSC) unit in Basel, as shown in Figure 12. One of the tasks of CLI is Chemicals Management, specifically "to efficiently and cost-effectively provide researchers access to commercial and proprietary chemicals in order to save time and resources."[45]

The typical customers of Chemicals Management are within the Global Discovery Chemistry platform, but also include scientists from other platforms and from the Disease Areas. Though local chemists are the primary users of the chemical libraries, they are expected to be able to serve customers in a variety of locations around the globe. Hence, compound management requires global utility that can benefit a wide variety of physically dispersed customers.

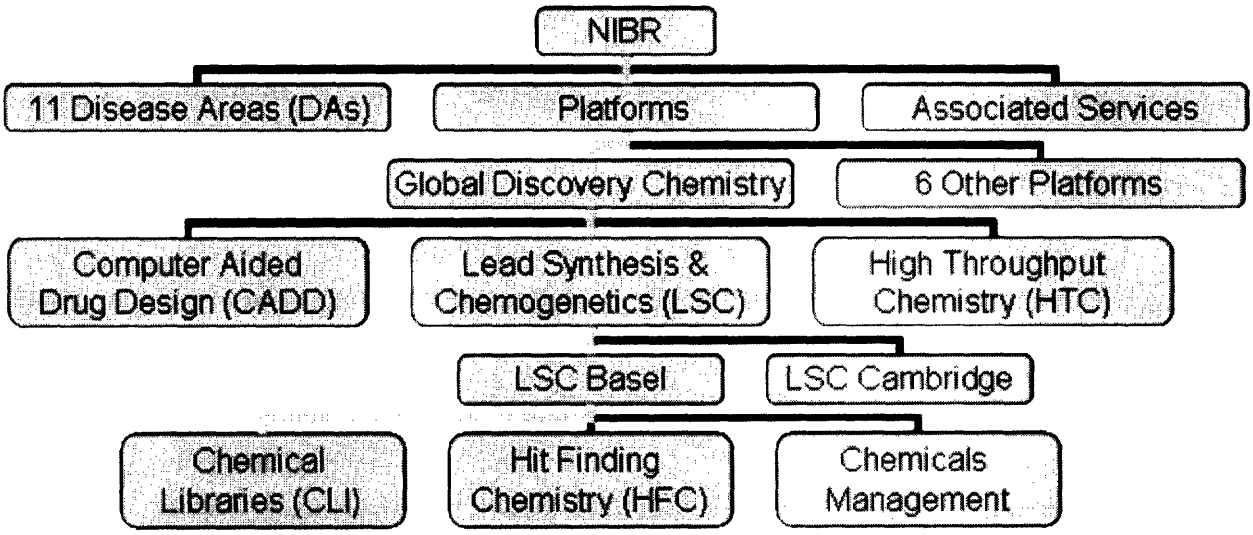

Figure 12 - NIBR Organizational Chart

4.2 Goals for Internship

The goal of this internship was to approach the Chemicals Management processes as an outsider and to identify areas for potential improvement in the ordering, storage, and delivery of chemical

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[45] Source: Chemicals Management homepage <http://nibr.novartis.intra/GDC/LSC/chemmanage.jsp>

compounds. The research took a two-pronged approach; the first goal was to look at current practices from a near-term tactical viewpoint and the second was to look at the long-term strategic direction of the group.

The short-term investigation looked at the current processes that were being used for acquisition of new compounds for the archives, storage of these compounds, and delivery of the compounds to the customer. The scope of the processes included, the customer ordering experience, the information technology system used, the workflow in the archives, and the sharing of information of compound between various archives and Novartis sites. The following major goals were specified:

- Determine the viability of automation of the storage and distribution of chemical reagents in the archives
- Suggest the optimum location and quantity of archives on the Basel site
- Evaluate the operations of the archives and suggest short-term improvements as well as long-term design improvements
- Determine the best point to make compound sourcing decisions

The long-term evaluation focused on creating an initial design for a compound archive as part of the Novartis Campus Project. The Novartis Campus Project is a program to redesign the Novartis Basel campus and create an academic university-style environment. As part of this project, the buildings that are currently housing archives will no longer be available and the archives will be moved into a newly constructed building.

4.3 Approach

The general approach taken in this project was to learn as much as possible about the system and its current state, evaluate possible improvements to the system, critique the evaluations, and finally discuss potential implementation. Because this research considered largely long-term changes, it was not possible to become involved in implementation of changes, with the exception of improvement projects that were currently underway at the outset.

The specific approach is as follows:

Step 1 was to have preliminary informal discussions with the operators and customers of the current archives and labs, observe daily use and operation of the archives and associated software and engage in an initial survey of associated literature.

Step 2 began with a medicinal chemistry course to further understand the day to day activities of chemists and to gain further appreciation for the effects of materials properties on the processes involved in

building block and intermediate delivery and storage. This was followed with further literature review, an appraisal of the Information Technology (IT) systems that support the compound libraries, and a study of automation systems that can be used for chemical storage and retrieval.

Step 3 included mapping the workflow in the Novartis Intermediates Archive and developing a system dynamics model for evaluating benefits gained from improvement projects. This model was further bolstered from data gained from a usage survey of customers.

Step 4 was an investigation into possible improvements by analyzing the process maps and visiting competitor facilities.

Step 5 was to utilize the knowledge gained from the first four steps to produce a recommendation for the design and operation of an archive as part of the Novartis Campus Project.

5 Service Overview

5.1 Compound Management Options

There are several ways that a chemist can acquire chemical reagents and building blocks. The most significant options that are internally managed by Novartis are the on-campus stockrooms. Chemicals Management has defined the following three types of stockrooms:

Novartis Chemical Stockrooms (NCS) – These stockrooms store commercially available compounds that are "overstock". They are searchable via the CIMS/SciQuest database tools.

Novartis Intermediates Archives (NIA) – These archives store reaction intermediates that are not commercially available. They are searchable via the CIMS/SciQuest database tools.

Building Blocks Archives (BBA) – These archives contain a specially picked selection of both commercially and non-commercially available reagents that are desired for their parallel synthesis friendly properties.

In addition to the three types of archives listed above, chemists have several other sources to select from for their reagents. Several groups have developed their own local archives that are accessible only within those groups. Of course, labs keep small collections of frequently used compounds in local stores. These compounds can also be shared with neighboring labs on an informal basis. Occasionally, small amounts of some useful compounds can also be retrieved from the backup solid storage archive for the Novartis Compound Archive (NCA), but this is a rare occurrence.

If a compound is commercially available, it can be ordered from a commercial supplier. Commercial providers are divided into two tiers, labeled Preferred Vendors and non-Preferred Vendors. Preferred vendors are generally more convenient sources because they offer a negotiated discount, have more automated ordering processes, and maintain more up-to-date catalogues with Novartis. Non-Preferred Vendors are generally found by searching the Elsevier MDL Available Chemicals Directory (ACD) or by searching standard vendor catalogs. Though it recently switched from semi-annual to quarterly updates, the ACD is still a lagging data source and often contains erroneous information. Similarly, vendor catalogs are generally not updated frequently.

If none of the above resources provide the necessary compound and the chemist cannot determine a suitable substitute, than s/he may need to synthesize it from precursors. This can be done within the lab or by labs that specialize in compound synthesis as a service to other labs. Either way, this method is costly in time and resources.

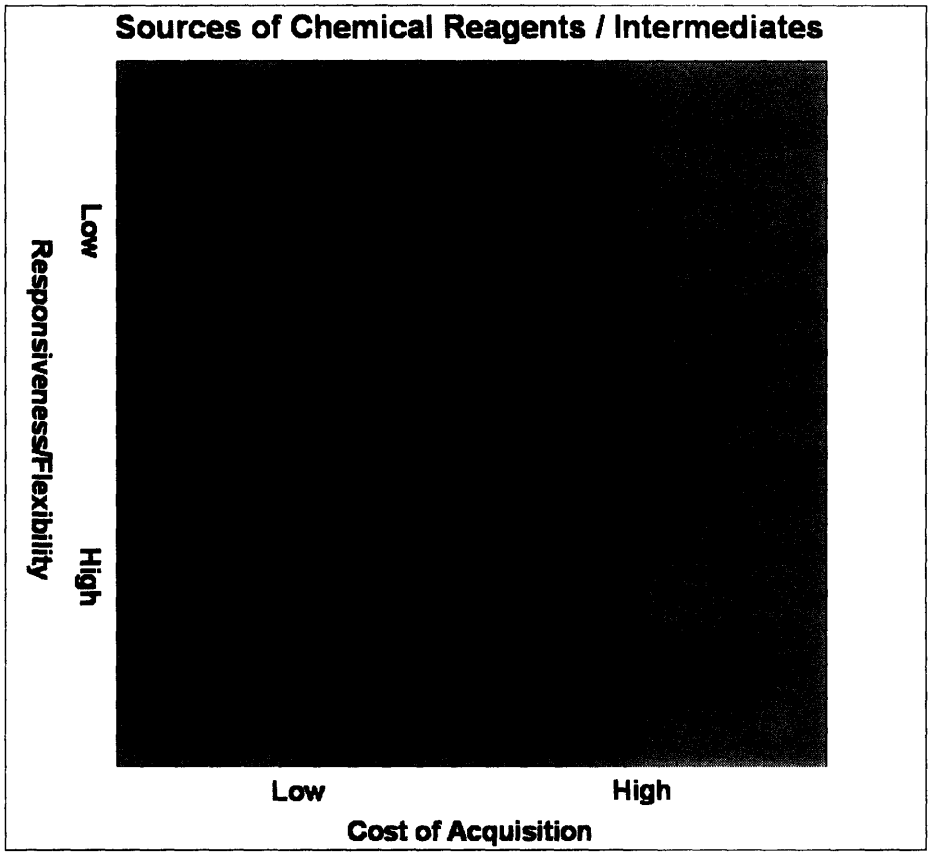

Figure 13 – Reagent Acquisition Options

It should be noted that these labels and the distinctions between them are somewhat fuzzy. The legacy definition of a building block as synonymous with an intermediate is often used. In fact, what is currently called the NIA was previously called the BBA. Also, the NIA has many compounds that belong in the NCS under this taxonomy. When a compound is registered it is often a proprietary compound, but becomes commercially available sometime after commercial registration. Figure 14 depicts the various compound classifications and the overlap among them.

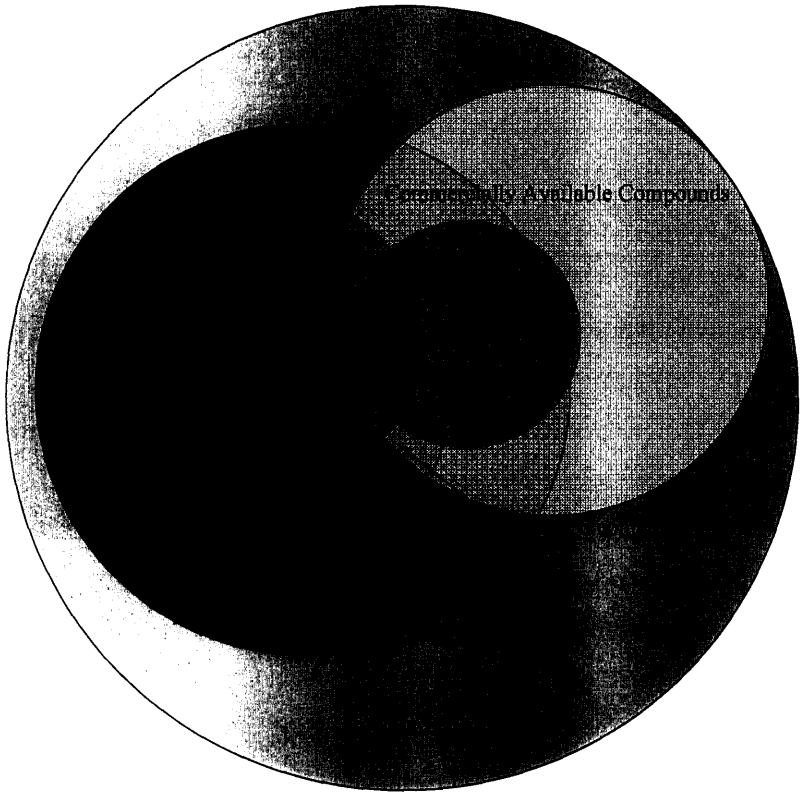

Figure 14 - Compound space

5.2 Compound Search Methods

5.2.1 Local Archives

The two principal database search tools that are used to access chemical reagents are CIMS and SciQuest. SciQuest is used in Cambridge and CIMS is used in the European locations. During this internship, the European sites are in the midst of a transition from CIMS to SciQuest. Consequently, this internship will focus on workflow utilizing the SciQuest system.

The introduction of SciQuest provides a number of significant possibilities for improving compound management. The principal difference between SciQuest and the legacy CIMS system is that the SciQuest database is indexed by bottle while the CIMS database is organized by compound. When a bottle is checked out in the SciQuest system, ownership is transferred to the user so that others determine where a compound is located. SciQuest also allows user to have her own local collections of compounds tracked with the system and users can dispose of bottles that they have emptied.

5.2.2 Commercial Compounds

If a compound cannot be procured from the local archives, then the lab begins a search of the commercial vendors. Approximately 80% of commercially fulfilled compound orders are satisfied through a select group of about ten preferred vendors. These vendors provide regularly updated catalogs and negotiated pricing, saving the labs both time and money. For any compounds that are not available from one of the regular commercial vendors, the labs must search through retail databases and catalogs. This can be a very time consuming and frustrating process.

The online catalog that is used by NIBR is the Available Chemicals Database (ACD), provided by Elsevier MDL. Users can search by structure, name, or CAS Registry Number. This database provides quarterly updates, but the catalog is generally further out of date because many of the vendors fail to update their inventory lists. Additionally, many vendors are in the habit of listing compounds as in stock when they have not been synthesized. This leads to significant delays in delivery to the customer.

Several other indexes exist, including ChemCATS from CAS and ChemACX from CambridgeSoft. ACD is generally regarded as the most thorough and complete database, but the author considered the value of joining the databases to provide an even more thorough list. Unfortunately, there is no common format for the databases and there are usage restrictions for some. CAS, for example, only allows interfaces to ChemCATS through their proprietary search applications, such as SciFinder. Additionally, increasing the size of the database would not necessarily improve the quality of information provided by the vendors. This can only be done through specific agreements with preferred vendors.

5.3 Customer Locations

Global Discovery Chemistry has approximately 770 lab heads and associates throughout the world. This is a good general approximation of the population size and demographics of the Chemicals Management group. Figure 15 illustrates the number of lab heads and associates by location.

