GLOBAL PHARMACEUTICAL OUTSOURCING STRATEGY REPORT FOR SMALL PHARMACEUTICAL COMPANIES

by

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Global Pharmaceutical Outsourcing Strategy Report For Small Pharmaceutical Companies

Abstract
By
MUYANG HU

Diabetes is a global health issue that threatens millions of lives. Thermalin Diabetes, LLC is striving to commercialize new types of insulins that fulfil unmet market needs for both Type I and Type II diabetes patients. However, as a small pharmaceutical company, Thermalin Diabetes faces obstacles operationally and financially due to its size and limited funding sources. As Thermalin is exploring the option of outsourcing its production activities, it is challenging to allocate the right amount of capital while still trying to mitigate the risks at a minimum level. In this thesis, I will analyze different risks associated with outsourcing in the pharmaceutical industry as well as an internal and external cost analysis to evaluate the cost efficiency for Thermalin. Ultimately, a structured framework will be provided for Thermalin to make strategic decisions on outsourcing.
1. Diabetes

The word diabetes comes from Latin which is adopted from Ancient Greek that means a siphon\(^1\). The meaning of the word came from patients with an excessive discharge of urine, as the name of the disease\(^2\). Diabetes is a complex disease which is caused by our body’s lack of insulin production or insulin resistance. In healthy individuals, the pancreas\(^3\) releases insulin to help our body store and use the sugar and fat from the food we eat\(^4\). However, in diabetic patients, the pancreas either does not produce any insulin, or produce very little insulin, or the body does not respond appropriately to insulin\(^4\).

Therefore, the “un-metabolized” sugar will pass through in urine for diabetes patients. Diabetes patients are exposed to an increasing risk of long-term complications such as blood vessel damages, cardiovascular disease, coronary artery disease\(^5\) and stroke. It is also common for diabetes populations to have eye damage, known as diabetic retinopathy; kidney damage, known as diabetic nephropathy; and nerve damage, known as diabetic neuropathy. These complications may lead to vision loss, chronic kidney disease, and diabetes-related foot problems (Fig. 1)\(^7\).

\(^1\) The pancreas is a long flattened gland located deep in the belly (abdomen). (http://pathology.jhu.edu/pc/BasicOverview1.php?area=ba)

\(^2\) Coronary artery disease develops when the major blood vessels that supply your heart with blood, oxygen and nutrients (coronary arteries) become damaged or diseased plaque in your arteries and inflammation are usually to blame for coronary artery disease. (http://www.mayoclinic.org/diseases-conditions/coronary-artery-disease/home/ovc-20165305)
According to the World Health Organization (WHO), about 347 million people worldwide now have diabetes. In 2012, diabetes was the direct cause of deaths for 1.5 million people, and this number is projected to rise by more than 50% in the next 10 years. In the United States, there were 29.1 million Americans having diabetes in 2012 (Fig 2). Among the 29.1 million diabetes population, only 21 million were diagnosed which leaves the other 8.1 million people undiagnosed.
The cost of diabetes is also skyrocketing high. The cost of diagnosed diabetes alone in the U.S. was $245 billion in 2012\textsuperscript{13}. It’s roughly about $176 billion dollars for direct medical costs\textsuperscript{14}. The collateral damage of reduced productivity caused by diabetes is about $69 billion in the U.S. alone\textsuperscript{15}.

### 1.1 History

Diabetes was one of the very first diseases described in human history with an Egyptian manuscript from c. 1500 BCE\textsuperscript{16}. At the time, physicians have found “honey urine” in some of their patients and noted that the urine would attract ants\textsuperscript{17}. Mellitus, the Latin word for honey, is therefore added to the term “Diabetes”\textsuperscript{18}. Up to 11\textsuperscript{th} century, the way of diagnosis of diabetes was often made by “water tasters” who drink the urine of those suspected of having diabetes\textsuperscript{19}. Since then, for thousands of years, nobody knows how to live with diabetes, let alone treat or cure it\textsuperscript{20}. Children with diabetes usually die within days of disease onset and older people have to deal with devastating complications\textsuperscript{21}.
1.1.1 The Breakthrough

During that time, people have tried numerous ways to cure diabetes such as the “sugar treatment” from the French physician, Priorry. Priorry advised diabetes patients to eat an extra-large quantity of sugar as a treatment. There wasn’t a breakthrough until in 1869, a German medical student, Paul Langerhans (Fig. 3), discovered that pancreas contains two systems of cells. In his doctoral dissertation, Paul claimed that one set of cells secretes the normal pancreatic juice, but the function of the other was unknown. Later, these cells are identified as the “islets of Langerhans”, which help produce insulin.

![Paul Langerhans](image)

*Figure 3. Paul Langerhans.*

The findings of Langerhans were a big milestone for insulin discovery because people started drawing attention on the pancreas. In 1908, Georg Zuelzer (Fig. 4) successfully developed
the first injectable pancreatic extract, which was called acomatrol at the time, to suppress glycosuria, the presence of glucose in urine, in a diabetic patient in the coma\textsuperscript{26}. The patient got slightly better after the injection, but suffered from side effects later on and eventually died due to the shortage of acomatrol\textsuperscript{27}.

Figure 4. Georg Zuelzer.

The Zuelzer’s experiment encouraged many pancreas-related types of research activities in the 1920s. In 1923, Eli Lilly and Company commercially manufactured the very first insulin product called Iletin (Fig. 5)\textsuperscript{28}.
Figure 5. First Insulin Product Made by Eli Lilly and Company in 1923.

The primary insulin sources at that time were living organisms such as pigs and cows that were destined for our dinner plates (Fig 6). Specifically, their pancreas glands were waste products of the meatpacking industry. Pigs and cows were used simply because both pork- and beef-derived insulins are nearly identical to human insulin and can be utilized by our bodies. According to the article in Diabetes Forecast, more than two tons of pig parts were needed to extract just eight ounces of purified insulin.
Because insulin was extracted from bovine and porcine pancreata during that time, the purity became the biggest issue, not to mention the complicated purification process to purify the extract to be acceptable for human uses. Therefore, many researchers were working on identifying alternative insulin sources. Thanks to the classic structural studies on DNA by Watson and Crick and on insulin by Sanger, in 1978 scientists from Genentech were able to synthesize the first recombinant DNA human insulin using A- and B-chains expressed in E.coli and an A+B-chain combination procedure (Fig. 7). Later in 1978, Genentech and Lilly signed an agreement to commercialize rDNA human insulin. In 1983, Eli Lilly started producing biosynthetic human insulin, which is called
Humulin, in the U.S. after getting the FDA approval with recombinant DNA technology\textsuperscript{35}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig7.png}
\caption{Two Pathways for Producing BHI. From Frank and Chance (43).}
\end{figure}

Since then, diabetes became a relatively controllable disease which required multiple insulin intakes for the patients during the day because the available insulin products during that time were short-acting insulins mimicking human endogenous insulin. Furthermore, oral drugs treating type II diabetes and basal insulin products were introduced in the late 1960s\textsuperscript{36}. Now, diabetes is more a chronic disease for the most patients with minimal short-term lethal threats. Death due to diabetes complications like
cardiovascular diseases is actually declining\textsuperscript{37}. However, the battle with diabetes is still ongoing since there is no cure for diabetes at present\textsuperscript{38}.

1.2 Types of Diabetes
Diabetes comes in two different types. One is type I diabetes, and the other is type II diabetes.

1.2.1 Type I Diabetes
Type I diabetes is also known as juvenile diabetes which means it mainly affects children and young adults under the age of 20. However, it may occur at any age (Fig. 8)\textsuperscript{39}. In terms of prevalence, type I diabetes only accounts for 5\% to 10\% of the people with diabetes globally\textsuperscript{40}. It’s estimated, in the United States, that about one to three million people are affected and about 80,000 children develop the disease each year\textsuperscript{41}.

![Figure 8. Ages Affected by type I diabetes.](image-url)
Type I diabetes happens when the autoimmune system from our body destroys the insulin-producing beta cells in the pancreas\textsuperscript{42}. However, the exact cause of type I diabetes is still unknown\textsuperscript{43}. As a result, the patients will have an increase in blood and urine glucose. Therefore, administration of insulin regularly is essential and necessary for type I diabetes patients\textsuperscript{44}. Also exercise and diet control are equally important for living long and healthy lives. A proper blood sugar management can make a big difference in lifespan for type I diabetes patients\textsuperscript{45}. Based on statistics, men with type I diabetes generally lose 11 years of life expectancy compared to men without the disease, and this number goes up to 13 for women\textsuperscript{46}. However, the researchers found that type I diabetics younger than 50 are dying in large numbers from conditions caused by issues in the management of the disease\textsuperscript{47}. Many of which could be avoided with intensive blood sugar management\textsuperscript{48}.

1.2.2 Type II Diabetes
Type II diabetes, once known as adult-onset or noninsulin-dependent diabetes, is a chronic condition that affects the way your body metabolizes glucose due to either insulin resistance or relative lack of insulin\textsuperscript{49}. Type II diabetes is primarily due to obesity and lack of exercise in lifestyle for people who are genetically predisposed\textsuperscript{50}. Type II diabetes is a more common condition comparing to type I which counts 90\% of the diabetic population worldwide, but it tends
to affect older populations, typically 45 or older (Fig 9). As of 2013, 368 million people were diagnosed with type II diabetes globally.

![Ages affected]

*Figure 9. Ages Affected by Type II Diabetes.*

Unlike insulin-dependent diabetes, type II diabetic patients do not initially need insulin injections. Patients can manage the disease by eating well, exercising and maintaining a healthy weight. If needed, several oral anti-diabetic medications are often used at first such as Metformin (Fig. 10).

---

**iii** Metformin is an oral diabetes medicine that helps control blood sugar levels for people with type 2 diabetes. It can also be used in combination with insulin or other medications ([http://www.drugs.com/metformin.html](http://www.drugs.com/metformin.html)).
Injections of insulin may either be added to oral medication or used alone\textsuperscript{55}. When insulin is used, a long-acting formulation is typically added at night to cover the sleeping period, with oral medications being used during the daytime\textsuperscript{56}. For many cases, if nightly insulin is insufficient, daily fast-acting insulin injections, such as Humalog from Eli Lilly and Co., may achieve a better control\textsuperscript{57}. Similar to type I, type II diabetes is associated with a ten-year-shorter life expectancy for both men and women\textsuperscript{58}. However, a strict and well-executed management for blood glucose plays an important role to prolong type II patients’ lifespan.
1.3 Pathology

Glucose is the primarily energy resource for cells to function properly.