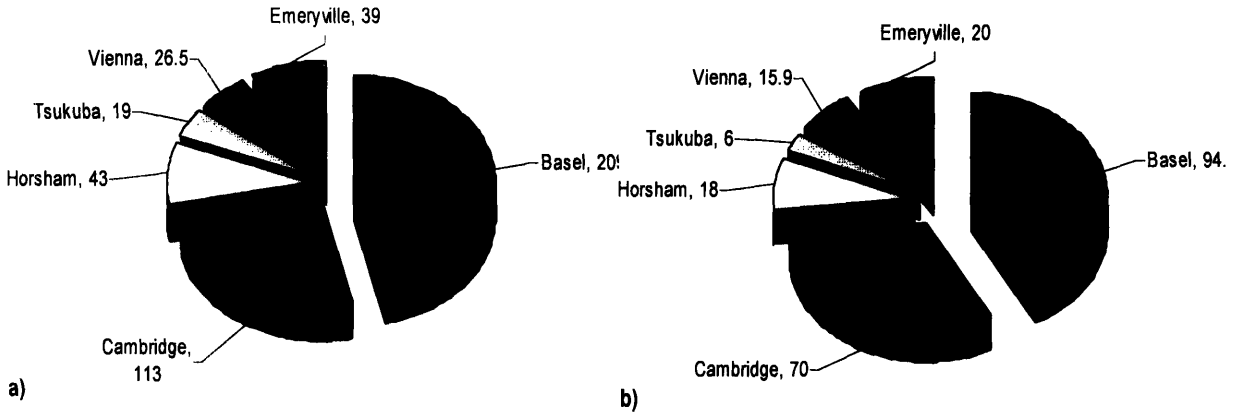

Figure 15 - a) GDC associates by location and b) lab heads by location

5.3.1 Basel, Switzerland

Because it is the oldest and largest location, Basel has the most thorough and complicated compound storage facilities. NIBR has a presence in the St. Johann and Klybeck sites in Basel, which are separated by the Rhine river. The Basel NIA is located in a building in Klybeck, the former Ciba-Geigy site, along with a small NCS which is manned but allows self-serve usage. The larger NCS is located in St. Johann, the former Sandoz site. There are also several small, restricted stockrooms located throughout the campus.

Basel runs the CIMS system for compound search and ordering but is currently in the process of upgrading to a SciQuest system.

Deliveries between the campuses are handled by a third party contractor. All compound orders from vendors are also delivered to the contractor for check-in and then are distributed directly to the proper lab or archive for use.

5.3.2 Cambridge, Massachusetts

The Cambridge site is designed from scratch and is not burdened with the legacy layout that complicates compound acquisition in Basel. Hence, the intermediates archive and compound storeroom share a common location that is easily accessible to all labs.

Cambridge was the pilot facility for the new SciQuest system and has been using it for a while.

A single archive acts as a storage location for all compounds in Cambridge. Unfortunately, this archive is burdened by size constraints. Additionally, it is currently maintained by a contract service that staffs the archive with employees that do not have knowledge of chemistry. Novartis has had difficulty

keeping the lab staffed with personnel that have a chemistry background because there are not sufficient career advancement opportunities.

5.3.3 Horsham, England

The Horsham facility has a central storage area that has been estimated to contain between 12,000 and 14,000 compounds but is not actively maintained. Compounds are initially checked in, but the record is not updated after the initial receipt.

Horsham also uses the CIMS system, though there are no central archives to order compounds from. CIMS is used for ordering commercial compounds and for ordering compounds for delivery from Basel and Cambridge. The Horsham site is also in the process of an upgrade to the SciQuest system.

5.3.4 Vienna, Austria

There is no central storage in Vienna. All the compounds for each lab are handled by the lab directly. Some informal sharing of compounds occurs between labs.

Currently, there is a manually maintained database of bottles contained at the site. However, there is no barcode on the bottles to sort between them. Additionally, the database is considered unreliable because it is not always updated as bottles are used and disposed. The Vienna site will also be upgraded to the SciQuest system so that many of these deficiencies are addressed. It is estimated that there are approximately 30,000 containers in the Vienna site.

5.4 Current Utilization

The pie chart in Figure 16 illustrates the origins of 759 orders from the NIA in Basel for the first quarter of 2006. It is clear from this chart that the vast majority of orders from the Basel NIA come from within the Basel community. This can be explained by a couple of factors. First, because the different sites use different, unconnected IT systems, it is difficult for a scientist in Cambridge or Vienna to search the compound archives in Basel. Second, shipping can be difficult. Samples larger than a gram are subject to strict customs scrutiny in the United States and chemists often do not want to risk the potential problems of shipping an unknown and unlabeled compound overseas.

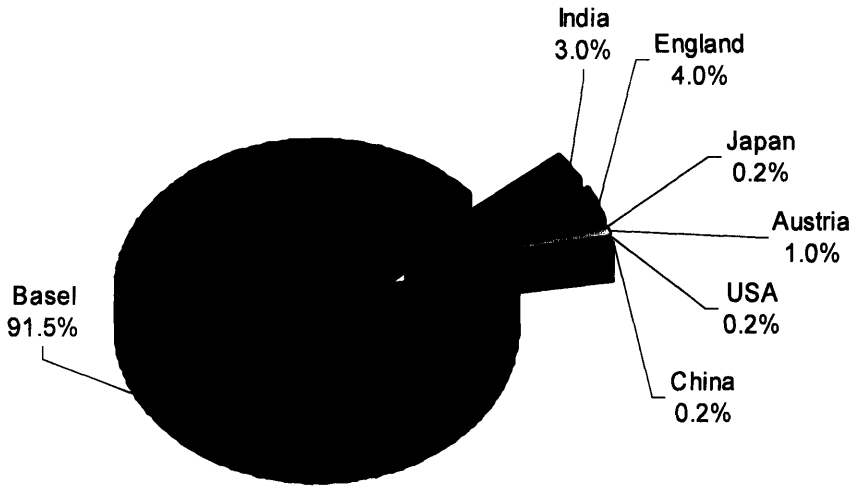

Figure 16 - Origin of orders from NIA for Q1, 2006

The Novartis Intermediates Archive in Basel delivered 2710 compounds, or 10.5 per workday, in 2005 as shown in Figure 17. 1952 of these orders, amounting to 7.5 per workday, required metered dispensing in the archive and the other 758 were shipped as full bottles. Additionally, the NIA had 694 returns and 7934 new registrations, for a total of 8628 deposits, or 33.2 per workday, as shown in Figure 18. Compounds are rarely disposed unless the containers are leaking irreparably.

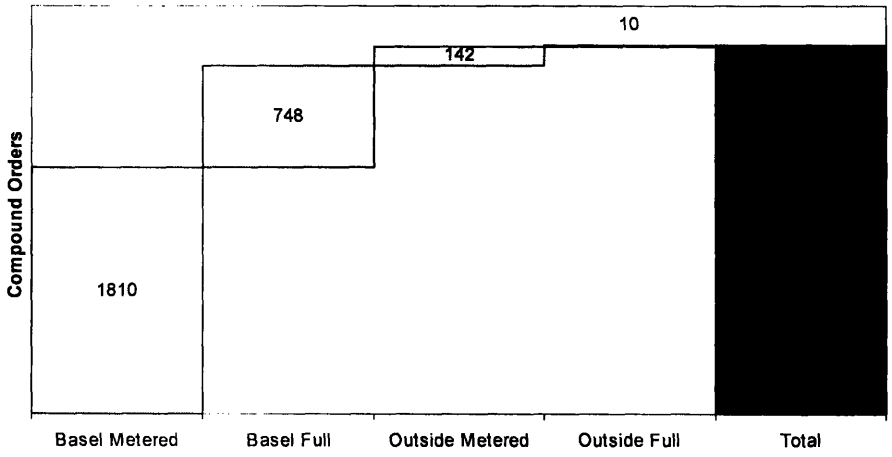

Figure 17 - NIA compound withdrawals 2005

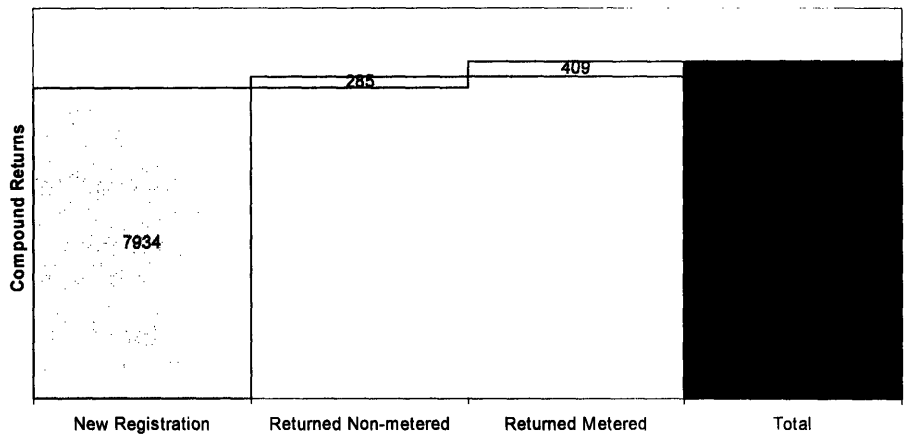

Figure 18 - NIA compound registrations 2005

The Novartis Chemical Stockroom sent 8260 compounds, or 31.8 per workday, to its customers in 2005. This is shown in Figure 19. It also received 7558 returns and registrations in 2005, averaging 29 per workday. Additionally, the NCS disposes of approximately 2000 compounds per year, or 7.7 per workday. Currently, the NCS does not handle metered dispensing of custom weights.

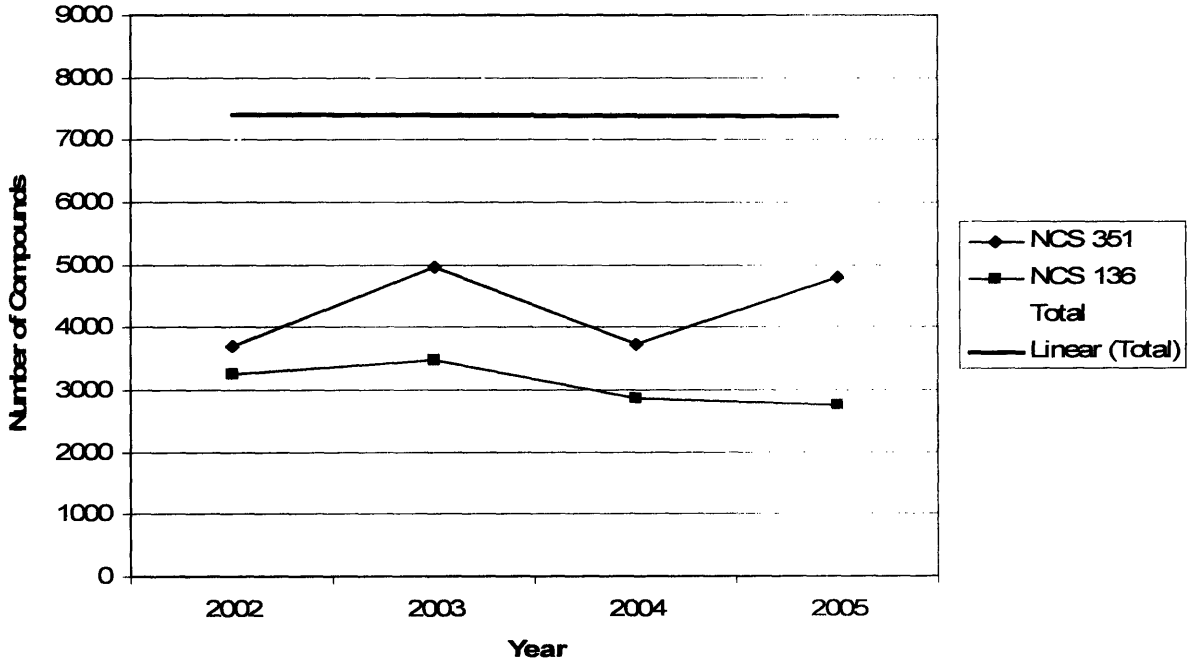

Figure 19 - NCS compound deposits

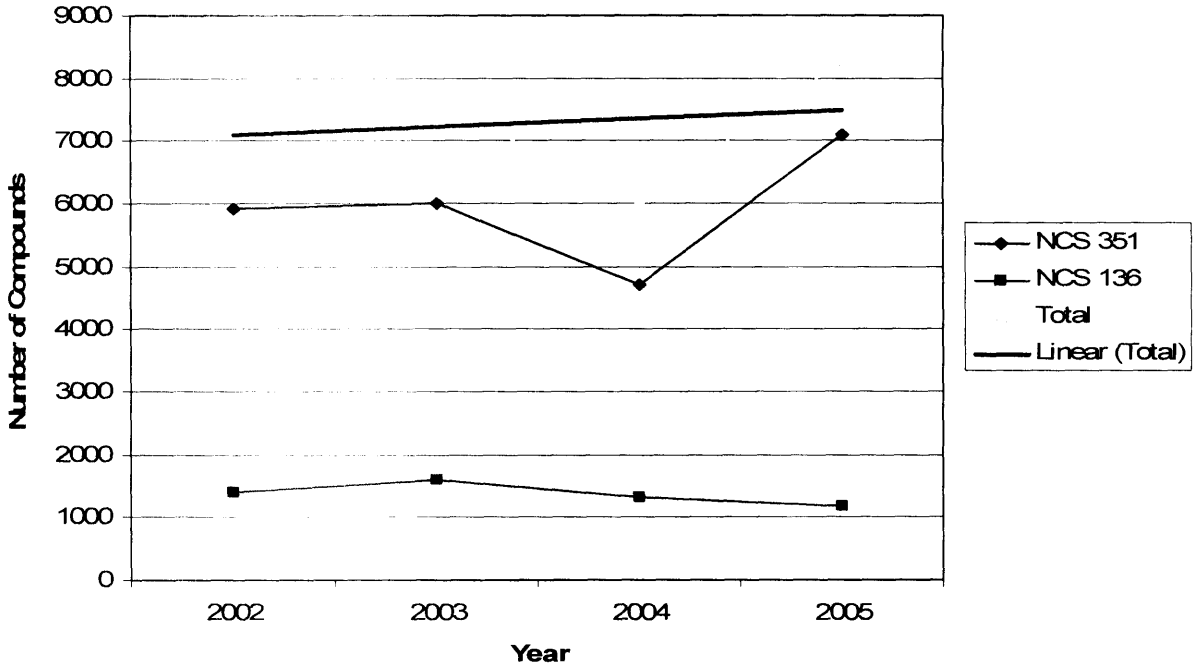

Figure 20 - NCS compound withdrawals

6 Evaluation of Improvement Opportunities

6.1 Determination of Value

The appropriate measure of value of any process and, consequently, any improvement project on that process, is the benefit that the customer derives from the process that s/he would not have experienced without the process. As discussed in the seminal book Lean Thinking[46], this customer-oriented view ensures that resources will not be wasted on activities that in no way enhance the end product. It is very important to engage in discussion with the customer to avoid needless optimization of qualities of a product or service based on the provider's often antiquated view of value, rather than the actual measure of value from the consumer of the good or service.