Food that we eat on a daily basis is broken down into glucose and is carried to the cells via the bloodstream\textsuperscript{59}. Glucose uptake from the bloodstream is dependent on insulin receptor-mediated translocation of glucose transporters to the cell surface in response to insulin (Fig. 12)\textsuperscript{60}. 

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure11.png}
\caption{Humalog U-100 Insulin from Eli Lilly and Company.}
\end{figure}
Blood glucose increases typically after meals, which is higher than 10mmol/L\textsuperscript{61}. To balance out the glucose increase in the bloodstream, the pancreas secretes insulin directly into the bloodstream (Fig. 13)\textsuperscript{62}.

Insulin in the blood stream can unlock the membrane receptors so that glucose can be transported into the cell. The insulin receptor is composed
of two extracellular α subunits and two transmembrane β subunits linked together\textsuperscript{63}. Binding of insulin to the α subunit induces a conformational change resulting in the autophosphorylation of a number of tyrosine residues present in the β subunit (Fig 14)\textsuperscript{64}. These residues are recognized by phosphotyrosine-binding (PTB) domains such as members of the insulin receptor substrate family (IRS)\textsuperscript{65}. The receptor activation leads to the phosphorylation of key tyrosine residues on IRS protein, which leads to downstream AKT\textsuperscript{iv} activation and GLUT4 translocation to the plasma membrane\textsuperscript{66}. As a result, the blood glucose level is lowered as glucose is transported into cells to be stored as glycogen. Insulin also activates phosphofructokinase and glycogen synthase that are involved in glycogen synthesis which increases glycogen production\textsuperscript{67}. However, in diabetes patients, either the mechanism of insulin production is defective or there are not enough membrane receptors. Therefore, glucose in the bloodstream will remain in the bloodstream, which leads to increasing blood glucose levels.

\textsuperscript{iv} AKT or Protein kinase B is a serine/threonine kinase, which is activated in cells exposed to hormones, growth factors, and extracellular matrix components (http://www.ncbi.nlm.nih.gov/pubmed/11882383).
1.3.1 Type I Diabetes
Type I diabetes occurs as a result of the body’s immune system attacking the insulin-producing beta cells of the pancreas, although it is still not clear what causes the attack.\textsuperscript{68}
A lack of insulin in the blood means inadequate amounts of glucose are taken up by cells of the body to provide energy for cellular functions. Consequently, glucose remains in the blood leading to a high blood sugar level. The potential causes for type I diabetes include coxsackievirus and rubellavirus viruses, genetic inheritance, presence of antibodies against beta cells, and beta cell damaging drugs or chemicals such as pyrinuron.

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v Coxsackievirus is a virus that belongs to an enterovirus family. It causes hand, foot, and mouth disease (https://en.wikipedia.org/wiki/Coxsackie_A_virus).


vii Pyrinuron is N-3-pyridymethyl-N′-p-nitrophenyl urea, which is used as a rat poison and is no longer used in the USA (http://www.news-medical.net/health/Diabetes-Mellitus-Type-I-Pathophysiology.aspx).
1.3.2 Type II Diabetes

Understanding the pathogenesis of type II diabetes is more complicated than type I by several factors\textsuperscript{71}. Patients often present with a combination of varying degrees of insulin resistance and relative insulin deficiency, and it is likely that both contribute to type II diabetes\textsuperscript{72}. Insulin resistance can be defined as the inability of insulin to produce its usual biological actions at circulating concentrations that are effective in normal subjects (Fig. 16)\textsuperscript{73}. Insulin resistance has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leading to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased the breakdown of fat\textsuperscript{74}. The induction of insulin resistance is caused by high-calorie diets, steroid administration, or physical inactivity\textsuperscript{75}. Additionally, insulin resistance is found in hypertension, hyperlipidemia, and ischemic heart disease\textsuperscript{viii} patients\textsuperscript{76}.

\textsuperscript{viii} Ischemic heart disease is a common heart disease caused by plaque buildup in heart muscle (\url{http://www.publichealth.va.gov/exposures/agentorange/conditions/ischemicheartdisease.asp}).
Insulin deficiency is caused by beta cell dysfunction which is initially characterized by an impairment in the first phase of insulin secretion during glucose stimulation\(^77\). Later in the course of the disease, the second phase release of newly synthesized insulin is impaired\(^78\). This secondary phenomenon is the result of a paradoxical inhibitory effect of glucose upon insulin release and may be attributable to the accumulation of glycogen within the beta cell as a result of sustained hyperglycemia\(^\text{ix}\) \(^79\). Beta cell dysfunction develops early in the pathologic process and it can easily be neglected for treatment\(^80\). However, singular focus on insulin resistance is gradually shifting and hopefully better treatment options that address the beta cell pathology will emerge for early therapy\(^81\).

1.4 Diabetes Markets Overview

Diabetes Mellitus has been growing at an exponential rate and the World Health Organization (WHO) estimates that the diabetic population is likely to reach 366 million in 2030\textsuperscript{82}. The United States is expected to have an increase of >100 percent in the diabetic epidemic from 2000 to 2030\textsuperscript{83}. Asia-Pacific is expected to witness a 130 percent increase and Africa and Middle East is likely to face a huge 162 percent increase in diabetic population\textsuperscript{84}. The diabetes market, consisting mainly of products used in the treatment of type I and type II diabetes, is large and also growing significantly\textsuperscript{85}. In 2012, the global market for diabetes reached $118.7 billion with a five-year compound annual growth rate\textsuperscript{x} (CAGR) of 5.7\%\textsuperscript{86}. The global market is also expected to reach nearly $157 billion in 2017 (Fig. 17)\textsuperscript{87}.

\[ \text{CAGR} = \left( \frac{V_f}{V_i} \right)^{\frac{1}{n}} - 1 \]

\textsuperscript{x} CAGR can be calculated by dividing the value of an investment at the end of the period by its value at the beginning of that period, raise the result to the power of one divided by the period length, and subtract one from the subsequent result (http://www.investopedia.com/terms/c/cagr.asp).
1.4.1 Diabetes Market Till 2015

The United States is the biggest diabetes market in the world taking up 47.7% in 2008 and 43.3% in 2015 (Fig. 18)\(^8\). The second largest market is Europe which represents one-third of the market share\(^9\). Although, Japan and rest of world together don’t take the market as much as the United States and Europe, the diabetic population is growing fast\(^9\).

![Figure 18. Diabetes Market Growth (2008 to 2015).](image)

In 2015, around $116 billion is spent towards direct costs due to diabetes in the U.S. alone\(^9\). The U.S. market is the major geographical market, but the market is maturing\(^9\). Therefore, it forces pharmaceutical companies that are active in the diabetes market to look for emerging areas\(^9\). Currently, European diabetes population is estimated at 30 million\(^4\). It has been studied that the European Union incurred around Euros 29 billion towards diabetes treatment\(^5\).
In 2010, approximately 135 million adults were affected by diabetes in Asia (Table. 1). In 2009, the total revenue from China, India, South Korea, and Taiwan was approximately $2.5 billion (Table. 2). 60% of the total comprised of non-insulin therapeutics while the insulin market made up the remaining 40 percent. However, the percentage of insulin market in Asia has been increasing in the past few years.
1.4.2 Future Diabetes Market

With the predicted increase in disease prevalence, the global diabetes market is expected to grow to $157 billion in 2017 (Table 3).

Table 3. Diabetes Market Breakdown by Regions, Through 2017 ($ Billions).

<table>
<thead>
<tr>
<th>Region</th>
<th>2011</th>
<th>2012</th>
<th>2017</th>
<th>CAGR% 2012-2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>America (U.S., Canada, Mexico, Brazil)</td>
<td>41.53</td>
<td>42.95</td>
<td>54.05</td>
<td>4.7</td>
</tr>
<tr>
<td>Europe (major western economies + Russia)</td>
<td>25.98</td>
<td>26.80</td>
<td>35.40</td>
<td>5.7</td>
</tr>
<tr>
<td>Asia (China, India, Japan)</td>
<td>42.54</td>
<td>48.90</td>
<td>67.32</td>
<td>6.6</td>
</tr>
<tr>
<td>Total</td>
<td>110.05</td>
<td>118.65</td>
<td>156.77</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Source: BCC Research

In terms of diabetes medications, including insulin and non-insulin drugs, it is predicted that annual sales will reach $55.3 billion in 2017\(^9\) and $67.7 billion in 2022, with $38.8 billion in the U.S. alone\(^10\). Pharmaceutical manufacturers are now developing more diabetes medications to address unmet needs (Table 4)\(^11\). Many of which are in phase three investigation, and most of the pipeline consists of “me-too” drugs\(^12\). Unfortunately, Eli Lilly ended the late-stage basal insulin Peglispro, a long-acting basal insulin, development program in 2015\(^13\). The decision was made because many patients experienced liver fat changes in Phase 3 trials\(^14\).
Table 4. Future Therapies by Major Pharmaceutical Companies (FDA; GlobalData).

<table>
<thead>
<tr>
<th>Drug Manufacturer</th>
<th>Status</th>
<th>Regimen Information</th>
<th>Pivotal Studies</th>
<th>Expected Approval</th>
<th>Anticipated Peak Year Sales/Pricinga</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY2005541 (insulin peglispro) Eli Lilly and Co.</td>
<td>Phase 3</td>
<td>5–10 units via SC injection QD</td>
<td>IMAGINE program</td>
<td>2015</td>
<td>Priced at a 20% discount to Tresiba</td>
</tr>
<tr>
<td>Lyxumia (lisinamide) Sanofi Aventis US</td>
<td>Phase 3</td>
<td>Starting dose: 10 mcg QD for 14 days; maintenance dose: 20 mcg QD starting on day 15</td>
<td>NCT02200591 NCT0240034 NCT02276156</td>
<td>2015</td>
<td>Priced at $3,189</td>
</tr>
<tr>
<td>Semaglutide Novo Nordisk</td>
<td>Phase 3</td>
<td>0.8–1.6 mg SC injection once weekly</td>
<td>SUSTAIN program</td>
<td>2016</td>
<td>Priced at a 10% discount to Trulicity (which now costs about $6,348 a year)</td>
</tr>
<tr>
<td>Omartiglitin (MK-3102) Merck Sharp &amp; Dome</td>
<td>Phase 3</td>
<td>10–25 mg once weekly, orally</td>
<td>NCT01717313 NCT01704261 NCT01682759 NCT01697592 NCT01703221 Total of 10 key studies</td>
<td>2016</td>
<td>Priced at a 10% premium to Januvia (which now costs about $1,099 a year)</td>
</tr>
<tr>
<td>Tofoglifloxin® Chugai Pharmaceutical Co.</td>
<td>Phase 3</td>
<td>10–40 mg QD, orally</td>
<td>Japtic CTI-10351 Japtic CTI-10352</td>
<td>2016</td>
<td>Priced at a 5% discount to Tardifluce (which now costs about $3,660 a year)</td>
</tr>
</tbody>
</table>

LA: long-acting; QD: once daily; SC: subcutaneous

Prices of existing drugs, if given, were calculated using wholesale acquisition costs and regimens provided in the following tables and rounded to the nearest dollar.

2 Insulin

Insulin is a peptide hormone produced by beta cells in the pancreas. The insulin structure is composed of two different types of peptide chains. Chain A has 21 amino acids and chain B has 30 amino acids. Both chains contain alpha helices but no beta sheets. It also has two conserved interchain disulfide bridges which help keep the two chains together, and an intrachain linkage in the A-chain (Fig. 19). Insulin can form dimers in solution due to hydrogen...
bonding between the B chains\textsuperscript{108}. The dimers can further interact to form hexamers stabilized by Zn due to the interaction between hydrophobic surfaces (Fig. 20)\textsuperscript{109}. After injection, the zinc dissociates and the hexamer disassembles into dimers and active insulin monomers\textsuperscript{110}.

Insulin regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the bloodstream to skeletal muscles and fat tissue\textsuperscript{111}. As a result, it keeps our blood sugar level from getting too high, which is called hyperglycemia\textsuperscript{112}. When control of insulin levels fails, it can
lead to diabetes mellitus\textsuperscript{113}. As a consequence, insulin is used medically to treat certain forms of diabetes\textsuperscript{114}.

2.1 Discovery

Before the discovery of insulin, diabetes was a feared disease leading to premature death\textsuperscript{115}. The discovery begins with German medical student Paul Langerhans’ discovery of islet of Langerhans with beta cells which eventually shown to be the insulin-producing cells\textsuperscript{116}. In 1921, a young unknown surgeon named Fredrick Banting and his assistant graduate student Charles Best successfully removed a dog’s pancreas and extracted insulin from the pancreas extract (Fig. 21)\textsuperscript{117}.

![Figure 21. Banting and Best With one of the Diabetic Dogs Used in Experiments With Insulin.](image)

In January 1922 in Toronto, Canada, a 14-year-old-boy, Leonard Thompson, was chosen as the first person with diabetes to receive insulin
injection. The test was a success and Leonard, who before the insulin shots was near death, rapidly regained his strength and appetite.

Frederick Banting and John Macleod, who was a professor at University of Toronto, were awarded Nobel Prize in 1923. In the same year, a pharmaceutical company Eli Lilly started large-production of the extract to supply the entire North American continent.

2.2 Development
Since the mass production of insulin in 1923, insulin has become a hot topic in research. In 1936, the first long-acting insulin, protamine zinc insulin, was introduced by Danish researcher Hans Christian Hagedorn. This long-acting insulin provides a greater flexibility for diabetic patients. During the same year, Neutral Protamine Hagedorn (NPH) insulin, also known as Humulin N and Novolin N, was created. NPH is an intermediate-acting insulin given to help control the blood sugar level (Fig. 22). NPH has an onset of 1-4 hours with its peak between 6-10 hours and duration about 10-16 hours.

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xi Humulin N is manufactured by Eli Lilly and Company.
xii Novolin N is manufactured by Novo Nordisk.
In the mid-1950s, oral medications such as metformin and carbutamide were developed for people with type II diabetes. Previously, the only course of medication was insulin. These oral medications can be used alone for early diagnosis or combined with insulin therapy.

In 1996, the FDA approved the first recombinant DNA human insulin analogs, lispro, which is also known as Humalog from Eli Lilly. The introduction of Humalog solved purity issues of extracting insulin from pigs or cows. Three years later, Novo Nordisk launched Novolog. Both Humalog and Novolog are rapid-acting insulin analogs that have fast onset time. Glargine, the first long-acting insulin analog became available in 2000. As of now, insulin is still going strong in research and academia. The main focuses are insulin patch, inhaled insulin, and ultra-rapid insulin.
2.3 Available Types of Insulin

There are five basic types of insulin depending on onset of action, peak of action, and duration of action: rapid-acting, regular or short-acting, intermediate-action, long-acting insulin, and pre-mixed insulin (Table 5). Rapid-acting insulin, including Humalog, Novolog, and Apidra, begins to work about 15 minutes after injection, peaks in one hour, and continues to work for two to four hours (Fig. 23). Rapid-acting insulin is usually taken right before or after meals to control spikes in blood sugar. This type is typically used in addition to a long-acting insulin. Regular or short-acting insulin, such as Humulin R and Novolin R, covers insulin needs for meals eaten within 30-60 minutes. Comparing to fast-acting insulin, regular insulin has a longer onset time and it lasts longer than fast-acting insulin. Therefore, diabetics don’t need to take it at each meal. Humulin N and Novolin N are intermediate-acting insulins and they offer baseline insulin coverage for about half day or overnight. It is usually recommended to be used with rapid-acting insulin.
Table 5. Summary Table of Different Types of Insulin

<table>
<thead>
<tr>
<th>Insulin preparation</th>
<th>Onset of action</th>
<th>Peak</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro (Humalog)</td>
<td>&lt;15 minutes</td>
<td>1-2 hours</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Aspart (Novolog)</td>
<td>&lt;15 minutes</td>
<td>1-2 hours</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td>&lt;15 minutes</td>
<td>1-2 hours</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Regular (Novolin R, Humulin R)</td>
<td>30-60 minutes</td>
<td>2-4 hours</td>
<td>6-10 hours</td>
</tr>
<tr>
<td>Humulin R Regular U-500</td>
<td>30-60 minutes</td>
<td>2-4 hours</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td>NPH (Novolin N, Humulin N, ReliOn)</td>
<td>2-4 hours</td>
<td>4-8 hours</td>
<td>10-18 hours</td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>1-2 hours</td>
<td>Usually no peak</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>1-2 hours</td>
<td>Usually no peak</td>
<td>Up to 24 hours**</td>
</tr>
<tr>
<td>Glargine Injection (Toujeo)</td>
<td>6 hours</td>
<td>No true peak</td>
<td>24-36 hours</td>
</tr>
<tr>
<td>Afrezza</td>
<td>&lt;15 minutes</td>
<td>Approx. 50 minutes</td>
<td>2-3 hours</td>
</tr>
</tbody>
</table>

Long-acting insulins, such as Lantus and Levemir, have one to two hours of onset time and they can last for 20 to 26 hours with no peak (Fig. 23). This type is used to provide a full-day coverage and it is often taken at bedtime. Because of its long-lasting effect, the patients only need to take one shot per day which reduces burden to the patients.

The last type is pre-mixed insulin. This type of insulin combines intermediate and short-acting insulin so that it can provide patients a great
flexibility. The common brands include Humulin 70/30\(^{xiii}\), Humulin 50/50, Novolin 70/30, and Novolog 70/30. Pre-mixed insulin takes effect in five to 60 minutes and its effects last from 10 to 16 hours (Fig. 23).\(^{142}\)

It’s usually taken 10 minutes to 30 minutes before eating. Pre-mixed insulin is often recommended for elders who have regular meal times and activity patterns.\(^{144}\) The benefit of pre-mixed insulin is that the fast and long-acting insulin is combined and also there is no mixing necessary.\(^{145}\) With that being said, only one injection is needed each time.\(^{146}\)

![Figure 23. Action Profiles of Different Types of Insulin.](image)

Insulin regimens should be tailored to the patient’s needs and lifestyle which often vary greatly.\(^{147}\) One of the most important considerations in choosing the right insulin is matching the lifestyle, such as eating and bed

\(^{xiii}\) Humulin 70/30 means 70% is in insulin protamine crystal form and 30% is in aqueous human insulin (http://www.rxlist.com/humulin-70-30-drug.htm).
times, to the pharmacokinetics of the insulin used\textsuperscript{148}. Currently, a long-acting insulin analogue prescription is always the first choice for new starters\textsuperscript{149}. Often times, twice-daily premixed insulin injections are combined with the long-acting insulin\textsuperscript{150}.

2.4 Advanced Insulin Pump Therapy

Daily insulin injections create a huge burden for patients who don’t have regular meal times and lifestyle. For those people, it is highly recommended to use insulin pumps. An insulin pump is a small, computerized device carried by the patients that delivers insulin continuously throughout the day (Fig. 24)\textsuperscript{151}.

![Figure 24. A Diabetes Patient Carries an Insulin Pump.](image)

The pump can deliver precise doses of rapid-acting insulin to closely match our body’s needs\textsuperscript{152}. The pump itself can monitor and control blood glucose levels by constantly measuring it\textsuperscript{153}. The pump also has a reservoir
which is a plastic cartridge that holds the insulin that is locked into the insulin pump (Fig. 25)\textsuperscript{154}. A reservoir can hold up to 300 units of insulin and needs to be changed when insulin is depleted\textsuperscript{155}.

The advantages of using insulin pump include improved quality of life, fewer daily injections, and precise dosing\textsuperscript{156}. On the other hand, insulin pumps also have drawbacks. Since the insulin pump needs to be worn most of the time, the pumps must be small enough to carry around and pump users need strategies to participate in activities that may damage the pump, such as rough sports and water activities\textsuperscript{157}. In addition, due to the size limitation of the reservoir, patients need to refill insulin supply frequently.
which not only generates burdens to patients but also causes waste of many units of insulin during transfers\textsuperscript{158}. In order to optimize user’s experience using insulin pumps, Thermalin Diabetes is working on a type of ultra-rapid and highly concentrated insulin which elongates the pump usage cycle and provides a much tighter control of blood glucose levels.