In the case of the compounds management team, the customers are largely chemists. The reward systems within Novartis for chemists vary by group but generally exhibit the same characteristics. They reward primarily on the number of compounds delivered within a predetermined time frame and place secondary emphasis on ensuring that some percentage of the synthesized compounds are used as precursors for later stage compounds. This secondary metric is important because increasing the quality of early drug candidates has a significant impact on cost and effort downstream, where the discovery costs per compound are much larger. Consequently, any investments in compound management should work toward the goal of improving the customer's ability to quickly synthesize structurally significant, high quality compounds.

It is helpful to view this mission within a well defined operations strategy framework[47]. The potential objectives for any operations improvement can be categorized as improving (1) cost, (2) quality, (3) delivery or (4) flexibility. Of course, cost improvements are always welcome, but it is important that this does not infringe on the customer's ability to create high quality compounds. Hence, cost is somewhat inconsequential, relative to the other three objectives. Quality is a significant parameter for the customer because increasing the quality compounds in synthesis will have an effect on the number of syntheses that fail due to low quality reactants, increasing the quantity of compounds that can be synthesized. Reagent quality also helps determine the end quality of synthesized compounds, with regard to bioavailability and intellectual property protection. Delivery time directly impacts the customer, because a quicker turnaround time allows the chemist to begin synthesis more immediately. Finally,

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[46] Source: Womack, James P. and Daniel T. Jones. Lean Thinking. New York: Free Press, 2003, 29 – 36.
[47] Source: Pyke, David. "A Note on Operations Strategy." The Amos Tuck School, Dartmouth College

flexibility is of importance because increased flexibility increases the number of potential users and, hence, the net benefit.

This chapter will discuss the results of an intensive investigation of the compound archives, including the ordering processes, the archive operations, and the compound delivery and return processes. First, the customer viewpoint will be discussed. Next, the compound ordering experience will be considered, with special consideration paid to the optimum point for sourcing decisions. After this, the workflow within the archive will be discussed. The next section will then discuss the contents of the archives and rules to optimize the library. Finally, a brief competitor analysis will be provided to compare the operations at Novartis to the state of the art elsewhere. The next chapter will provide a special focus on archive automation.

6.2 User Interviews

After sketching the ways that value can be delivered to the customer, investigations were made to quantify the value to determine the benefit of improvement projects. This was largely done with customer interviews. However, because the chemists' time is highly valued, these interviews were kept to a short and specific survey[48] to quantify the general level of satisfaction and desire for improvement followed with a few more detailed interviews to further understand how the customer used the service.

Customer interviews revealed that satisfaction with commercial compound delivery time was fairly linear in the ten to two day range as shown in Figure 21. As expected, customers tend to care less about incremental improvements outside this range. Exceptionally long delivery times have already had a significant effect on workflow by ten days and other resources tend to be limiting at one day or less. The results appear to be fairly similar for proprietary compounds, as illustrated in Figure 22, with the exception that most interviewees showed a significant drop-off in satisfaction after two or three days. This is because, with this level of delay, it now becomes attractive to synthesize the majority of compounds or find a substitute compound.

[48] The surveys conducted were short, multiple question surveys that assessed a user's satisfaction with quality with, speed of delivery from, and ease of use of the various archives. They also asked several, optional short-answer questions that inquired about potential improvements to or specific problems with the current system.

Figure 21 - Customer satisfaction with delivery time for commercial compounds

Figure 22 - Customer satisfaction with delivery time for proprietary intermediates

The general interviews show that customer satisfaction with the NIA and NCS is generally fairly high. However, there remains room for improvement. To find some of these specific areas, more focused interviews were conducted and several chemists walked the author through a typical ordering procedure.

In spite of corporate initiatives to place more compounds in general archives, the typical inclination for chemists is to hoard compounds in local storage in their labs. Every chemist has the same basic root desire to have the fastest access possible to the largest variety of compounds possible. Unfortunately, depositing chemicals to the common archive presents a variety of prisoner's dilemma. If all chemists register and deposit all of their compounds, the variety and delivery time will be optimized overall. However, if an individual chemist deposits all of his compounds, and no one else does, s/he has reduced access to his own compounds for no gain in variety or delivery time on compounds that s/he does not own. Consequently, chemists tend to choose a local optimization over a larger, global optimization.

Several customers expressed confusion about the specific process for depositing compounds to the archives. There is no specific process detailed for who is responsible for registering compounds and what libraries they should be sent to. Others were hesitant to deposit chemicals if they were not certain about the quality of the compound and did not have the time or money to test each individual compound using analytical methods such as NMR.

6.3 Compound Search and Ordering Evaluation

Figure 23, Figure 24, and Figure 25 below illustrate the compound ordering process from preferred vendors, non-preferred vendors, and archives, respectively. The sourcing decision is made in the lab using the process illustrated in Figure 26. The NIA, NCS and preferred vendors are searched simultaneously using the new SciQuest implementation, but non-preferred vendors must be searched separately, using ACD. Synthesis techniques are generally developed through literature review. The order is then sent either to the vendor directly for preferred vendors, to the purchasing group in Research Operations for the non-preferred vendors, or to the appropriate archive for processing. For non-preferred vendors, Research Operations must negotiate a delivery time and price for the desired compounds and communicate any irregularities to the lab. This can be a very time consuming and inefficient process. Similarly, the archive staff must communicate any problems with an order directly with the chemist, who will then make any new ordering decisions.

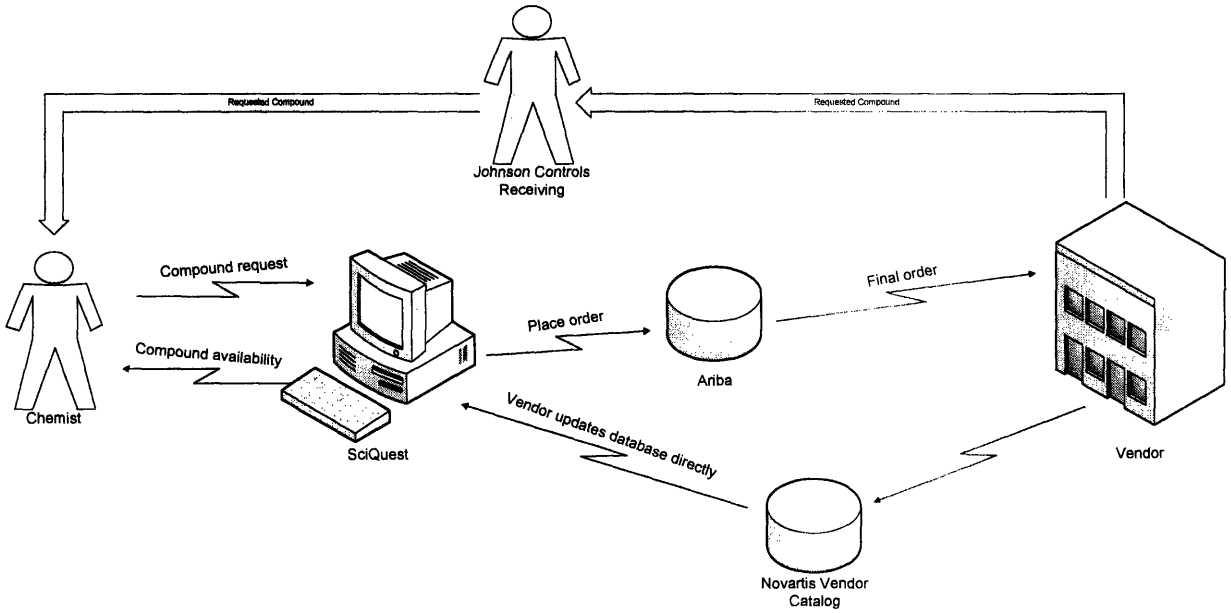

Figure 23 - Preferred vendor sourcing information and material flow

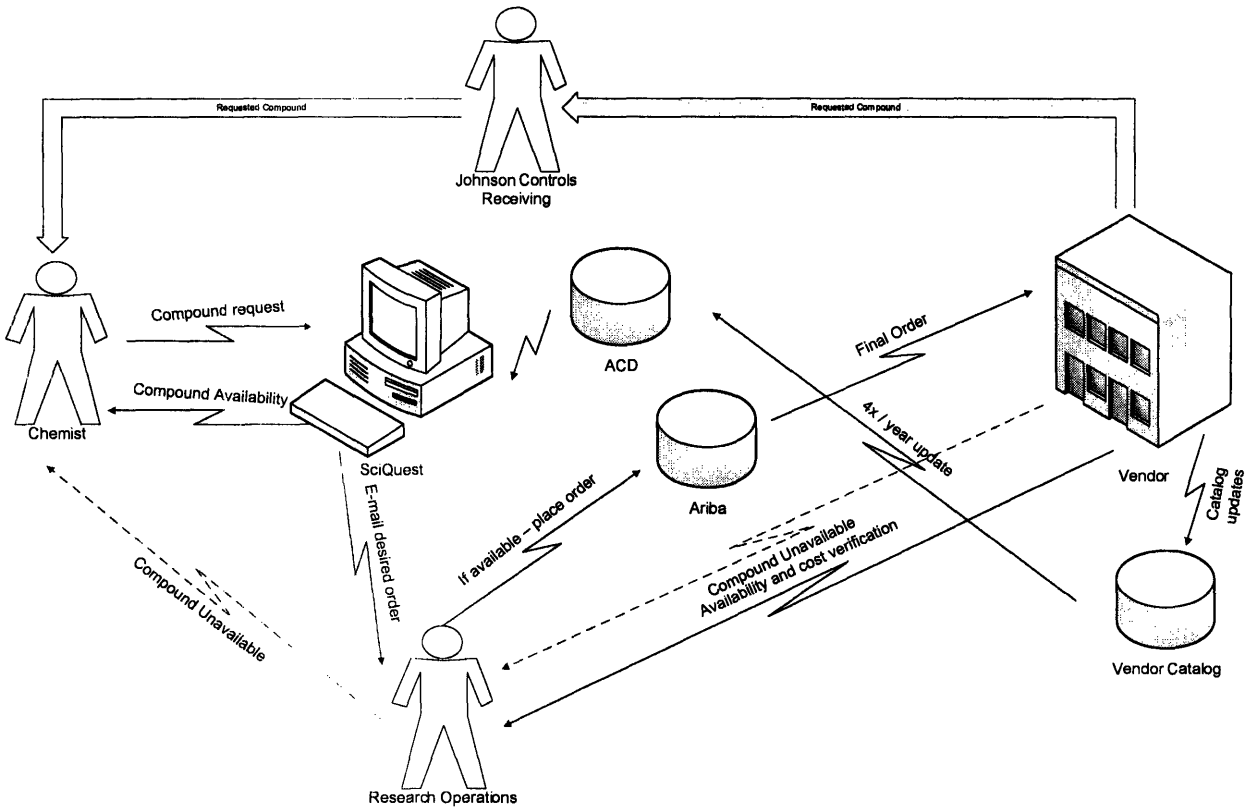

Figure 24 - Non-preferred vendor sourcing information and material flow

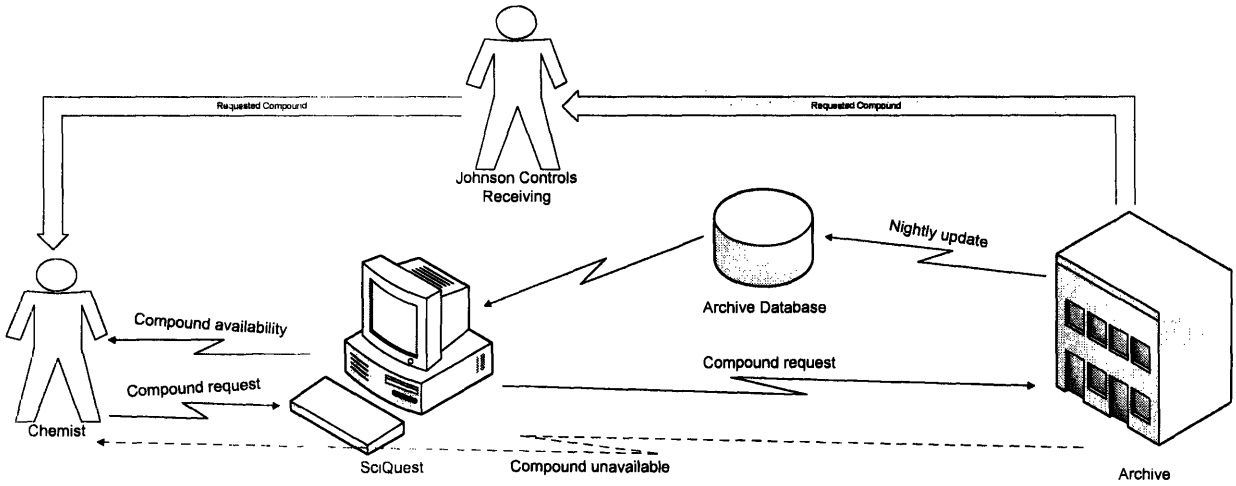

Figure 25 – Archive sourcing material and information flow

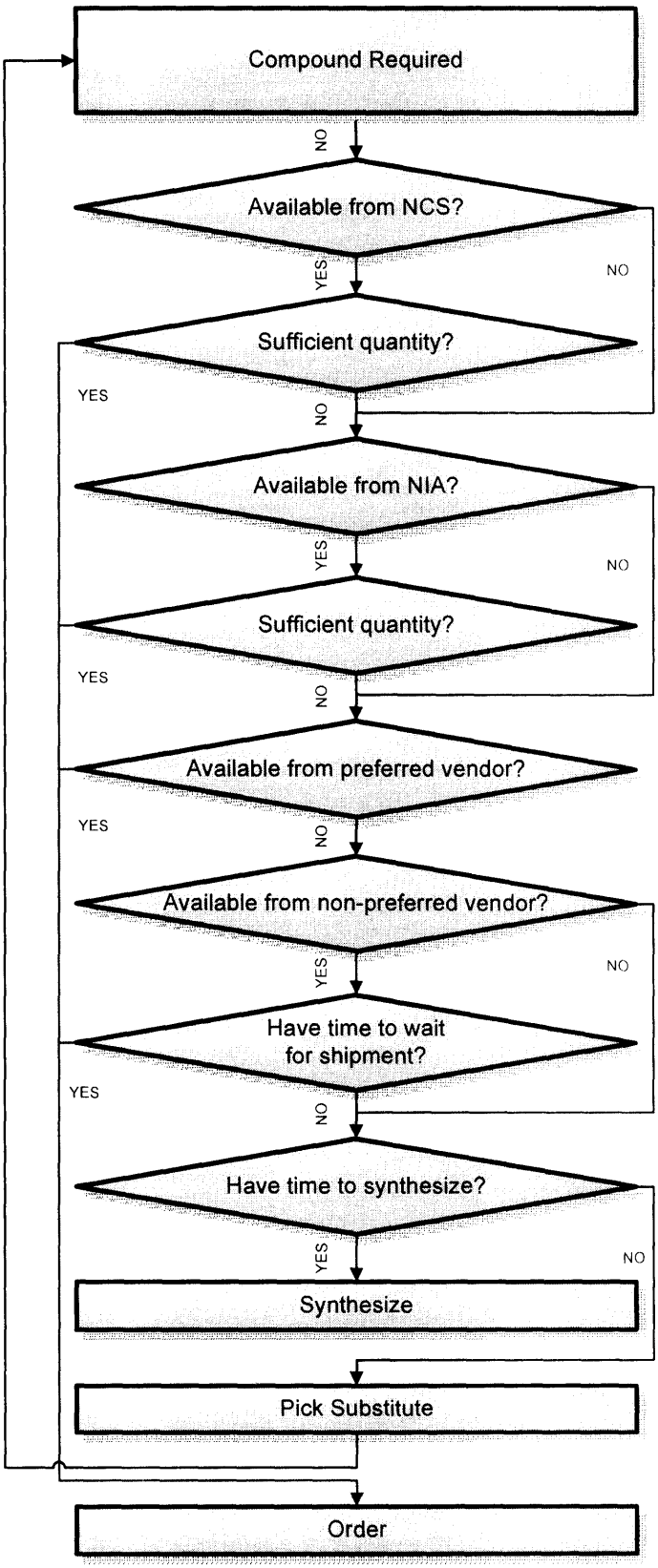

Figure 26 - Compound procurement decision tree

This procedure has several inherent inefficiencies. Ordering decisions are made in isolation in the labs, precluding any scheduling or price benefits that could be had by ordering the compounds in aggregate from vendors. Also, learning effects that would result from one person handling all of the orders, such as gaining familiarity with the more popular non-preferred vendors are lost. Additionally, basic ordering tasks are often being performed by PhD level scientists, whose time is more appropriately spent on drug discovery.