2.4.1 Drawbacks of Commercially Available Insulin
Humalog, Novolog, and Apidra are rapid-acting insulins, developed more than a decade ago, that have the fastest onset time after injection\textsuperscript{159}. However, it still takes roughly 15 - 30 minutes to make the insulin work\textsuperscript{160}. It may seem negligible at first, but for diabetes patients who need to calculate the injection time before each meal for three times a day, the 15-minute onset time is still a big burden. Moreover, many patients in the type II population are insulin resistant. For patients with extreme insulin resistance, the absorption problem is even more pronounced because absorption rate slows down with higher volume injections\textsuperscript{161}. Most commercially available insulins today are formulated at U-100, which equals to 100 potency units per milliliter\textsuperscript{162}. Highly insulin resistant patients require large volumes of U-100 each time\textsuperscript{163}. These large volume injections are painful, which discourages compliance, and also slow-absorbed\textsuperscript{164}. All in all, large volume injections would complicate treatment protocols and exacerbate side effects\textsuperscript{165}. 

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2.4.2 Ultra-Rapid Insulin by Thermalin Diabetes

Most insulin products today are formulated as hexamers because it maintains the product stability\textsuperscript{166}. However, the hexamer is too large for immediate absorption in the bloodstream\textsuperscript{167}. Therefore, the rate of absorption of an insulin is limited by the time required for dissociation of hexamers into smaller units (Fig. 26)\textsuperscript{168}.

![Figure 26. Dissociation of Insulin Hexamers Into Monomers.](image)

Scientists at Thermalin Diabetes designed an insulin product that can circumvent this complexity by creating a stable monomer refractory to hexamer-formation (Fig. 27)\textsuperscript{169}. Therefore, an ultra-rapid action profile can be achieved while maintaining the product stability.
Aside from the ultra-rapid insulin products, Thermalin is also developing a U-500 ultra-rapid product which is highly concentrated. This product will be ideal for use in miniature pumps that require a much higher concentration formulation as well as a quick onset time.

2.4.2.1 Manufacturing Process
Thermalin is bringing a technology platform that provides multiple shots on opportunities to achieve a higher success rate. The manufacturing process may vary on each different molecule. However, two major processes have been utilized: semi-synthesis and direct synthesis. The trypsin-mediated semi-synthesis is used to produce two-chain insulins with non-natural amino acid substitutions\textsuperscript{170}. One example of the overall manufacturing process is illustrated in Figure. 28.
The semi-synthesis includes expression of a recombinant miniproinsuline gene, generation of intermediate insulin, semi-synthesis using trypsin condensation, and product purification (Fig. 29).

The direct synthesis is applied for single-chain insulins and two-chain insulins without non-natural amino acids substitutions. It’s similar to the semi-synthesis process but without the semi-synthesis step. The overview of the direct synthesis process is showing in
2.4.2.2 Current Outsourcing Strategy

Thermalin Diabetes was founded in 2009 based on extensive work on insulin performed in the laboratories of Dr. Michael Weiss. Dr. Michael Weiss is also the Chairman of the Department of Biochemistry at Case Western Reserve University in Cleveland, Ohio\textsuperscript{171}. Thermalin’s sequence designs for novel insulin analogs are developed by Dr. Weiss. Recombinant expression clones are established in Thermalin’s facility for secreted fermentation, synthesis, and purification. For the majority of the processes, Thermalin is currently doing in-house. Some testing analysis, such as long-term stability studies\textsuperscript{xiv}, that need more advanced equipment are outsourced to contract research organizations (CRO). A similar situation applies to animal studies. Small animal studies are conducting in collaboration with Case Western Reserve University and big animal studies are performed with an outsource partner.

\textsuperscript{xiv} The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environment factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf).
Due to the fact that Thermalin is developing a platform for new types of insulin, it has a variety of molecules in its pipeline. Each molecule stands at a different checkpoint in the process. For example, some are proven to be promising plasmids that are ready for expressions (Fig. 31). Some are further down the line and are proven to be effective in rats, so they are ready for pig studies (Fig. 31). For analogs that progress into the clinical phase of development, Thermalin is planning to outsource the final fill and finish step in a GMP\textsuperscript{xv} qualified facility.

![Drug Discovery Cycle]

\textbf{3 Pharmaceutical Industry Overview}

The pharmaceutical industry is the part of the healthcare sector that deals with medications\textsuperscript{172}. The industry comprises different subfields pertaining to the development, production, and marketing of medications\textsuperscript{173}. These more or less

\textsuperscript{xv} GMP stands for Good Manufacturing Practice which is a system for ensuring the products are consistently produced and controlled according to quality standards (http://www.ispe.org/gmp-resources).
interdependent subfields consist of drug manufacturers, drug marketers, and biotechnology companies (Fig. 32).

As one of the world’s largest industries, many of pharmaceutical companies achieve annual sales of over $10 billion. The global pharmaceutical industry was worth an estimated $1 trillion in 2014. American and European markets together control over a third of the market. In 2013, global pharmaceutical markets generated revenues of $980 billion. North America contributed 41% of sales while Europe contributed 27.4%.

3.1 Introduction
The main goal of the pharmaceutical industry is to provide drugs that prevent infections, maintain health, and cure diseases. The industry directly affected the global population, so a number of international
regulatory bodies monitor things like drug safety, patents, quality, and pricing\textsuperscript{181}. Due to the fact that drug discovery and development are very expensive and slow, pharmaceutical industry often adjusts to changes and innovations slower than many other industries. According to Forbes, by 2010 development costs of new drugs were between $4 billion to $11 billion per drug (Table 6)\textsuperscript{182}. 
On the other hand, the pharmaceutical industry has made a great deal of progress over the last decade due to a research-oriented approach that has improved technologies, developed infrastructures, and increased research in the field of bioscience\textsuperscript{183}. The key drivers behind this growth include the aging population, changes in lifestyle and increased income, and rise in chronic diseases (Fig. 33).
Another critical element in the pharmaceutical industry is patent protection. A patent offers a set of exclusive rights granted by a sovereign state to an inventor or assignee for a limited period of time in exchange for detailed public disclosure of an invention. For patents issued for drugs, they typically last for 20 years. However, the pharmaceutical industry has been facing the threat of “the big patent cliff” since the 2000s because many of the most sellable drug patents were developed back in 1980s and 90s. The imminent expiration of a large number of patents allows generic drug manufacturers to produce cheaper versions of blockbuster drugs. In the U.S., the patent exclusivity of more than 110 products was set to expire between 2012 and 2014, among them 14 blockbuster drugs (Fig. 34). On the other hand, according to the Factbook, the
pharmaceutical industry only discovered and released on the global market just 21 “new molecular entities” in 2010\(^{188}\). The majority of new drugs each year are derived from already marketed drugs\(^ {189}\). However, due to rapid growth in the biotechnology/biopharma sector, 2015 or 2016 could be “the year of the product” as the industry sees years of research coming to fruition\(^ {190}\).

<table>
<thead>
<tr>
<th>Company/Ticker</th>
<th>Top Drug* (Disease)</th>
<th>2010E Sales (bl)</th>
<th>Patent** Exp.</th>
<th>Key Pipeline Drug</th>
<th>Disease (2015 Sales Potential bil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bristol-Myers/BMY</td>
<td>Plavix (stroke)</td>
<td>$5.8</td>
<td>2012</td>
<td>Ipilimumab</td>
<td>Melanoma ($1.0)</td>
</tr>
<tr>
<td>Eli Lilly/LLY</td>
<td>Zyprexa (schizo.)</td>
<td>4.8</td>
<td>2011</td>
<td>Semagacestat</td>
<td>Alzheimer’s ($0.3)</td>
</tr>
<tr>
<td>Merck/MRK</td>
<td>Singular (asthma)</td>
<td>5.0</td>
<td>2012</td>
<td>Vrapaxar</td>
<td>Stroke ($1.5)</td>
</tr>
<tr>
<td>Pfizer/PFE</td>
<td>Lipitor (cholesterol)</td>
<td>11.1</td>
<td>2011</td>
<td>Tasocitinib</td>
<td>Rheum. arthritis ($1.3)</td>
</tr>
</tbody>
</table>

**Figure 34. Big Pharmaceutical Companies Faces Patent Expiration Threats.**

### 3.2 Regulatory

The pharmaceutical industry is a highly-regulated industry because the use of ineffective, poor-quality, or harmful medicines can result in therapeutic failure, exacerbation of the disease, resistance to medicines, and sometimes death\(^ {191}\). In order to protect public health, governments need to approve comprehensive laws and regulation and to establish effective national regulatory authorities to ensure the manufacture, trade, and use of medicines are regulated appropriately and also the public has access to
accurate information on medicines. There is a web of regulations in the research-intensive, highly dynamic pharmaceutical sector. In fact, the industry regulates the entire drug life cycle, including the patent application, competition with generics, marketing approval, and patent expiration, not just clinical trials. Regulations also control all prescribing physicians, wholesalers, retailers, and manufacturers in the pharma industry. The entities that set the regulations and controls include but are not limited to World Health Organization (WHO), US Food and Drug Administration (FDA), Medicines and Healthcare Products Regulatory Agency (MHRA) (Fig. 35).

Figure 35. International Drug Regulators.

### 3.2.1 The FDA
The FDA is the U.S. government agency charged with ensuring the safety and efficacy of the medicines available to the population in America. For new drugs development and approval, FDA’s Center for Drug Evaluation and Research (CDER) is the organization oversees the activity. Before a drug can be tested in clinical trials,
the pharmaceutical company must perform laboratory and animal tests to discover how the drug works and its safety and efficacy\textsuperscript{199}. Once the lab works are finished, the company may submit an Investigational New Drug (IND) application to CDER\textsuperscript{200}. Once the IND application is approved, the company could begin their clinical trials\textsuperscript{201}.

3.2.2 The Clinical Trials
Clinical trials are conducted in a series of steps, also called phases\textsuperscript{202}. Each phase is designed to answer a separate research question\textsuperscript{203}. According to Fig. 32, phase I studies assess the safety of a drug within a small group of healthy volunteers, around 20 to 80\textsuperscript{204}. If the drug is proven to be safe, the phase II studies will test the efficacy of the drug which involves up to several hundred patients\textsuperscript{205}. Most phase II studies are blinded meaning one group receives the experimental drugs while a second group receives a placebo\textsuperscript{206}. Phase III is essentially a larger scale of patient pool than phase II which involves thousands of participants\textsuperscript{207}. Phase III is conducted to validate its effectiveness, monitor side effects, compare to commonly used treatments, and also collect useful information that will allow the drug to be used safely\textsuperscript{208}. Once the research shows that the drug works well, the pharmaceutical company can apply for FDA approval for its specific use\textsuperscript{209}. Lastly, the phase IV studies are typically done after the drug has been marketed to compare a drug
with other marketed drugs and monitor its long-term effectiveness\textsuperscript{210}. Failures during phase IV studies can result in a drug being taken off the market or restrictions of use could be placed on the product depending on the findings in the study\textsuperscript{211}. The time it takes to finish the clinical trials vary greatly in the industry\textsuperscript{212}. It might take 10 to 15 years or even more to complete all three phases before the licensing stage\textsuperscript{213}.

![Figure 36. The Clinical Trial Phases.](image)

### 3.3 Pharmaceutical Industry Trend
The pharmaceutical industry will face significant challenges in 2016\textsuperscript{214}. With an increase of the instance of chronic diseases, it places great pressure on already stretched healthcare budgets\textsuperscript{215}. In addition, healthcare policy-makers and payers are increasingly mandating what doctors can prescribe\textsuperscript{216}. Also, according to Deloitte notes in its 2016 life sciences outlook, both public and private insurers are flatly refusing to pay for
expensive treatments that don’t represent a significant benefit to patients\textsuperscript{217}. With that being said, the pharmaceutical industry is starting to turn into a customer-centered industry not like what it was used to be when the pharmaceutical companies and doctors had the most deciding power. Maintaining innovation is another key element to be competitive in the industry. Innovation will also be driven by an increase in collaboration across the pharma sector\textsuperscript{218}. To thrive in the increasingly competitive modern pharma market, companies will have to work together to develop innovative products as well as share skills and expertise\textsuperscript{219}.

From the regulatory perspective, the environment is simultaneously getting more rigorous\textsuperscript{220}. The European Medicines Agency (EMA) recently introduced a new, three-pronged approach to the management of adverse reactions\textsuperscript{221}. The FDA is also building an active surveillance system called Sentinel to oversee the safety of all medicines on the U.S. market\textsuperscript{222}. Regulators around the globe are also collaborating more closely, so a drug that’s rejected in one region is more likely to be rejected in others\textsuperscript{223}. As the market is getting much tougher with tighter regulation, it is not surprising to see more mergers and acquisitions happening in 2016\textsuperscript{224}. Although the trend is unsustainable, a way to preserve it is by altering our concept of healthcare itself\textsuperscript{225}. Instead of focusing on the treatment of disease, we need to focus on curing, or even preventing it\textsuperscript{226}. The pharmaceutical industry has a crucial role to play in making the transition\textsuperscript{227}. 
4 Outsourcing Strategies for Pharmaceutical Startups

Pharmaceutical startups, especially in early stages, are facing many obstacles including finance, team structure, cost controls, legal support and etc. Because innovations in the pharma industry take a quite long time, it’s crucial for pharmaceutical startups to make wise choices about how to allocate funds. For research-based pharma startups such as Thermalin Diabetes, government grants are favorable. In the U.S., the funding from the National Institutes of Health (NIH) via Small Business Innovation Research (SBIR) program encourages domestic small businesses to engage in research and development that has the potential for commercialization\textsuperscript{228}. These types of grants typically have time limits. For example, in SBIR phase I, the project has to finish within six months, and it is up to two years for phase II\textsuperscript{229}. Therefore, having well-thought out cost planning in hand is the key to survival in the startup world. However, delivering an acceptable outcome within a time frame for a startup is often challenging. This is also the reason why many small pharmaceutical companies are outsourcing many of their testing or analysis to outside vendors. In the following sections, a more thorough outsourcing strategy for small pharmaceutical companies will be discussed.
4.1 What is Outsourcing

Outsourcing is the term used when an entity transfer portions of work to outside suppliers rather than completing it internally\textsuperscript{230}. For example, a large pharmaceutical manufacturer might outsource its complex quality control testing to firms that specialize in those types of work since they are not related to strategic to the business\textsuperscript{231}. Almost every organization outsources in some way\textsuperscript{232}. The main goal of outsourcing is to allow the company focus on developing internal capabilities that can both provided a strategic advantage and cannot be easily obtained outside the company\textsuperscript{233}. Outsourcing also allows a company to focus limited capital on key activities instead of on building corporate infrastructure. Because of its cost-effective benefit, outsourcing has become popular across the industry over the past decade\textsuperscript{234}. In 2014, the global market size of outsourced services was $104.6 billion U.S. dollars, the highest point to date\textsuperscript{235}. In the pharmaceutical industry, outsourcing is a strategic business option for companies to flourish and survive in the hypercompetitive global marketplace\textsuperscript{236}. Outsourcing once considered as a cost-saving initiative is now viewed as a “strategic competitive weapon” for many pharmaceutical companies\textsuperscript{237}. With an increase in price and cost pressures, regulatory requirements, and time needed to bring new products, pharmaceutical companies are looking for new business models, accomplished through contract manufacturing and research\textsuperscript{238}. The global market for contract manufacturing drugs/active pharmaceutical ingredients (APIs) in various
dosage forms was $52.2 billion in 2012 and is projected to increase at a five-year compound annual growth rate (CAGR) of 6.0%, reaching $79.4 billion by the end of 2018 (Fig. 37).

![Figure 37. Global Market for Pharmaceutical Contract Manufacturing, Research, and Packaging, 2011-2018 ($ Billions).](image)

**4.1.1 Reasons for Outsourcing**

Pharmaceutical outsourcing has become a viable and a beneficial business strategy that allows firms to leverage resources, spread risk, and focus on issues imperative to survival, competitive advantage, and future growth. Pharmaceutical companies outsource for various reasons. Lower operational, labor, and R&D costs are among the primary reasons why companies choose to outsource (Fig. 38). When properly executed it has a defining impact on a company’s performance. For many pharma companies, cost saving is the
primary reason for outsourcing but is not the only reason\textsuperscript{243}. Focusing on its core is another important reason (Fig. 38). Core competencies are the company’s strengths and abilities developed over a long period of time and are difficult to replicate\textsuperscript{244}. Core competencies are also the most important factor to a company’s success\textsuperscript{245}. Therefore, in order to maintain control over core competencies, companies choose to outsource for their non-core processes which allow them to focus on their core competencies\textsuperscript{246}.

Sometimes it is difficult for companies to maintain sufficient internal resources. More importantly, this limitation creates bottlenecks for company’s efficiency on production. Therefore, choosing to outsource provides small pharma businesses much more capacity so that the speed to market of new drugs can be increased (Fig. 38).
In summary, companies undertake to outsource for a variety of reasons depending on their vision and purpose of the exercise\textsuperscript{247}. While it may vary from company to company, the fruits of labor are visible among some of the leading enterprises worldwide, where outsourcing has become a core component of day to day business strategies\textsuperscript{248}.

4.1.1.1 Advantages of Outsourcing

As a small pharma company, Thermalin Diabetes would benefit from outsourcing in many different ways. The most obvious and visible benefit is related to the cost savings that outsourcing can provide (Fig. 39)\textsuperscript{249}. For analytical testing such as pharmacokinetic studies, if outsourced, it eludes the need to purchase equipment and hire individuals in-house\textsuperscript{250}. Hence, recruitment and operational costs can be minimized to a great extent\textsuperscript{251}. This is one of the prime advantages of outsourcing\textsuperscript{252}. Furthermore, if we expand the outsourcing strategy to the global market, countries like China and India will provide further cost reductions due to the difference in wages between western countries and Asia\textsuperscript{253}. The same kind of work that is done in the U.S. can be done in India at a fraction of the cost\textsuperscript{254}. According to statistics, the cost savings are about 60\% by outsourcing the work to India\textsuperscript{255}. 

Figure 38. Top Reasons for Outsourcing.
It is difficult for Thermalin to handle all aspects of a business or every technical process internally for the most times. Thus, outsourcing becomes a viable option to bring outside expertise and help Thermalin effectively complete the tasks (Fig. 39)\textsuperscript{256}. By doing so also helps Thermalin concentrate on its core processes such as small-scale insulin analog production and characterization\textsuperscript{257}.

![Benefits of Outsourcing](image)

*Figure 39. Benefits of Outsourcing.*

Again, outsourcing is a prudent business decision that, if implemented properly, can benefit Thermalin for years\textsuperscript{258}. However, certain strategies have to be in place for a successful outsourcing. For example, Thermalin needs to have clear needs, goals, and objectives for outsourcing\textsuperscript{259}. A rigid vendor selection criteria is also necessary as well as a properly executed contract. More importantly, the support and involvement of senior executives
is crucial.  

4.1.1.2 Disadvantages of Outsourcing
While mostly positive results arise from outsourcing, be aware of a few possibly negative consequences. Like any other business venture proper planning and research are necessary before choosing an outsourcing partner whether it is onshore or offshore. No matter what process Thermalin is planning to outsource, Thermalin is turning the management and control of that process over to another company (Table. 7). Although it is true that a contract is effective between the two parties, the managerial control of project execution will ultimately belong to another company. Thermalin is able to define the outcomes of the project, but often times it is not practical to provide close supervision during the project so that project delays due to a misunderstanding of two parties or cost increase may occur. This is because that the vendors are not driven by the same standards and mission that drives Thermalin. They are driven to make a profit from the services that they are providing to Thermalin and other business like Thermalin.

Outsourcing is usually associated with cost savings. However, outsourcing can be expensive too by having hidden costs (Fig. 40). Anything that is not covered in the contract will be the basis for

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xvi Offshore outsourcing means when companies outsource to organizations located in other countries or to foreign subsidiaries.
Thermalin to pay additional charges\textsuperscript{267}. The hidden cost issue might get more serious when dealing with foreign companies across international boundaries\textsuperscript{268}. This increased cost might reduce or even eliminate the savings by having an offshore outsourcing vendor in some cases.

### Hidden Costs of Outsourcing

- Attractive low hourly rates distracted CIO/CTO’s from hidden costs which result in higher Total Cost of Engagement

![Figure 40. The Hidden Costs of Outsourcing.](image)

As shown in table 7, there are many disadvantages of outsourcing. Among these disadvantages, the intellectual property (IP) issue is another critical one. For Thermalin, as an early-stage pharma company, the IP portfolio is one of the biggest assets. Outsourcing to outside vendors unavoidably involves sharing confidential information with them. There is a risk that the confidentiality may
be compromised even when a non-disclosure agreement\textsuperscript{xvii} (NDA) is signed\textsuperscript{269}. Some good practices may prevent security issues from happening are to keep track the NDA status with each vendor constantly, control the information exchanged with vendors after the NDA execution, and make sure the contract has a penalty clause if an incident occurs\textsuperscript{270}.