There is also a great deal of communication involved in the current ordering system when an order is delayed, a compound is unavailable, or there are problems with pricing. For non-preferred vendors, chemists or associates must negotiate with the vendor to secure the appropriate price and delivery time.

A proposed solution for this problem is illustrated in Figure 27. This solution prescribes staffing the Novartis archives with employees who have a chemistry background, but not necessarily a PhD, and are tasked with sourcing all of the compounds for all labs. The lab would supply information about the compound being ordered and the basics of its anticipated use. It would then be the responsibility of the archive staff to determine the optimum source and quantity for compound. The archive staff would be able to quickly remedy many of the pricing or delivery problems by immediately selecting a new source if the initial vendor is unsatisfactory. For more ambiguous problems, the choice would return to the lab with specifics of the problem and any alternative options, so that the lab can quickly make a decision. In addition to providing a faster response time to problems, this frees up chemists to spend their time discovering drugs rather than searching vendor databases.

There are a few potential drawbacks to this approach, however. The archives must be staffed with employees that have a reasonable knowledge of chemistry. Consequently, archive staffers will demand a higher salary. Also, steps must be taken to avoid gaming of the system by the labs. It would be tempting for every lab to assign the highest priority to all of its compound requests so that it receives undue attention from the archive. Since pricing negotiations and decisions will be made by the archive staff that impact budgets for individual labs, the archive might be temped to simply order compounds from the easiest vendor, rather than the best priced.

Most of these problems are easily remedied. The increase in salary for the archive staff will be more than offset by the improved efficiency of the scientists that no longer have to spend their days searching for compounds. To help inhibit scientists from gaming the system, rules could be implemented that limit the number of rush orders before final approval is required from a unit head. Finally, the archive performance metrics should be closely tied to the budgets of the individual labs and their year over year savings on reagent spending.

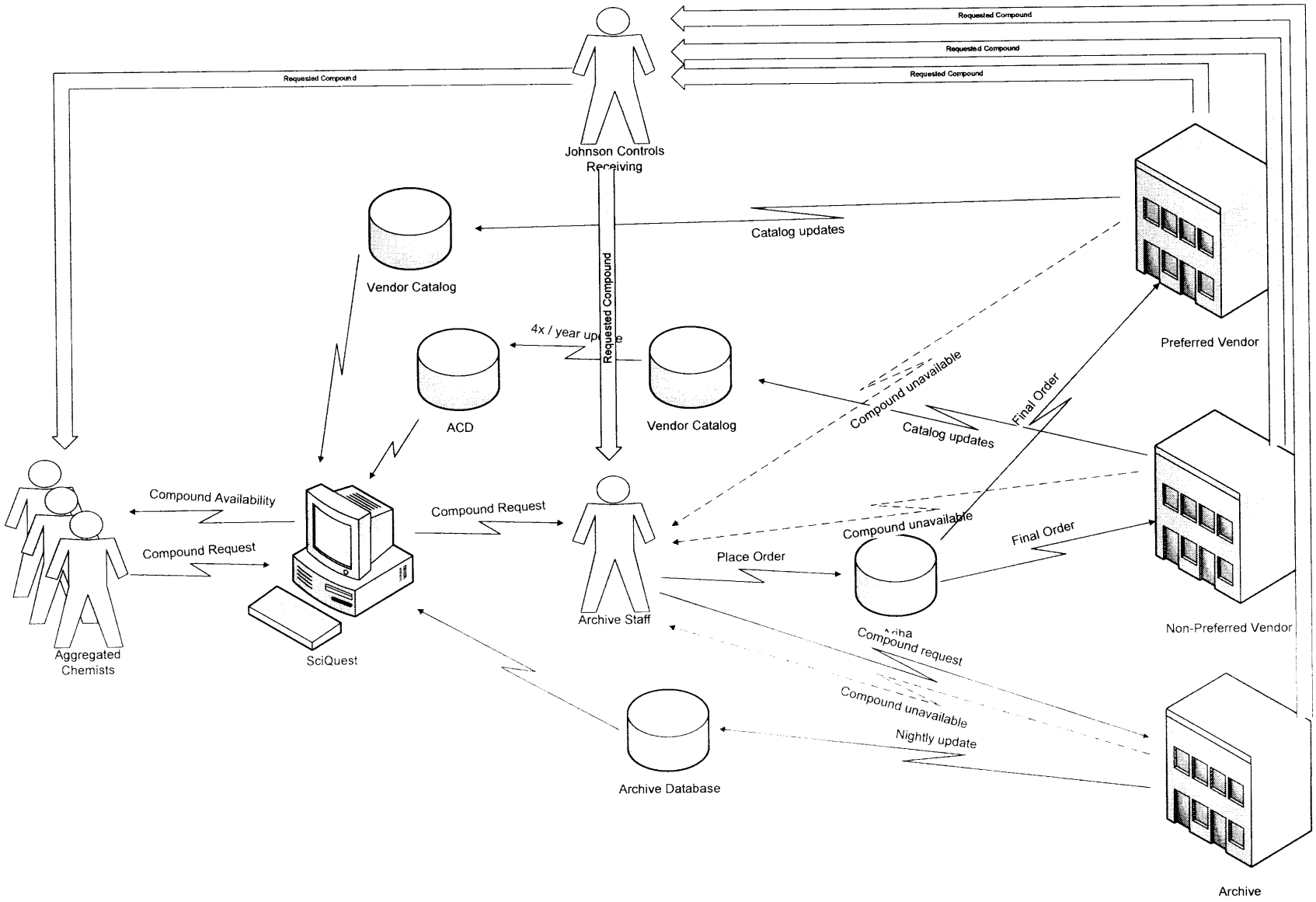

Figure 27 - Proposed solution for compound sourcing

6.4 NIA Workflow Evaluation

The Novartis Intermediates Archive in Basel was selected for a workflow evaluation because it will remain in service for several years in the future. The Novartis Compound Archive is in the process of being moved to a new location, so time was not spent on process evaluation and improvement.

The principal goal of the workflow evaluation was to discover and eliminate *muda* in the process. *Muda* is the Japanese word for waste and a key component of the Lean vernacular. Any action that does not create, or even destroys, value as defined above, is *muda*. In Lean Thinking Womack and Jones identify the eight types of *muda*, attributing the first seven to Taiichi Ohno, the legendary Toyota executive, and adding the eighth themselves. The eight types of *muda* are as follows[49]:

- Type 1 – overproduction ahead of demand
- Type 2 – waiting for the next processing step
- Type 3 – unnecessary transport of materials
- Type 4 – over-processing of parts due to poor tool and product design
- Type 5 – inventories more than the absolute minimum
- Type 6 – unnecessary movement by employees during the course of work
- Type 7 – production of defective parts
- Type 8 – design of goods and services that do not meet the user's needs

The order fulfillment process was observed for several days to gain a hands-on understanding of the exact steps that were actually implemented when filling orders. The information and material flows were then documented in a current state process map, shown in Figure 29, which was constructed with the help of the archive owner. Special attention was paid to the amount of time required for each step, the time spent in transition between locations and any safety or quality problems. Several assumptions were made in the representation of the process. While the size and daily composition of the orders is generally extremely variable, it was assumed for this example that the order consisted of 16 specific requests, 8 to be filled upstairs and 8 to be filled downstairs, that were divided amongst 5 customers. Half the samples required metered distribution.

Currently, there is more than sufficient time available for order fulfillment and the process bottleneck generally occurs in the delivery service. However, attention was paid to all steps because it is anticipated that the required throughput rate will increase as the NIA becomes more popular. As the

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[49] Source: Womack, James P. and Daniel T. Jones. Lean Thinking. New York: Free Press, 2003, 351.

delivery step is a batch process that has nearly infinite capacity, the bottleneck will eventually relocate to another step. Additionally, reducing order fulfillment time will have positive effects on other processes because the archive manager will have more time to work on compound registration and help with the Klybeck NCS. At present, a second employee works part time to register compounds in the NIA. If order fulfillment time can be reduced, than this is not needed.

The order fulfillment process begins when the archive operator checks his order database for unprocessed requests using the CIMS system[50]. This typically happens first thing in the morning when the operator begins his day. He then prints a set of labels, one for each order, and sorts them based on physical location of the source bottles, which is listed on the label, and whether the requests involve metering. He then proceeds to the storage rack and retrieves the compounds that are located in the upstairs storage, generally in order of location from furthest from scale to closest. Next, he travels to the scale, under a fume hood, and weighs out specific amounts of the compounds to be metered. This step requires him to select a destination bottle by eye. Occasionally, he chooses the incorrect bottle and is required to select a new bottle and restart the weighing process.

After he completes the upstairs orders, the archive manager travels downstairs and performs a similar operation with the compounds located in the basement. After he has selected and weighed all of the requested compounds, he then carries them back upstairs, by hand or on a cart, via the elevator. Once upstairs, he batches the two sets of orders together by location. Orders that are deliverable to local Klybeck labs are dropped off by the archive manager. If the lab is empty, he is forced to return later for a second visit. Orders that go to the St. Johann campus are put in plastic buckets with packing peanuts and the labels are taped to the outside. All the orders that are shipped outside Basel are placed together in a container to be sent to Johnson Controls central receiving for processing, packaging, delivery. All containers that are not dropped off by hand are placed on a specially labeled shelf on the building loading dock for pick up by Johnston Controls to be taken to the correct lab or to central receiving. Johnson controls generally comes twice per day, once in the early morning and once in the late afternoon.

The total process in this example from acknowledgement of the compound request until the requests are successfully hand-delivered or placed on the loading dock for pickup is approximately 72 minutes, but this time is extremely variable and difficult to predict. The size and composition of the compound request list varies largely from day to day. The number of requests that require metering drastically increases the processing time, as do any locally requested compounds that require more than one attempt for hand delivery. The amount of time between placing an order and receiving a compound

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[50] The CIMS system is currently in the process of an upgrade to the newer SciQuest system, but the fulfillment process will largely remain the same.

for a chemist varies by site. Chemists on the Klybeck sight generally receive their compounds within 24 hours, chemists in St. Johann wait between 24 and 48 hours, and chemists outside Basel wait up to a week, or longer if the compounds are held in customs.

The following problems were noted with the NIA order fulfillment process:

- *Muda* Type 4 or Type 7 - Container picking was done manually with no verification that the correct bottle was selected, leading to possible time loss due to picking the incorrect bottle.
- Safety consideration - All containers were stored in a somewhat open air environment, especially in the basement storage area, exposing the archive administrator unnecessarily to compound fumes. This is illustrated in Figure 28.
- *Muda* Type 4 - Selection of compound vials was done by eye, generally with the goal of locating the smallest vial that would fit the requested quantity of the compound. This often resulted in replacing the bottle with a more appropriate size.
- Safety consideration and *muda* Type 7 - Compounds were often carried by hand, creating potential for dropped compound bottles
- Safety consideration - Compounds were carried on the standard elevator.
- *Muda* Type 6 - Compounds in the basement and on the main floor are located a good distance from each other, causing a significant amount of wasted time moving between the two locations.
- *Muda* Type 2 - Johnson Controls pickup service was an obvious bottleneck in the process, and pickup times were inconveniently timed. The early pickup time is often before the archive can prepare compounds for delivery and the later pickup time results in compounds arriving too late for the lab to begin using them.
- Order processing time is highly variable due to uncertainty of quantity of metered compounds, uncertainty about success of hand delivery and general variations in lab work.
- *Muda* Type 7 - Packing peanuts in plastic buckets often caused compound vials to be lost. Occasionally, a lab will receive an order that has an extra vial that had fallen to the bottom and was missed in the previous unpacking.

Figure 28 - Current open air archive

A few of these problems are not easily remedied. The compound storage units are fixed and cannot be relocated without making structural changes to the building. Also, installing a special elevator for chemicals is not possible without a major structural overhaul to the building, nor is changing the compound storage system to a sealed, ventilated storage unit. However, it is important to note these problems for consideration with future archive designs.

The following proposals are designed to eliminate some of these problems and inefficiencies with the current process. An improved future state map is shown below. The numbered clouds indicate changes.