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
Possible loss of cost control in developing the product. \\
Possible loss of quality of the product. \\
Possible delays in product development due to scheduling issues. \\
Possible confusion about accountability in the decision-making process. \\
Breach of security as intellectual property is exchanged between companies. \\
Information exchange can lead to information being lost or even leaked. \\
Possible delay in product manufacturing due to government and political issues. \\
Extensive technical training is required to provide in-depth knowledge of specific drug manufacturing. \\
Overall drug manufacturing cost may increase due to indirect expenses such as technical training. \\
Technical training of CMO staff may increase competition in the future. \\
\hline
\end{tabular}
\caption{Key Disadvantages of Outsourcing.}
\end{table}

\textit{Source: BCC Research}

4.1.2 The Decision-Making Process

Contract manufacturing or research firms are in great demand as pharmaceutical and biotech companies often prefer to contract out their manufacturing or complex analytical testing rather than building their own manufacturing facilities\textsuperscript{271}. Prior to signing the agreement with the vendors, it is very important to conduct a series of careful

\textsuperscript{xvii} A non-disclosure agreement, also known as confidential disclosure agreement (CDA), is a legal contract between at least two parties that outlines confidential material, knowledge, or information that the parties wish to share with one another for certain purposes, but wish to restrict access to or by third parties (https://en.wikipedia.org/wiki/Non-disclosure_agreement).
assessments\textsuperscript{272}. Conducting due diligence when selecting a contract manufacturer is not only done to choose the best vendor with great technical capabilities but also a vendor that can be trusted\textsuperscript{273}. Building a relationship and a partnership with the vendor is necessary because if the vendor is equally involved in Thermalin’s projects, then the outcome is more structured, productive, and mutually beneficial\textsuperscript{274}. From a decision-making perspective, it is always a good practice to start off with asking the question: which activities should we outsource, and which tasks should we do in-house\textsuperscript{275}? In order to answer the questions, a decision-making matrix is used. As shown in Fig. 41, four quadrants are divided by strategic importance and contribution to operational performance from low to high\textsuperscript{276}. For the strategic importance, we need to ask questions: is it part of what makes Thermalin’s business unique\textsuperscript{277}? From the operational performance, we need to decide how important this task is to Thermalin’s day-to-day operations\textsuperscript{278}. Will Thermalin’s operations be severely compromised if it is done badly\textsuperscript{279}? Then the answers will be plotted into these quadrants.
4.1.2.1 Form a Strategic Alliance

For tasks that fall into “form a strategic alliance”, they are high in strategic importance but contribute little to operational performance\textsuperscript{280}. Therefore, they are relatively insignificant in terms of smooth running, so they are not worthy of full in-house focus\textsuperscript{281}. However, we still need to retain control of them to ensure they are done exactly as what we want\textsuperscript{282}. The animal studies fall into this category as they are a critical piece during the new insulin analog development, but Thermalin’s core focus is developing the analogs and these studies have a relatively low impact on the day-to-day operational performance of Thermalin\textsuperscript{283}.  
4.1.2.2 Retain
The tasks in “retain” quadrant are high in strategic importance and have a big impact on operational performance\textsuperscript{284}. These tasks should be kept in-house so that Thermalin keeps maximum control\textsuperscript{285}. For example, the expression and purification of insulin analogs are core competencies of Thermalin’s business so they should be done in-house.

4.1.2.3 Outsource
For quadrant “outsource”, it’s self-explanatory that these tasks could safely be outsourced\textsuperscript{286}. They are usually important for successful operational performance but are not strategically important\textsuperscript{287}. It is simply not worth spending in-house time managing\textsuperscript{288}. The fill/finish of Thermalin’s product that will be used in clinical trials is a great example for this quadrant. Supplying the patients with Thermalin’s product as they need them is important during clinical trials so they are important for successful operational performance. However, the fill/finish can be done at many different CMOs’ facilities, which means it is not strategic important.

4.1.2.4 Eliminate
The last quadrant “eliminate” shows the tasks that are not important to Thermalin’s overall strategy and nor do they make a significant contribution to our operational performance\textsuperscript{289}. Although it is not
necessary to eliminate these tasks completely, it is important to check why we are performing them\textsuperscript{290}.

4.1.2.5 The Decision Tree
For tasks in the “outsource” quadrant, they will then enter the decision tree process to determine whether they can be outsourced or not to a certain vendor as shown in Fig. 42. The decision tree is a vendor specific tool that can help Thermalin screen vendors.
Figure 42. The Decision Tree of Making the Outsource Decision for Thermalin.
4.1.2.6 Vendor Evaluation and Selection Criteria

Contract manufacturing/research has undergone a tremendous change from a tactical to a strategic form of outsourcing\(^{291}\). Consumer awareness regarding FDA warnings due to misconducts and low-quality products/services along with global competition has made it essential for vendors in the pharma industry to provide high-quality services at the lowest cost possible\(^{292}\).

Service/product quality, cost competitiveness, delivery schedule, and vendor/customer relationship are important factors in achieving success in the outsourcing market\(^{293}\).

Selection of the best-qualified CRO is critical to the success of a project\(^{294}\). The vendor-sponsor relationship is also important. Insufficient communication or miscommunication between two parties can result in the delay or even the failure of a project\(^{295}\). When interacting with vendors prior to signing the contract, it’s critical to evaluate their speed of response and how well they are willing to coordinate. When the contract is established, Thermalin needs to make sure the communication between the vendor and sponsor is defined such as how, how often, from whom, to whom, and under which conditions\(^{296}\). Table 8 is showing the key selection factors while evaluating vendors. GLP, GMP, and clinical experience are nice-to-have items but not required for all
outsourcing projects. Among all factors, the readiness and cost are the two most important criteria for selecting a right vendor.

Table 8. Key Factors in Selecting a Vendor for Thermalin.

<table>
<thead>
<tr>
<th>Expertise to conduct the type of study needed</th>
<th>Reputation in the industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reputation of all associated laboratories</td>
<td>Capacity to do all types of studies</td>
</tr>
<tr>
<td>Responsiveness to the hiring company’s needs</td>
<td>Qualifications of the staff</td>
</tr>
<tr>
<td>Experience level of the staff</td>
<td>Organization in performing the studies</td>
</tr>
<tr>
<td>Cost of hiring the contract research organization</td>
<td>Reliability to finish the project in a timely manner</td>
</tr>
<tr>
<td>GLP (Good Laboratory Practice) compliance</td>
<td>Ability to perform the clinical trial</td>
</tr>
<tr>
<td>Ability to supply qualified and adequate resources</td>
<td>Ability to form a partnership and relationships with the hiring company</td>
</tr>
<tr>
<td>Assurance that no associated employee has been debarred by the FDA</td>
<td>The employees should have good clinical practice training</td>
</tr>
<tr>
<td>Properly trained clinical research associates available.</td>
<td>Good relationship with subcontractors</td>
</tr>
<tr>
<td>Good relationship with subcontractors</td>
<td>Fully trained and available clinical investigators</td>
</tr>
<tr>
<td>Knowledge of regulatory affairs</td>
<td>Ability to handle complex clinical trials</td>
</tr>
<tr>
<td>Ability to gather large participants for clinical trials</td>
<td></td>
</tr>
</tbody>
</table>

4.2 Potential CMOs/CROs for Thermalin’s Projects

Leveraging the experiences interacting with many different CMOs and CROs, here are some good examples that I would recommend for Thermalin in consideration for future references.
4.2.1 Albany Molecular Research INC, (AMRI)

Found in 1991, AMRI is a contract research and manufacturing organization that provides drug discovery, development, cGMP manufacturing and aseptic fill/finish services. In December 2012, AMRI extended a commercial supply agreement with GE healthcare for aminobisamide hydrochloride, through Dec. 31, 2016. This new contract extended the existing supply contract that was initiated in 2005. In February 2013, AMRI and Codexis partnered for improved process development. The partnership aims to integrate their capabilities and technologies to find and implement new manufacturing routes for selected active pharmaceutical ingredients. With a very strong background in pre-clinical API production and GMP manufacturing, AMRI is one of the best options for Thermalin in terms of downstream fill/finish project and API development. The wide spectrum of services that AMRI provides can potentially save lots of logistics costs for Thermalin if multiple projects need to be outsourced at the same time. It is rare to find CROs that offers upstream activities, such as API manufacturing, as well as downstream activities, such as fill/finish and packaging, at the same time because many CROs in the pharmaceutical industry are only specialized in one area.

xviii Aminobisamide hydrochloride is an intermediate material used in diagnostic imaging agents. (contract research p 58)
4.2.2 Lonza

Lonza was founded over one hundred years ago in Switzerland. Starting from a chemical reagent manufacturing company, Lonza has been constantly expanding its business in biotechnology. It has a variety of services to offer ranging from API and stem-cell therapies to drinking water sanitizers, from the vitamin B compounds and organic personal care ingredients to agricultural products. In October 2010, Lonza expanded its operations to include viral vaccines and gene therapy vectors by acquiring Vivante GMP Solutions. The acquisition extended Lonza’s strategy to broaden its biologics custom service offering for the growing viral vaccine and gene therapy markets. In 2013, Lonza completed the validation of its viral induced cell processing Good Manufacturing Practice suites in Houston, Texas. With this validation, Lonza will begin manufacturing autologous virus-induced immunotherapy products. Just in 2016, Lonza announced its expansion in Portsmouth to further expand its manufacturing facilities. With its broad spectrum of services provided, Theralin can potentially collaborate with Lonza on numerous projects such as drug candidate development and analytical testing assays.
4.2.3 Covance

Covance, headquartered in New Jersey, is a CRO that provides drug development and animal testing services\(^{311}\). Covance has a long-term relationship with Eli Lilly and Co. In August 2008, it purchased an early drug development facility in Greenfield, Indiana from Eli Lilly for $50 million\(^{312}\). In a contract valued at $1.6 billion, Covance agreed to provide Eli Lilly with drug development services for 10 years\(^{313}\). In 2011, Covance introduced new chemistry, manufacturing, and controls (CMC) pharmaceutical development services, including the development and supply of APIs, and API characterization, pre-formulation, formulation, and regulatory submission\(^{314}\). Covance is one the contract research organizations that Thermalin has done collaborations with in the past. The projects Covance and Thermalin have done together provide a steady foundation for continuous collaborations, potentially small animal studies.