- Compounds can be checked out of the software database with a handheld barcode reader as they are removed from the storage racks. This provides an auxiliary verification that the archive manager removed the correct bottle while eliminating the possibility that a bottle is removed from storage and not checked out of the software database. (cloud 1)
- The current storage is ventilated as well as possible, but future installations should use closed, well ventilated storage systems.
- Compounds should, as a rule, be placed into a vial that is considerably larger than the expected required size. The cost difference between the vials will be more than overcome by the savings in fulfillment time by reduced errors.
- A cart can be made available for carrying compounds at all times. This cart should have a specially designed grid on the top shelf for holding various sized bottles so that they do not slide when the cart is moved.
- Rearrange delivery from Johnson Controls so that the pick up containers before lunch and at the end of the day. These pickup times would significantly reduce the amount of time that compounds wait on the loading dock. If process time is reduced sufficiently so that the archive manager can complete three cycles per day, then three pickups should be arranged near the time of completion of each of the three cycles.
- Metering of compounds can be eliminated. The new SciQuest system is able to track compounds in labs, so that they can be located when in use. Consequently, a chemist can withdraw the whole bottle, use the quantity that s/he requires, and return the bottle when finished. Other chemists will be able to locate the bottle if necessary[51]. (cloud 3)

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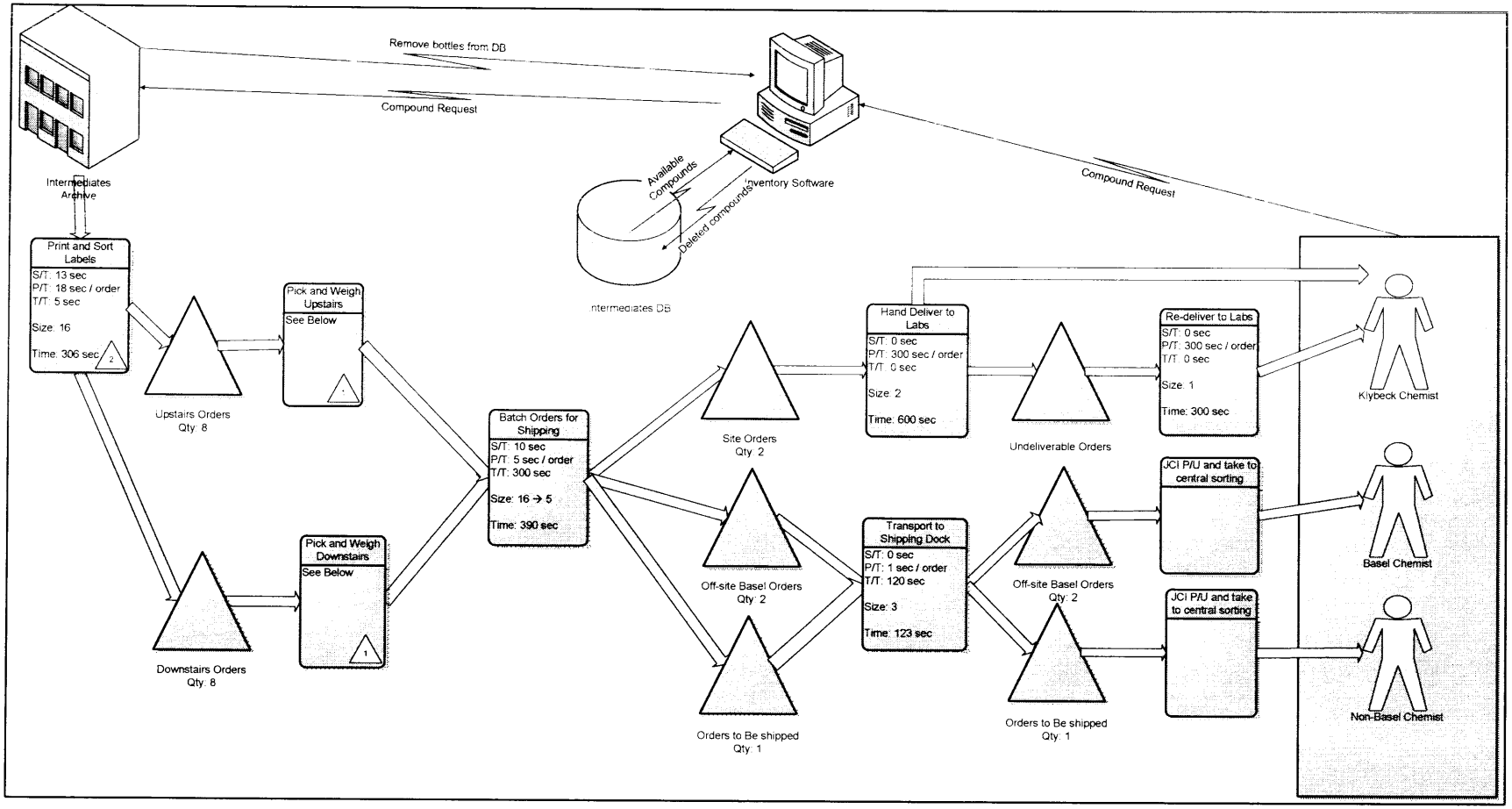
[51] A potential exception to this rule should be made for especially valuable compounds which are rationed. Also, metering is likely an appropriate solution for the future Building Block Archive

- Rather than delivering compounds by hand, the archive manager should place local orders in a general pickup depot and send an E-mail to the chemist stating that the compound is ready for pickup. This way, the chemist can arrange to acquire the compound when it is convenient for him and no time is wasted with attempts to deliver to an empty lab.
- Install foam padding in the buckets rather than packing peanuts. The foam padding can be used to protect the vials without allowing them to fall to the bottom of the bucket and become lost.


Remove bottles from DB
Compound Request
Intermediates Archive
Available Compounds
Deleted compounds
Inventory Software
Intermediates DB
Compound Request
Print and Sort Labels
S/T: 13 sec
P/T: 18 sec / order
T/T: 5 sec
Size: 16
Time: 306 sec
Upstairs Orders
Qty: 8
Pick and Weigh Upstairs
See Below
Downstairs Orders
Qty: 8
Pick and Weigh Downstairs
See Below
Batch Orders for Shipping
S/T: 10 sec
P/T: 5 sec / order
T/T: 300 sec
Size: 16 → 5
Time: 390 sec
Site Orders
Qty: 2
Off-site Basel Orders
Qty: 2
Orders to Be shipped
Qty: 1
Hand Deliver to Labs
S/T: 0 sec
P/T: 300 sec / order
T/T: 0 sec
Size: 2
Time: 600 sec
Undeliverable Orders
Transport to Shipping Dock
S/T: 0 sec
P/T: 1 sec / order
T/T: 120 sec
Size: 3
Time: 123 sec
Off-site Basel Orders
Qty: 2
Orders to Be shipped
Qty: 1
Re-deliver to Labs
S/T: 0 sec
P/T: 300 sec / order
T/T: 0 sec
Size: 1
Time: 300 sec
JCI P/U and take to central sorting
JCI P/U and take to central sorting
Klybeck Chemist
Basel Chemist
Non-Basel Chemist

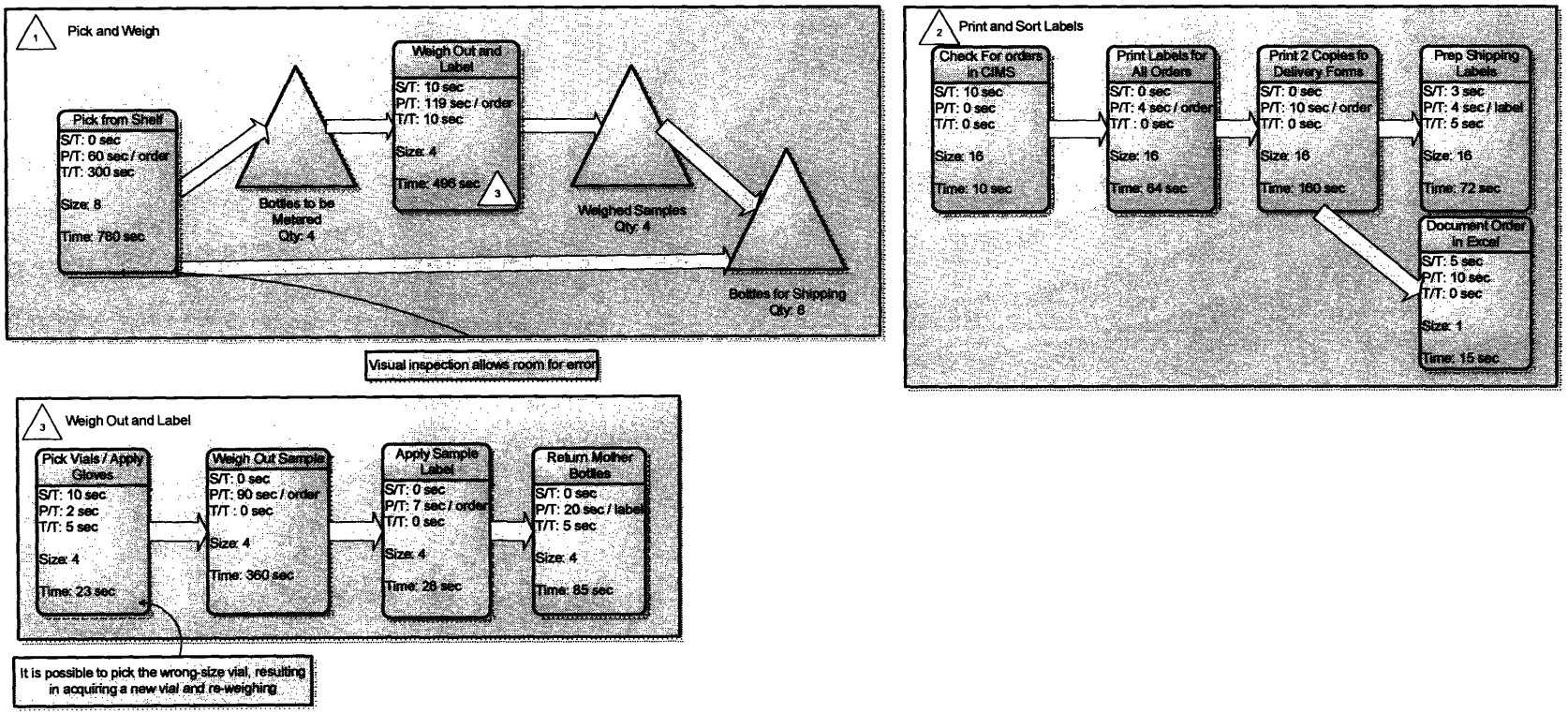


Figure 29 – NIA order fulfillment current state map

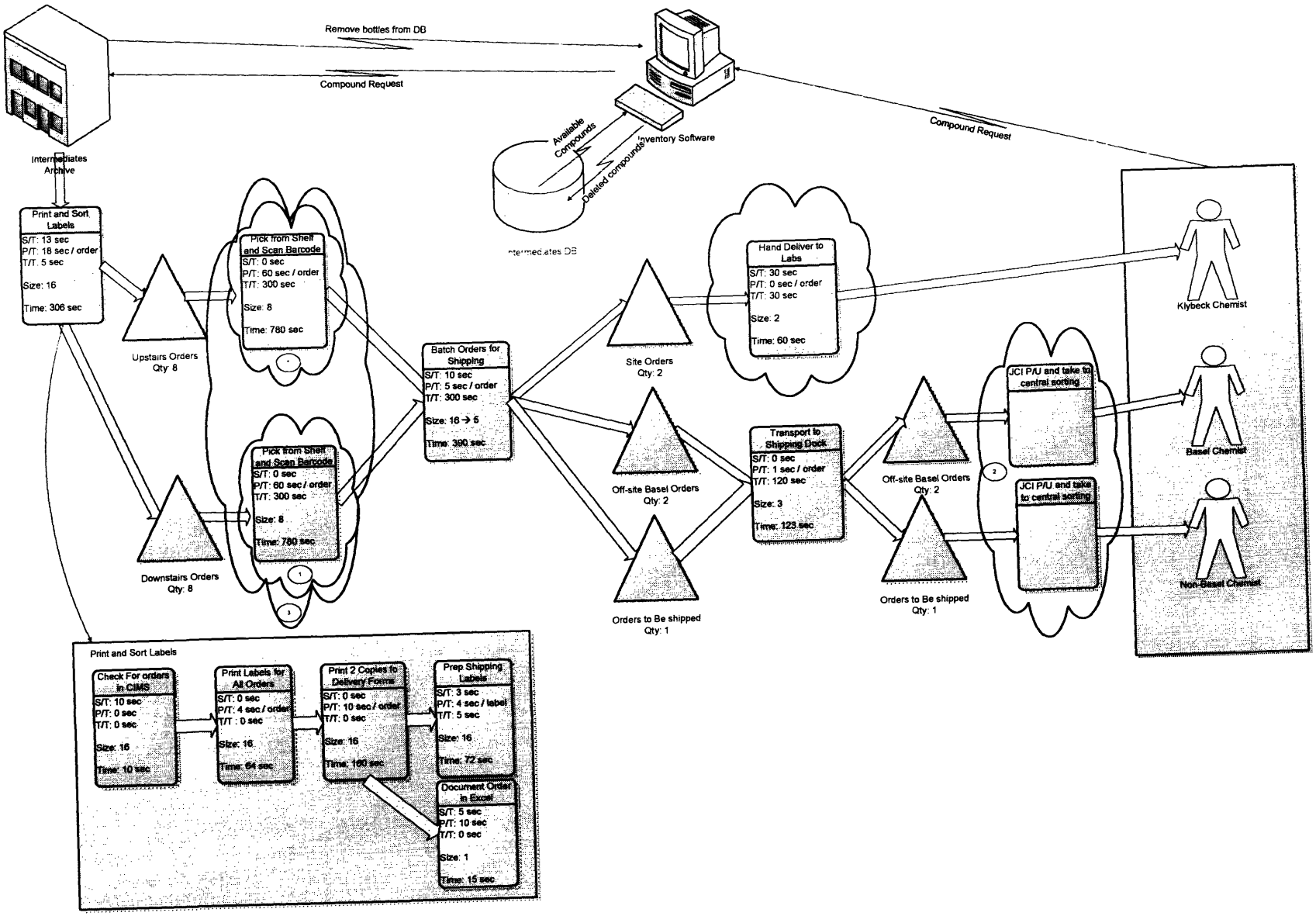


Figure 30 - NIA future state process map

Figure 31 is a travel map of the order fulfillment process. This map helps to illustrate any *muda* Type 6 and Type 3 that are inherent in the process. It is clearly obvious that locating the parts of the archive closely to each other would significantly reduce travel. Additionally, the layout should be changed to allow the operator to move in a circular fashion around the room, beginning at the computer workstation, traveling to the storage cabinets, and proceeding to the scales and packing desk. Unfortunately, the chemical storage cabinets are fixed so that their position cannot be altered, but this is important to note for future designs.

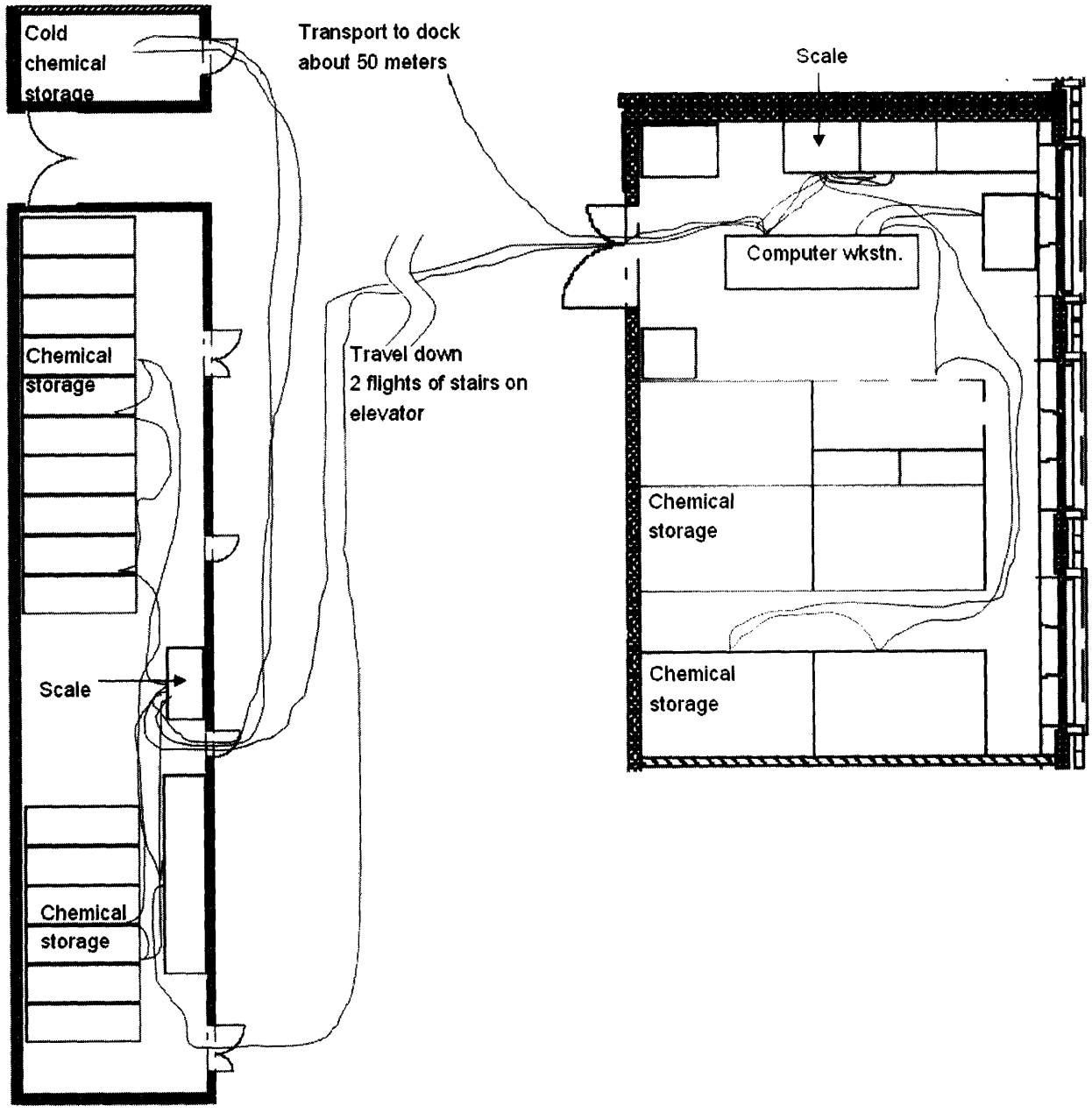
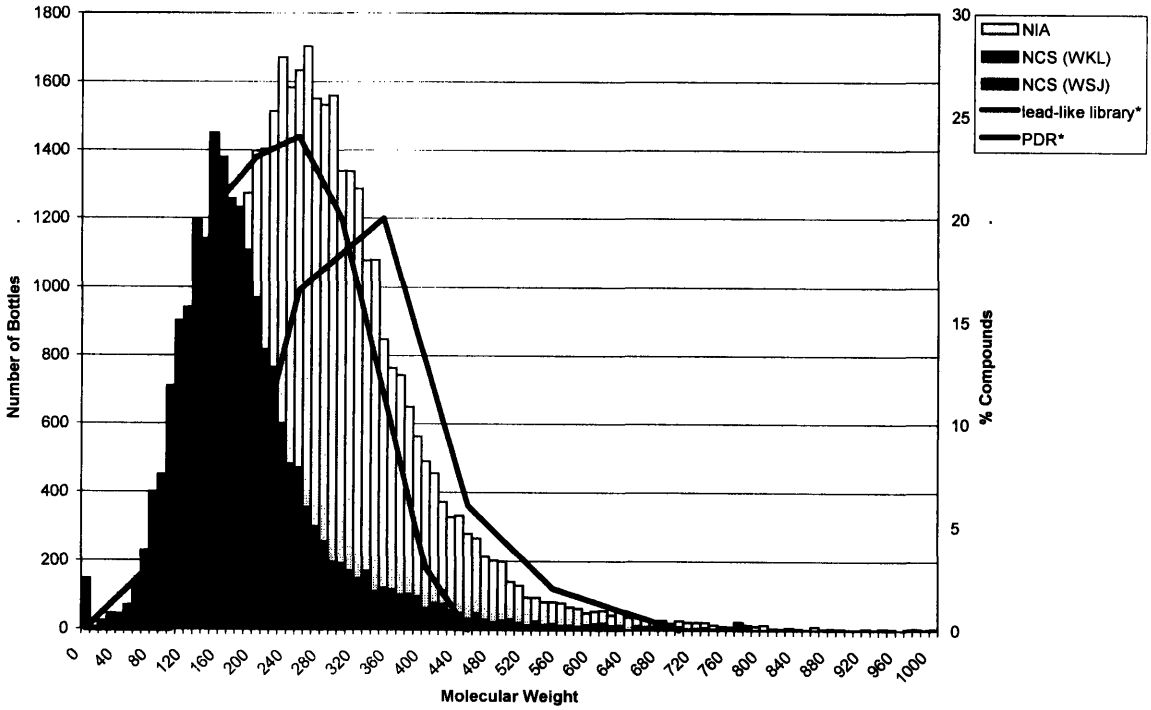


Figure 31 - Travel map of order fulfillment in NIA

6.5 Archive Content Evaluation

Customer demand should drive the functionality and content of the archives so that they are able to store and deliver exclusively compounds that will prove valuable to the customer, as measured by the four operational metrics discussed at the beginning of the chapter. Consequently, it is valuable to audit the current contents of the archives and reflect on how future operations can optimize the inventory and eliminate *muda* Type 8 and Type 5, described in the previous section.

As described above, the customer for the compound libraries is generally interested in producing lead-like and drug-like compounds as described by the "Rule of 3" and the "Rule of 5", respectively. Figure 32 plots the molecular weight profiles of the Novartis Intermediates Archive and the Novartis Compound Stockroom in Basel. The pink line represents the profile for a lead-like library that is governed by the "Rule of 3". The purple line depicts the molecular weight profile for drugs listed in the Physicians' Desk Reference, which acts a proxy for a drug-like library.



* Source: Teague, et al. *Angew. Chem. Int. Ed. 1999, 38, 3743-3748*

Figure 32 - Molecular weight profiles for archives in Basel

From this chart, it is apparent that the Novartis Intermediates Archive has experienced what is known as molecular weight creep. When chemists manipulate the properties of a candidate compound, they tend to favor additive processes that result in a final material with a greater molecular weight than the starting compound. Over time, as the newly synthesized compounds are added to the archive, the average molecular weight of the entire archive tends to drift higher. This is a problem for drug discovery

because higher molecular weight compounds are shown to have poor oral bioavailability. When viewed within the framework discussed earlier, this observation exposes potential opportunities for improvement in quality of compounds available, with secondary effects on cost of maintaining the archive and delivery time.

This problem can be partly remedied by instituting a rule requiring compounds over a specified molecular weight, likely close to 500, to be entered into the archive only after special consideration. Below this limit, filtering by molecular weight will have to be done at the discretion of the chemist, perhaps with help of an educated archive staff.

Compound quality could also be improved by instituting other filtering rules for depositing a compound into the NIA. The rules that are currently in place include the requirement that a compound is novel, of a sufficient quantity to be useful to the archive, and that the compound does not provide any intractable safety hazards. Additionally, rules can be added per the "Rule of 5" discussed earlier to ensure that the NIA provides a high density of useful synthesis intermediates.

The compound accumulation profile shown in Figure 33 below illustrates the growth pattern for the compound libraries and can be used to extrapolate future changes in population size. The population of the Novartis Compound Stockrooms has remained relatively stable, indicating that compound withdrawal or disposal and submission are at equilibrium. The NIA, on the other hand, appears to be growing at a steady rate. This is largely due to metered dispensing. Because compounds in the NIA are proprietary, novel substances, users are asked to only request the amount that will be used. Consequently, the number of bar-coded bottles in the compound generally increases with time. This linear growth must be noted when planning storage capacity for the NIA and has a significant on the archive operational cost with a secondary effect on delivery time.

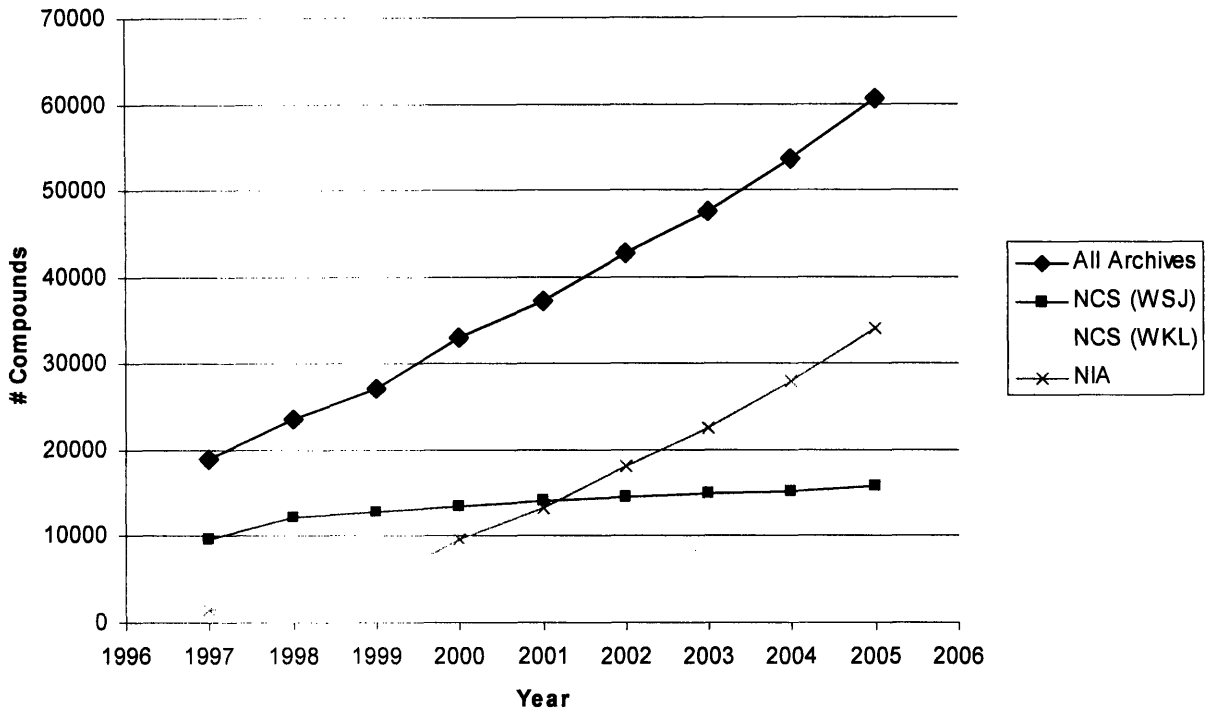


Figure 33 – Compound accumulation profiles for archives in Basel

A significant subset of the compounds that are in the NIA is not actually novel, proprietary compounds. This has occurred partly because some of the contents in the NIA are remnants of a legacy storage system, but also because, over time, many of the more useful proprietary substances eventually make it into general circulation and should be reclassified as commercial compounds. Of course, it is not practical to make regular checks of the entire archive contents for such compounds. A better solution is to merge, either physically or by utilizing a mutual database, the NIA and NCS. This would eliminate the creation of an overabundance of some compounds through the creation of redundant supplies in both archives.

6.6 Competitor Analysis

Competitor analysis is somewhat difficult to perform because many pharmaceutical firms hold their drug discovery processes as a closely guarded secret. However, the author was able to gain some insight by interviewing with Novartis employees that had previously worked for competitors and from touring a Hoffmann LaRoche facility.

For many pharmaceutical manufacturers, combinatorial chemistry is not considered a core skill. Consequently, there is a significant trend in the industry to outsource some aspects of combinatorial chemistry to specialist third parties. Most pharmaceuticals, however, continue to maintain a large

proprietary library of compounds onsite, as this is considered central to their intellectual property strategies. This arrangement would place less emphasis on the maintenance of archives, such as the NIA and NCS, which would be part of the scope of outsourcing. Other manufacturers, including Novartis, wish to maintain a large combinatorial chemistry group, but are interested in supplementing part of their work in collaboration with third parties.

A tour of the Roche chemicals storeroom presented an interesting point of comparison to the facilities at Novartis. The Roche storeroom uses a CIMS database similar to the one at Novartis to keep track of compounds. However, it uses a Kardex system with automated pick and place to store and retrieve the compounds. This system offers faster compound retrieval and depositing than the manual system at the NIA, requires barcode verification of retrieved compounds to check for errors in selection, and provides a climate controlled, isolated storage for the compounds. This significantly reduces travel in compound acquisition while providing a safer, cleaner environment for the archive staff.

The scope of the Roche storeroom is also somewhat different from that at Novartis. First, the storeroom acts as a central receiving for all compounds for all labs. Consequently, it can keep track of the number chemical entities that each lab has and restrict ordering until the lab has returned compounds if they have accumulated too many. Second, it handles the ordering of all compound substances, aggregating decisions and freeing chemists to perform higher value-added tasks, as described above. Third, it is responsible for all chemicals, including high volume, commodity orders. This allows for a smaller overall stock of compounds on hand because there is a reserve that is aggregated for all labs rather than a separate reserve for each lab, reducing *muda* Type 5. Additionally, it requires less effort to replenish a single inventory than to replenish many smaller inventories, decreasing *muda* Type 6. Finally, the workflow is designed to reduce travel, further reducing *muda* Type 6 and also decreasing Type 3. The archive manager works in a circle, starting with receipt of the orders and finishing by dropping off the orders at an adjacent pickup station.

7 Stockroom Automation

7.1 Overview

Stockroom automation was considered as a potential source for improving quality and delivery. The two separate types of automation that were considered for a stockroom were storage and retrieval of compounds and weighing of dispensed compounds. Currently, manual dispensing procedures are implemented in the NIA and are planned for the BBA, while the NCS only distributes whole bottles. It has already been decided that pick and place automation will be utilized in the new instance of the NCS. Consequently, this chapter investigates only implementation of dispensing automation.

7.2 Current Implementation Examples

Automated compound handling is commonly implemented for high-throughput screening archives, such as the Novartis Compound Archive (NCA). The NCA consists of three automated sections, shown in Figure 34. The Automated Compound Archive utilizes a pick and place algorithm to command a robot to retrieve and restock powdered compounds in uniform storage vials. This archive has a capacity of approximately 1 million compounds in 1 – 500 mg quantities and saw more than 9000 new submissions in 2005[52].