4.2.4 Eurofins Lancaster

Eurofins Lancaster is one of the largest contract laboratories in the U.S. and it has facilities worldwide\(^{315}\). Eurofins Scientific acquired Lancaster Laboratories in 2011 to form Eurofins Lancaster\(^{316}\). Eurofins Lancaster is specialized in pharmaceutical analytical services and it offers a portfolio of over 100,000 reliable analytical methods for characterizing drug substance’s identity, purity, and composition\(^{317}\). In May 2015, Eurofins acquired QC Laboratories in
the U.S., and in June, it announced the acquisition of Biomnis in France\textsuperscript{318}. The aggressive strategy of expansion has helped Eurofins Lancaster become competitive in the analytics industry. Thermalin is currently in discussion with Eurofins Lancaster for several testing assays using the LC-MS/MS\textsuperscript{xix}.

4.3 Cost Analysis
For most pharmaceutical companies, especially smaller size companies with limited funding sources, the outsourcing vs. in-house decision making comes down to one factor which is cost\textsuperscript{319}. In cost accounting, outsourcing is defined as purchasing a good or service from an outside vendor rather than producing the good or service in-house\textsuperscript{320}. It is also referred to as a make versus buy decision\textsuperscript{321}. Many pharma companies are looking into ways to cut costs to stay competitive\textsuperscript{322}. While enjoying the gains brought by outsourcing, it is easy to neglect the significant internal costs associated with outsourcing\textsuperscript{323}. In the following sections, two projects that have high outsourcing potential will be evaluated from both outsource and in-house perspectives based on costs including outside and internal costs. One project is the API purification and the other one is the diabetic rat model.

\textsuperscript{xix} LC-MS/MS is liquid chromatography-mass spectrometry. It is an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography with the mass analysis capabilities of mass spectrometry (MS). (https://en.wikipedia.org/wiki/Liquid chromatography%E2%80%93mass spectrometry)
4.3.1 Cost Analysis of Outsourcing API Purification

One project that is evaluated for outsourcing potential is the API purification. The API purification project starts after the fermentation process. Therefore, the CMO will receive the crude protein in bulk form and capture using the purification technique. If the semi-synthesis method is applied, the CMO needs to perform the semi-synthesis step using the polypeptide to incorporate unnatural amino acids, which Thermalin will supply, and trypsin for the condensation reaction. The last process will be the purification steps after the semi-synthesis process. Then, the purified product will be sent to our current CRO Covance for testing.

Based on the specific project scope, I was able to obtain several cost proposals from different CMOs from both international and U.S. based companies. Anthem BioScience was one of the CMOs that offered competitive price with extensive experiences in the field. In Table 9, the costs are broken down into different processes as well as different scales including technology transfer, small scale (500mg), medium scale (engineering run), and large scale (GMP run). In total, it would cost Thermalin $889,700 to finish the production at three different scales, which is similar comparing to the cost of internal production at Thermalin and significantly lower than other vendors. The total number is the key determinant when comes to make the outsourcing decision.
The only element is not considered in the cost analysis is manpower that could be saved internally by outsourcing the production. By outsourcing the API production to an outside CRO can potentially free up staff working hours that can be allocated to other projects. With that being said, Thermalin may focus on streamlining the insulin analog pipeline. It is a good direction for future studies.

### 4.3.2 Cost Analysis of Performing API Purification In-House
Thermalin currently does the API purification in-house. However, it is crucial for Thermalin to have a clear understanding of how much exactly it would cost to execute the project internally. To make the comparison easy, the in-house costs are also calculated based on small, medium, and large-scale operations (Table 10). As shown in Table 10, the total cost is $885,345 which is slightly lower than the
outsourcing cost. However, the GMP run cost in outsourcing is much lower than doing it in-house. It is indicative that outsourcing the GMP run is favorable to Thermalin in terms of costs.

<table>
<thead>
<tr>
<th>Cost Element</th>
<th>Cytovance</th>
<th>WPI</th>
<th>Polypeptide</th>
<th>Thermalin</th>
<th>Supplies</th>
<th>Covance</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tech Transfer</td>
<td>56,000</td>
<td>0</td>
<td>3,500</td>
<td>0</td>
<td>0</td>
<td>233,928</td>
<td>293,428</td>
</tr>
<tr>
<td>500mg Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Engineering Run</td>
<td>0</td>
<td>10,500</td>
<td>10,000</td>
<td>28395</td>
<td>47,000</td>
<td>0</td>
<td>95,895</td>
</tr>
<tr>
<td>GMP Run</td>
<td>199,000</td>
<td>0</td>
<td>55,000</td>
<td>50750</td>
<td>169,286</td>
<td>21,986</td>
<td>496,022</td>
</tr>
<tr>
<td></td>
<td>255,000</td>
<td>10,500</td>
<td>68,500</td>
<td>79,145</td>
<td>216,286</td>
<td>255,914</td>
<td>885,345</td>
</tr>
</tbody>
</table>

Similar to the outsourcing cost analysis, the analysis above doesn’t include the labor cost, which might increase the total cost to another level. However, in terms of cost efficiency, the decision of whether to outsource or not to outsource in this case is easy since there is not a huge price difference between two options. By retaining the production in-house, it may also create more involvements among the staff and increase the job satisfaction level.

5 Risk Assessment of Outsourcing

Many pharmaceutical companies choose to outsource parts of their drug development and operations in order to reduce risks. The process of developing drugs is complex and, time-consuming. Development of a new
drug is becoming more risky and costlier as an increased number of drugs have failed in clinical trials\textsuperscript{326}. Therefore, many companies use the strategy of risk sharing with outsourcing partnerships to allow them to lower operational risks by sharing management and financial responsibilities\textsuperscript{327}. However, the outsourcing activity itself brings a significant set of risks\textsuperscript{328}. A risk assessment process is helpful for Thermalin to identify potential “hazards” and analyze what could happen if “a hazard” occurs (Fig. 43)\textsuperscript{329}. In the following sections, different types of risks that are associated with outsourcing will be identified and analyzed. More importantly, ways to manage these risks will be discussed as well.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Risk_Assessment}
\caption{Risk Assessment Process.}
\end{figure}
5.1 Risks of Outsourcing

Outsourcing has proven to be effective in pharmaceutical industry, but it brings significant risks that must be recognized and managed\textsuperscript{330}. In outsourcing, Thermalin is relying on another company to run certain processes\textsuperscript{331}. If the outsourcing risks are not properly managed, they may negatively affect Thermalin’s operations\textsuperscript{332}. The product or service can often be outsourced, but the risk cannot\textsuperscript{333}. If “a hazard” happens in outsourcing, the time spent on fixing the problem could cause delays in Thermalin’s production timeline. The service quality may also suffer in outsourcing\textsuperscript{334}. Therefore, it is clear that outsourcing risk assessment is a critical tool in Thermalin’s business strategy. As shown in Fig. 39, the first step in risk assessment cycle is to identify all possible risks.

5.1.1 Planning and Management Risks

Project planning and management are critical disciplines to enable successful outsourcing initiatives\textsuperscript{335}. These risks are internal and can be controlled at the very beginning of each outsourcing project. According to a survey conducted by Nicholas A. Benvenuto, who is a founding managing director at Protiviti a technology risk and internal audit consulting firm, only one-third of respondents said the project planning and management risks are managed with only average
effectiveness. It shows that companies often underestimate the risks associated with poor planning and management.

The planning and management referenced in this section go beyond Gantt charts and critical path analysis, although they are important tools in project planning and management. The more important element is the effective use of the people who have the appropriate project management and risk management skills and experiences and the ability to use the right tools to get work done. The people working with the CMO or CRO should possess the technical understanding of the project and also related business objectives. Furthermore, they must be able to think critically about and assess what could go wrong and put risk mitigation plans in place to handle the situation. If the outsourcing team does not have enough knowledge of understanding the specific project objectives, it may cause pricing mismatches in the later stage and also project delays. Therefore, the team should have a diversity of skills and opinions with multi-disciplined backgrounds ranging from biotechnology to business management.

5.1.2 Provider Selection Risks

Once the risk assessment tool is implemented and completed, the next step should be evaluating service providers to determine their ability, both operationally and financially, to meet Thermalin’s needs. Provider selection is an important step in the outsourcing process.
which can give rise to a wide range of risks\textsuperscript{343}. The risks may include delays leading to increases in overall costs, loss of expensive test articles that are time-consuming to produce, discontinuity of the service provided, loss of influence in relationships with the existing essential vendors, and unauthorized disclosures of the confidential information\textsuperscript{344}.

5.1.3 Contracting and Negotiation Risks
The contracting and negotiation process is one of the most critical phases in outsourcing and is also the point where dialog and direct responsibility is often moving from the deal makers to the operators\textsuperscript{345}. Therefore, it is a time when issues may surface for the first time\textsuperscript{346}. Companies like Thermalin may encounter situations where service providers do not provide clear responsibilities and costs in the contract. This is not uncommon to see during the contracting phase. Other risks may include costly delays in the timetable and realization of benefits from the outsourcing, and long-term damage to the relationship with the vendor due to an adversarial approach being taken to negotiations\textsuperscript{347}.

5.1.4 Employee Resistance Risks
Employee resistance can be a major issue when outsourcing any type of operation that has been done in-house before\textsuperscript{348}. Losses in morale, productivity, and personnel are common\textsuperscript{349}. Based on Outsourcing
Center website, an online platform for outsourcing sources, it has conducted hundreds of interviews with employees. Most of the employees expressed their fears of job loss in outsourcing\textsuperscript{350}. Absenteeism due to “illness” may increase at such times\textsuperscript{351}. Some employees with valuable knowledge quit unexpectedly\textsuperscript{352}. Some make the process of knowledge transfer difficult which may slow down the production\textsuperscript{353}.