[52] Source: Novartis SOLAR poster presentation

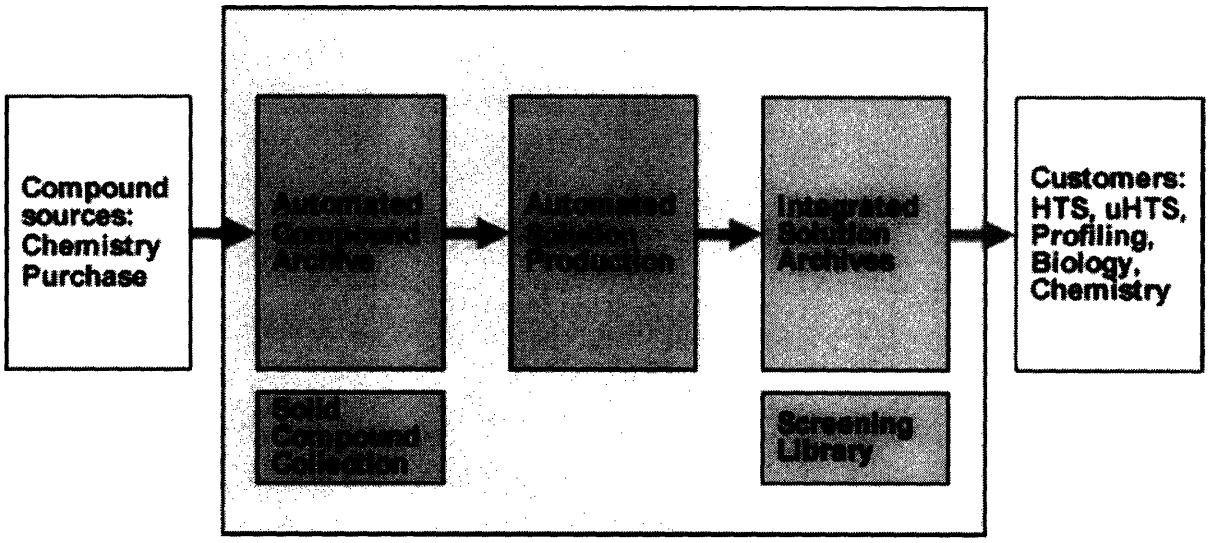


Figure 34 - NCA workflow[53]

The Automated Solution Production is an automated process for weighing precise quantities of powered compounds and creating water/DMSO solutions in 96 well blocks from powdered compounds and placing these solutions in storage. A single scale typically performs 100,000 weighing operations per year and the entire archive produces approximately 300,000 new solutions per year. This high volume is partly due to the strict policy of replacing solutions after three years to ensure purity.

Finally the Automated Solutions Archive (SOLAR) is capable of cherry-picking individual solutions and pipetting them into 96, 384 and 1536-well trays for testing. The goal of this process is to be able to produce error-free samples in the smallest quantity available. At the time of this writing, plans were being made to replace the pipetting system with an ultrasonic system that allows even smaller, ultra-high precision samples to be dispensed. A specifically tuned longitudinal is used to propel the solution from the source vial to the desired well.

7.3 Initial Assessment

The dispensing process in the chemical storerooms is comparable to the Automated Solution Production process in the NCA while the pick and place process is similar to the Automated Compound Archive. Table 6 is a quantitative comparison of the NCA with the chemicals stockrooms in several of the properties that are important when considering automation. This table illustrates that the throughput and size of the chemicals storerooms are considerably smaller than the NCA. Additionally, the

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[53] Source: Schopfer, et al. "The Novartis compound Archive – From Concempt to Reality." Combi Chem and High Throughput Scr, 8, 2005, 513-519.

uniformity and precision of deposit and withdrawal activities is much less important for these archives than for the NCA. The Law of Requisite Variety, which essentially states that the complexity of a controller must be greater than or equal to the complexity of the system being controlled, suggests that higher variability in the shape and size of the container and the quantity being deposited and withdrawn will require a more complex automation and control system. Also, because there is significantly less throughput, the costs of the system are spread over a smaller set of operations, meaning that the benefits per operation required to justify those costs must be greater.

Deposit Frequency	> 9000 / year	8600 / year	5000 / year
Deposit Volume	1 – 500 mg	1g – several kg	50g – 1kg
Withdrawal Frequency	300,000 / year	3000 / year	7000 / year
Withdrawal Volume	Few mgs	~50mg - kgs	Entire Quantity
Withdrawal Precision	Very High	Low	Low
Archive Size	1 million compounds	30,000 compounds	10,000 compounds
Container Uniformity	Very uniform	Variable	Variable

Table 6 - Comparison of NCA, NIA and NCS

7.4 Available Automation

7.4.1 Dispensing

Dispensing solutions were available from several vendors that have a working relationship with Novartis, including Mettler-Toledo, REMP and Autodose. The REMP solutions were designed for use almost exclusively with assay trays and were eliminated from consideration. The solutions from the remaining two vendors are detailed in Table 7.

System Name	Powdernium	Flexiweight 1000
Range of Physical Properties	High	85% of typical library
Throughput Time	20 to 40 s	Best 20 s Mean 70 s
Weight Range	0.05 mg to several g	1-20 mg FlexiCap II 1mg – 1g FlexiCap III
Precision	±1 – 5%	±0.2 mg FlexiCap II ±0.3 mg FlexiCap III
Target Container	Almost all	Any vial up to 15 cm diameter
Source Container	Almost any small	Up to 16 ml

Table 7 - Automation Solutions

The automation systems that are currently on the market are not ideally configured for application to the archives. The weight ranges for both systems listed above are considerably below the ranges of typical dispensing for the NIA. In 2005, only 1,002 of 1,952 requests were for weights of less than one gram. Additionally, they are configured for a small number of source containers rather than the tens of thousands that are currently available for dispensing from the NIA.

A quote was obtained from Mettler-Toledo for the Flexiweight solution. A basic configuration was priced at CHF 240,349 (USD 192,500). A back of the envelope calculation demonstrates the infeasibility of economic justification for this purchase. If it is generously assumed that this system is used to dispense 1,000 compounds per year for a ten year life, the cost per compound dispensed is CHF 24.03 (USD 19.25). Of course, it is unlikely that the system will receive 1,000 orders per year, since it will only be able to dispense a select subset of compounds in the NIA. Additionally, installation costs, and recurring costs, such as dispensing caps, have not been included in this calculation.

The anticipated Building Block Archive, on the other hand, might be an excellent use of dispensing automation. If it is assumed that this library only stores approximately 1000 compounds that are specially picked to be amiable to dispensing and for high-volume, common use, then the current technology is well suited for this application. It is generally expected that the BBA will handle approximately 75 requests per day. Again, using the same approximate calculation as above, the capitol costs are now CHF 1.33 (USD 1.07) per vial.

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[54] Source: Autodose homepage <http://www.autodose.ch/dispensing-capabilities.html>
[55] Source: Conversation with Mettler-Toledo representative and homepage <http://us.mt.com/mt/products/products/FlexiWeigh1000_Product-Product_1108485387750.jsp>

7.4.2 Pick and Place

At the time of this investigation, a pick and place system from Kardex AG was already evaluated and selected for implementation in the new NCS installation. Consequently, a financial evaluation of options or viability will not be performed. The previous discussion and Table 6 initially raise concern about justification because there are two orders of magnitude fewer withdrawals from the NCS than from the NCA. Additionally, implementation might appear challenging because the size and volume of the library contents vary considerably more for the NCS. However, pick and place automation differs from small-volume, high-variety compound dispensing automation in that it is a common source of automation among many different industries that often require storage of lower-volume, non-uniform inventories.

7.5 Conclusion

While pick and place solutions exist that are appropriate and justifiable for the NCS and NIA, there is currently no viable dispensing solution. However, pick and place should remain in consideration for the BBA. The costs of implementing the currently available automated dispensing systems are significantly greater than the in-place process. Additionally, the material property flexibility and source compound variety do not yet exist for the large variety of compounds that are used in these archives.

8 Vision for the Future

8.1 Objectives

The Novartis Campus Project is an ambitious undertaking that aims to transform the Basel St. Johann site "from an industrial complex to a place of innovation, knowledge and encounter."[56] Over the next several years, many of the current buildings on the campus will be raised and replaced with newly designed offices and labs that aim to provide a more collegiate environment.

The Campus Project is an excellent opportunity to redesign the NIA and NCA from the ground up, and to implement the lean principals discussed in this thesis. Because the new archive will not be built for several years, the following discussion is intended as a general guideline for future planning.

8.2 Archive Fundamentals

The NIA, NCA, and BBA will be combined into a single archive in order to eliminate the redundant inventories that contribute to *muda* Type 5 and to help level the highly variable throughput through each library. A potential layout for the archive is illustrated in Figure 35. The travel path for compound order fulfillment is a circle around the archive, beginning with order receipt at the workstation to the left of the entrance, traveling to the Kardex system for compound acquisition, proceeding to the fume hood for required metering, continuing to the packaging table to prepare compounds for shipping, proceeding to the outgoing depot to drop off completed orders, and finishing back at the Kardex to return the source vials. This path is designed to minimize operator and compound travel, *muda* Type 3 and Type 6, respectively. To minimize the risk of dropped compounds, a cart to hold the compound vials will travel with the archive staff member throughout the entire fulfillment process.

The global stockroom will handle all of the commercial and proprietary requests. Projections for future usage were made from the currently available data, discussed above. It is also assumed that approximately 75 daily withdrawals will be made from the 1000 available building blocks. The projections are summarized in Table 8, below. The storeroom is designed to hold 150,000 compounds. This value was derived from extrapolating Figure 33 eight years into the future.

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[56] Source: <http://www.novartis.com/about-novartis/locations/basel-campus-project.shtml>

Metered Withdrawals	83
Non-metered Withdrawals	34
Returns and Registrations	62
Disposals	10

Table 8 - Projected throughput for Novartis Campus Project archive

Metered dispensing will be included for a select group of approximately 1000 Building Blocks and, if desired, for chemical intermediates. Currently automation is not recommended for dispensing of intermediates, but should be considered for building blocks.

The compound storage system that was selected for this scenario is the ShuttleXP system by Kardex AG. This system consists of a series of enclosed shelves that are used to hold the compounds. Vials are picked and placed by an automated extractor that is able to move vertically and horizontally simultaneously. Compounds are generally placed in locations to minimize total travel for the extractor, but specific areas can be specified for volatile compounds or compounds that might react with their neighbors. Cold storage is also available. For more specific specifications of the suggested Kardex system, refer to the Appendix.

The Kardex system provides several benefits to the chemical storeroom. First, it significantly reduces the physical footprint of the storage unit compared to non-automated systems. It also contributes to reductions in *muda* Type 3 and Type 6. The barcode scanner that is attached to the access opening reduces errors caused by selecting the incorrect bottle because it will indicate an error if the incorrect bottle is selected. Finally, it is more airtight than a manually accessed shelf system, reducing the archive operator's exposure to compound fumes.

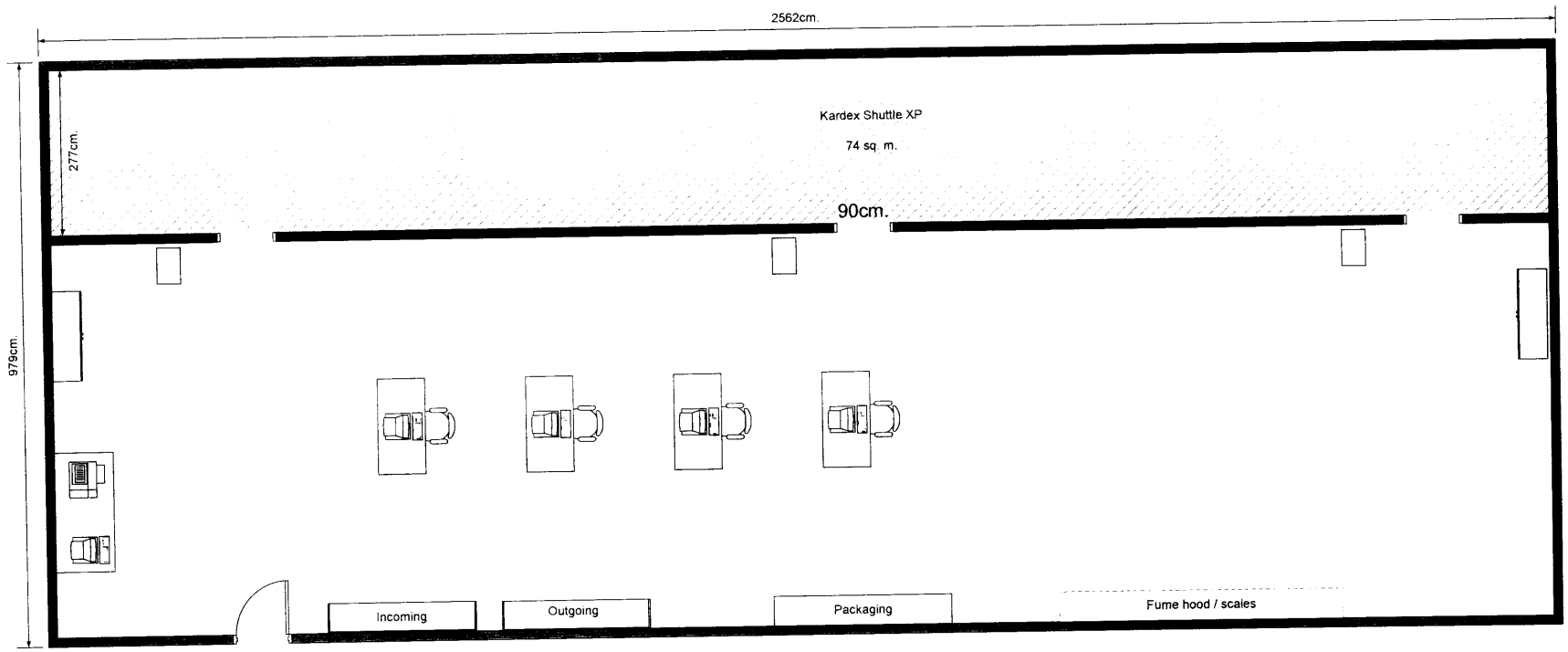

Figure 35 - Suggested design of Novartis Campus Project archive

8.3 Project NPV Analysis

Table 9 below is the result of a preliminary NPV analysis for the new archive. These calculations assume that the entire project is financed with cash upfront, that the new building will be constructed regardless of the decision to produce a new archive, and that the opportunity cost of occupying the new location is exactly balanced by the opportunity benefit of vacating the old location. Only the very large capital expenses have been included because the uncertainty in predicting costs this far into the future is greater than most of the smaller expenditures. The expected lifetime for the archive is projected at 20 years. The cost for the Kardex system and scales were extrapolated from quotes received for similar orders. The savings in commercial compound expenditures are calculated on the assumption that the new archive will be sufficiently attractive to reduce overall compound ordering by 1%. Under these conditions, the break-even point for NPV is a 0.111% decrease in overall compound ordering. If it is assumed that there are no reductions in staff (FTE[57]), then the break-even point is a 0.377% decrease in ordering.

Category	Description	NPV
Capital	Kardex	($687,000)
	Scales	($24,000)
Installation	Kardex	($140,533)
Operation	Commercial Comp Savings	$2,256,000
FTE	Required	($3,000,000)
	Old System	$3,600,000
	Net	$600,000
Total	Total	$2,004,467

Table 9 - NPV estimate for new compound archive

[57] FTE is a Full Time Equivalent, equal to the resources consumed or produced by one full-time employee.

There are several other benefits from this project that are not easily quantified. The following list details several of these improvements.

- Safety is improved in the archive due to better fume containment and removal in the Kardex system.
- Ordering errors are reduced because of increased automation.
- Service level and reliability increase as a result of the leveling effect of demand aggregation.
- Compound inventory is reduced because of elimination of redundant stocks.
- Compound ordering is faster for the chemist because the compound archive handles most of the ordering activities. Additionally, overall compound ordering time is reduced because there are fewer databases to search.

9 Conclusions

Procedures for using compound archives and libraries must be clearly presented to the end user.

Surveys and interviews with users indicate that chemists are often confused about the exact procedures for depositing to the compound libraries. It is important that a clear and global procedure is identified and clearly stated that defines the quantity of compound that is to be sent to the library, the libraries that should receive the compound, including the Novartis Compound Archive, and the testing that is expected before deposit. Additionally, clear rules should be established for determining whether a compound should be deposited to a library and which libraries it should be deposited to.

Compound libraries should be conglomerated into one large library that is also responsible for all compound acquisition.

The various Novartis Chemical Stockrooms and Novartis Intermediates Archives should be combined into a larger central archive. This will have several primary benefits. First, because the definition between an intermediate and a compound which belongs in the NCS is blurred and often changing, there is a large set of redundant compounds between the libraries. Elimination of this redundancy will significantly reduce the quantity of compound that is required on hand and will increase delivery and compound quality. Second, orders frequency from the stockrooms is highly variable and fluctuates erratically. Combining several highly variable demands into one larger demand pool will reduce this variability and result in better utilization of archive staff and facilities. Finally, combination of the archives sets the stage for moving all compound ordering responsibilities to the central archive. This would free chemists to spend their time on chemistry rather than compound ordering.

Compound metering for intermediates does not appear to be an effective use of resources.

The current method of delivering metered samples of compound intermediates to chemists may no longer be of value under the new SciQuest compound management system. The value in this process is considered to be two fold. First, it is said to save material because the chemist only receives the exact quantity that s/he requires. Second, it allows the compound to remain in a centralized location where it remains available to other users. However, because of the tendency for chemists to be conservative, a fixed, one-shot order system often encourages them to order more compound than they might actually require. Additionally, the metering process does not save any time for the chemist because s/he will have to reweigh and distribute the compound during the synthesis process. Because of the new SciQuest ordering system, all compounds will be searchable in all locations, including the labs, so other chemists will be able to locate and request a compound, even while it is in use.

Library automation currently makes sense for pick and place but not for compound metering and dispensing.

The current state of the art in available automation systems dictates that storage and retrieval of compounds should be automated, but that metering and dispensing should be done manually. Modern storage systems, such as the Kardex system reviewed above, allow for safe, clean storage with a considerably smaller footprint as well as error-free and fast depositing and retrieval. However, current metering systems are not yet up to the task of handling the high number of compounds and high variety of physical properties that are stored in the libraries.

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<http://www.novartisvaccines.com/>

11 Appendix A – Glossary of Drug Discovery Terms[58]

Assay	A biological test, measurement or analysis to determine whether compounds have the desired effect either in a living organism, outside an organism, or in an artificial environment.
Bioavailability[59]	The percentage of a drug's active ingredient that reaches a patient's bloodstream and body tissues.
Combinatorial chemistry	Set of techniques for synthesis of a large number of compounds, including parallel chemistry and production of mixtures in both solid phase and solution
Drugability	The term coined for a target that can be modulated by a small molecule ligand that has the appropriate bio-physico-chemical properties and bioavailability
High-throughput screening (HTS)	Approach to detect inhibitors, stimulators or modulators of a specific biological interaction by testing large amounts of chemical entities mostly with the help of automated systems.
Hit	Library component whose activity exceeds a predefined, statistically relevant threshold.
In silico	Describes an experiment that is done with a computer.
In vitro	Describes an experiment that is done in a test tube.
In vivo	Describes an experiment that is done in an animal or human body.
Lead	Chemical entity with biological activity for chemical optimization to improve potency & specificity. Selected as a starting point for drug development.
Lead finding	A process where early lead compounds can be identified from the existing compound libraries, normally by high-throughput screening using *in vitro* and/or *in silico* approaches.
Lead optimization	A process where the designed activity/efficacy/drugability can be improved/optimized by modifying the chemical structure of known scaffolds or switching to a new templates (or changing chemical space).
Lipid	

[58] Some terms are not uniformly defined throughout the industry. Where there is inconsistency this glossary is reflective of the Novartis definition. Other definitions come from http://www.combichemistry.com/medical-chemistry-glossary.html

[59] Source: Saftlas, Herman., et. Al. "Healthcare: Pharmaceuticals." Standard & Poor's Industry Surveys. May 25, 2006.

New Drug Application (NDA)	A document submitted to the FDA requesting permission to market a drug.
Parallel chemistry	A specific method of combinatorial chemistry by which large numbers of single compounds are synthesized in parallel.
Pharmacokinetics[60]	Analysis of a drug's absorption and distribution in the body, its chemical changes in the body, and how it is stored and eliminated from the body.
Rule of 5	A set of rules used to filter compounds for drug-likeness developed by Lipinski, formerly of Pfizer.
Scaffold	A structural backbone
Selectivity	A term used to distinguish between the desired activity of a drug and its other effects.
Singleton	A colloquial term for an active compound that lacks active neighbors in structural space.
Target	Biological molecule (gene, protein, bio-chemical) that is believed to be linked to a given disease. Modulation of target activity or levels by certain biologically active compounds represents therapeutic opportunities.

[60] Ibid.

12 Appendix B – CIMS and SciQuest Screenshots

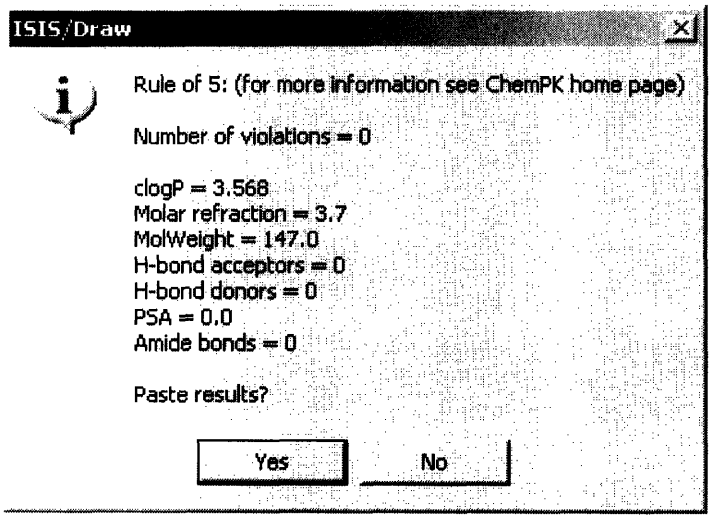

Figure 36 – CIMS "Rule of 5" screenshot

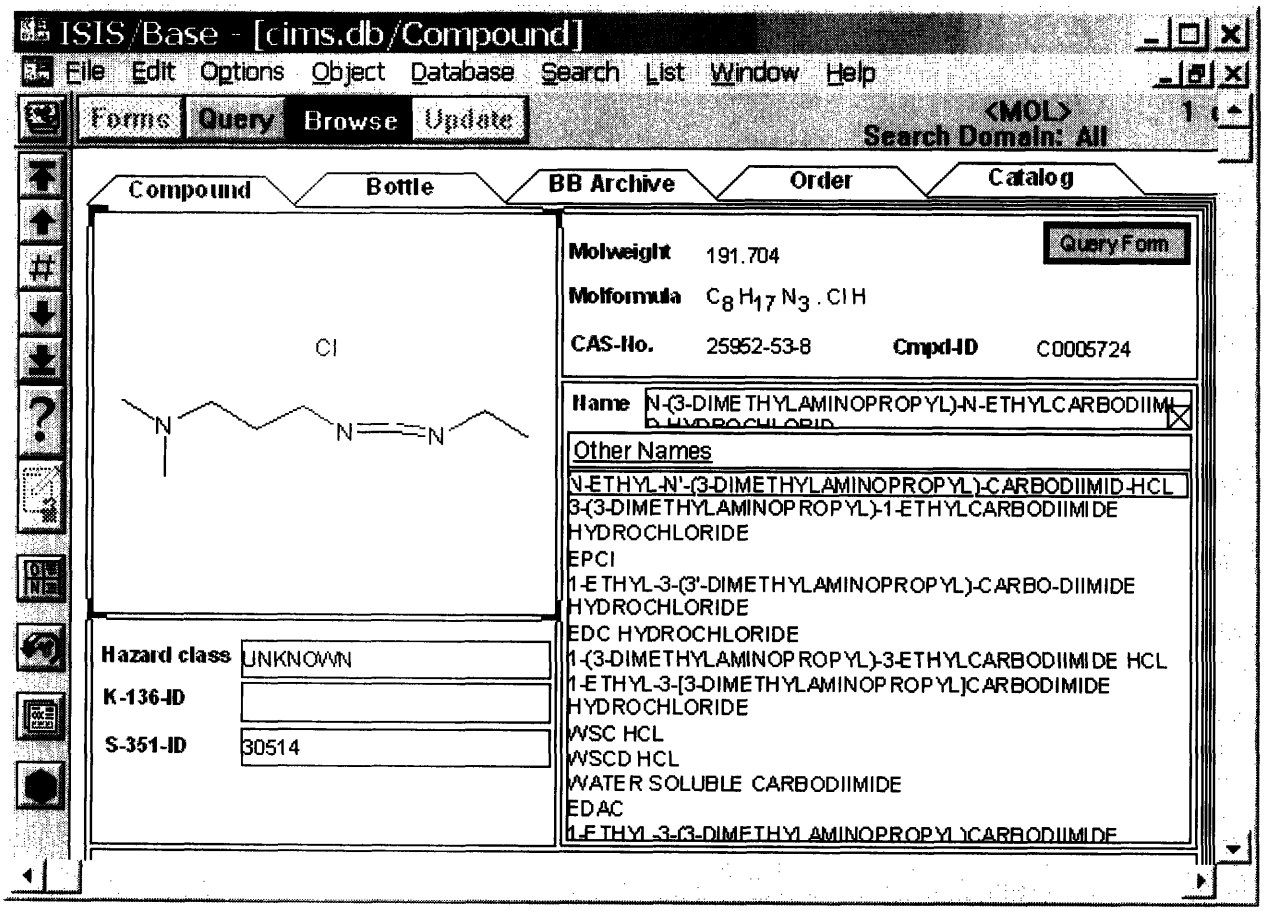

Figure 37 - CIMS search interface

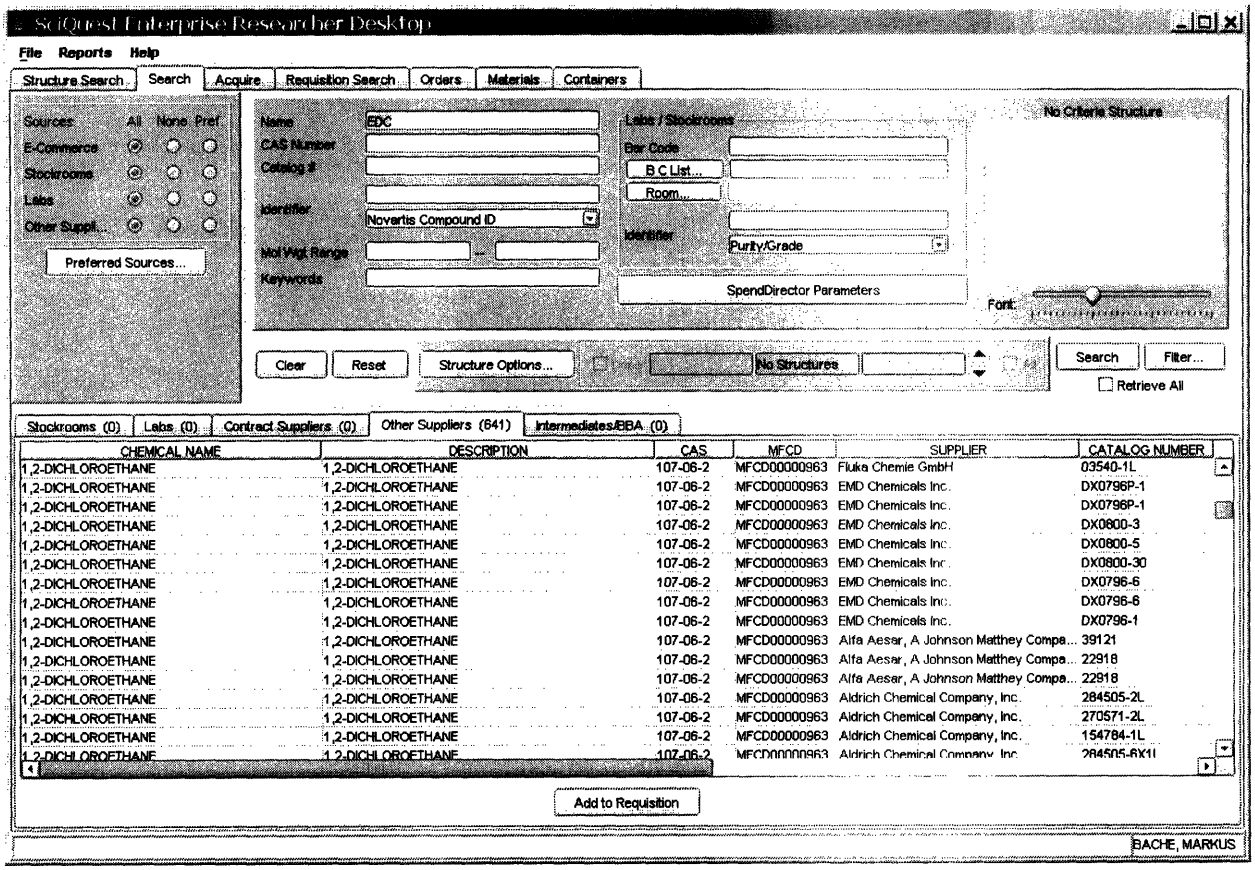

Figure 38 - SciQuest search interface

13 Appendix C – Proposed Kardex Configuration

The proposed Kardex implementation for the Novartis Campus Project assumed a storage capacity of 150,000 compounds with a composition described in Table 10. The model contains three access openings, that are 3,237mm x 813mm x 1850mm. The required volume without the openings is detailed in Table 11. When the volume required for the openings is added, the ShuttleXP system requires approximately 23 standard units[61] or 12 double-height units.

Small	40	70	105000	656	161
Medium	60	20	30000	336	90
Large	80	9	13500	168	81
Extra-Large	150	1	1500	44	35

Table 10 - Projected archive composition

Small	161	100	16100	24215
Medium	90	125	11250	16920
Large	81	150	12150	18274
Extra-Large	35	300	10500	15792
Total	367		53237	74202

Table 11 - Projected archive storage requirements

[61] A standard storage unit has 2371mm of useful height and a shelf surface of 813mm x 1850mm.