5.1.5 Vendor Shirking Risks
The research was conducted by Salanta Popa from Romania was to study the main outsourcing encountered risks of Failure by giving a three-part questionnaire to 88 different respondents from different companies\textsuperscript{354}. Then the mean of different risk frequencies was calculated. In the results, the researchers have found that companies do experience provider-quality related risks the most (Table 11). As shown in Table 11, poor provider competence and deterioration of service are the most encountered risks in outsourcing. The poor provider competence risk can be mitigated through a rigid vendor selection criteria. However, the risk of deterioration of service, also called shirking risk, is more difficult to detect and manage.
The simplest forms of shirking risk all involve lack of effort simply because the vendor has alternative uses for the same resources and shirking generally happens after the contracting phase. For example, the vendor can provide low levels of effort, either in the performance of the primary task or in subsequent quality assurance activities. The vendor can shift staff assignments and use more junior staff than client was promised. All the actions may lead to compromised service quality, elongated project timeline, and increased overall costs. These forms of risk are created simply because the vendor may have other uses for critical resources required to perform optimally. In such cases, the vendor does not work to what’s covered in the contract, or does not invest in training, or does
not assign appropriately trained personnel while claiming full payment$^{359}$.

5.2 Risk Management and Mitigation

Outsourcing presents many challenges regardless of what is being outsourced$^{360}$. Unlike risk analysis, which is typically a point-in-time assessment, risk management, and mitigation in outsourcing are ongoing processes that should be integrated into the entire outsourcing strategy system$^{361}$. The following sub-sections will thoroughly assess the possible management and mitigation plans for specific risks discussed in previous sections.

5.2.1 Planning and Management Risks

During the planning phase, a risk management model can be utilized (Fig. 44). In this model, the project is continually being evaluated in relation to goals and objectives that were set out initially$^{362}$. Evaluation meetings can be held weekly or monthly to go through a list of questions testifying if the goal is met or identifying barriers preventing objectives from being achieved. During these meetings, it would also be beneficial to ensure that risk management strategies and controls are in place and adequate. By doing so, gaps and obstacles that prevent the project from being successful can be identified.
5.2.2 Provider Selection Risks

One of the easiest management actions to put in practice to mitigate provider selection risks is a rigorous selection process\(^{364}\). Figure 45 is showing a good example of such a selection process. The steps included in this process should happen in a chronological order.

**Figure 45. An Example of a Provider Selection Process.**
Although outsourcing is becoming more distributed and globalized, the location of vendor’s facility is a key determinant during the selection process. Choosing the optimal location can save Thermalin much time and money spent on transportation and communication. If Thermalin is considering global outsourcing, it is necessary to give more attention to country-specific risks regarding local rules and regulations.\(^{365}\).

5.2.3 Contract and Negotiation Risks
It is crucial to have a clear contract with sufficient details provided for performance, reliability, security, confidentiality, and reporting.\(^{366}\).

More specifically, the contract should include but not limited to project scope, timeline, performance standards, data reporting frequency and method, regulatory compliance, payment terms, and transition requirements and provisions. If the service providers cannot or will not agree to terms that Thermalin requests to manage the risk effectively, Thermalin should either not contract with that provider or supplement the service provider’s commitments with additional risk mitigation controls.\(^{367}\).

5.2.4 Employee Resistance Risks
It is all human nature that people are resistant to changes and are afraid of losing power and control. However, relatively simple and
effective strategies and tactics can be employed to dramatically reduce the impact of these risks. Effective outsourcing communication should address specifically targeted audiences through the proper communication channels, with tailored messages, and timing. For example, some companies set up a small project management team dedicated to change management associated with their outsourcing initiative. Technical process owners and key management personnel can form the team. The team helps resolve issues with employees during the transition process. In addition, having up front and honest communication with the employees would also help mitigate the risks. The key points that need to be conveyed are: 1. How outsourcing will help the company become more competitive and meet the production timeline; 2. The outsourcing is due to strategic initiatives to support company growth and not due to employee’s poor performance. Also, it is extremely important to keep the communication frequent, not just in the initial stages. This would help the employees feel involved and engaged.

5.2.5 Vendor Shirking Risks
The nature of shirking is due to hidden action that is because the client is not able to observe closely and accurately what the vendor is doing during the project execution. One solution available is closer monitoring. However, this may be expensive and difficult if the vendor is distant. Another solution is to maintain two or more
competing vendors through horizontal chunkification\textsuperscript{xx}, compare their performance, and to discipline, fine, or drop the worst-performing vendor\textsuperscript{377}. The second solution is less expensive than close monitoring\textsuperscript{378}. The shirking risk can also be reduced by compensating the vendor better as performance increases\textsuperscript{379}. This is more effective than compensating the vendor for things that it offers at the beginning of the project and it also helps the sponsor company have a better control for things that cannot truly be observed such as effort\textsuperscript{380}. In fact, any action that reduces shirking enables the vendor to do a better job and to demonstrate the ability to do a better job\textsuperscript{381}.

5.3 Risk Assessment Application and Recommendation

In order to quantify cost efficiency of API production for Thermalin, a scoring system could be adapted to measure both risks and costs\textsuperscript{382}. The risks are scored in two main categories: internal and external (Table 12)\textsuperscript{383}. The internal risks include planning and management risks and employee resistance risks. The external risks include provider selection risks, contract and negotiation risks, and vendor shirking risks. Provider selection risks also cover regulatory compliance, supply assurance, quality, and service.

\textsuperscript{xx} Horizontal chunkification describes what portion or fraction of each activity will be allocated to the client and what portion will be allocated to the vendor (just right outsourcing p17).
Table 12. An Example of a Provider Selection Process.

<table>
<thead>
<tr>
<th>RISKS</th>
<th>SCORING SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internal Risks</strong></td>
<td></td>
</tr>
<tr>
<td>Planning and Management Risks</td>
<td>Capable team and adequate risk management model are in place</td>
</tr>
<tr>
<td>Employee Resistance Risks</td>
<td>Employees feel comfortable with the outsourcing activity</td>
</tr>
<tr>
<td><strong>External Risks</strong></td>
<td></td>
</tr>
<tr>
<td>Provider Selection Risks</td>
<td></td>
</tr>
<tr>
<td>Regulatory Compliance</td>
<td>Generally no compliance issues</td>
</tr>
<tr>
<td>Supply Assurance</td>
<td>Generally no specific issues</td>
</tr>
<tr>
<td>Quality</td>
<td>Generally no specific issues</td>
</tr>
<tr>
<td>Service</td>
<td>Responsive</td>
</tr>
<tr>
<td>Contract and Negotiation Risks</td>
<td>Responsibility and cost are presented clearly in the contract</td>
</tr>
<tr>
<td>Vendor Shirking Risks</td>
<td>Generally trustworthy vendor. No performance issues</td>
</tr>
</tbody>
</table>
The costs are scored in the two categories: manufacturing costs, and sponsor’s internal costs (Table 13). The manufacturing costs and sponsor’s internal costs are further traced to material costs, labor costs, and overhead costs. Examples of sponsor’s internal costs include project management, relationship building, process transfer, document translation for international business relations, and studies required by regulatory affairs.

Table 13. Breakdown of Outsourcing Costs.

<table>
<thead>
<tr>
<th>COSTS</th>
<th>SCORING SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Manufacturing Costs</td>
<td>Significantly lower than benchmark</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Comparable to benchmark</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Significantly higher than benchmark</td>
</tr>
<tr>
<td>Sponsor’s Internal Costs</td>
<td>Significantly lower than benchmark</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Comparable to benchmark</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Significantly higher than benchmark</td>
</tr>
</tbody>
</table>

The risk assessment can be estimated by the following calculation:

Risks = Planning&Management Risks * Employee Resistance Risks * Provider Selection Risks * Contract&Negotiation Risks * Vendor Shirking Risks

Costs = Manufacturing Costs * Sponsor’s Internal Costs

Risk Assessment Index = Risks * Costs

According to the equation above with the minimum value of 1 and maximum value of 3, Thermalin needs to mitigate risks and reduce costs at the same time, which means the smaller value of Risk Assessment Index the less risky to outsource. With that being said, the risks, costs, and risk assessment index are calculated for outsourcing API production to Anthem BioScience, which was previously discussed in the Cost Analysis.
section.

Table 14. Risks for Anthem-Led API Production.

<table>
<thead>
<tr>
<th>RISKS</th>
<th>SCORING SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Risks</td>
<td>1</td>
</tr>
<tr>
<td>Planning and Management Risks</td>
<td>√</td>
</tr>
<tr>
<td>Employee Resistance Risks</td>
<td>√</td>
</tr>
<tr>
<td>External Risks</td>
<td></td>
</tr>
<tr>
<td>Provider Selection Risks</td>
<td></td>
</tr>
<tr>
<td>Regulatory Compliance</td>
<td>√</td>
</tr>
<tr>
<td>Supply Assurance</td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>√</td>
</tr>
<tr>
<td>Service</td>
<td>√</td>
</tr>
<tr>
<td>Contract and Negotiation Risks</td>
<td></td>
</tr>
<tr>
<td>Vendor Shirking Risks</td>
<td></td>
</tr>
</tbody>
</table>

The analysis in Table 14 would provide the total score of 24. The scores of internal risks are subjective because they are based on my working experience with Thermalin team, which could be changed to better reflect the criticality of each risk. The regulatory compliance score is one because no warning letters have been identified for Anthem. Two would be given if warning letters are found for non-critical issues and three would be given if one or more warning letters are identified that lead to major plant shutdown or product recall. Due to the fact that Anthem is located in Bangalore India, the supply assurance is the most severe issue because it involves trans-national shipping. The project might delay unexpectedly if the test articles were held and investigated by local customs. As for Quality, Service, and Vendor Shirking Risks, the scores are based on the assumption that Anthem would strictly follow manufacturing guidelines and deliver the project on time and according to predefined specification. However, the assessment on this particular category can be done by
gathering references from Anthem’s former clients, searching for publications related to Anthem, and doing an on-site audit when possible. Lastly, two is given for Contract and Negotiation Risks according to the cleanliness and effectiveness of communication with Anthem previously comparing to other vendors at the same time.

<table>
<thead>
<tr>
<th>COSTS</th>
<th>SCORING SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Manufacturing Costs</td>
<td>√</td>
</tr>
<tr>
<td>Sponsor’s Internal Costs</td>
<td></td>
</tr>
</tbody>
</table>

As mentioned in the Cost Analysis section, the outsourcing cost to Anthem is comparable to performing the production in-house for Thermalin. Therefore, the scores are given accordingly in Table 15, which provide the total of 4.

Finally, the project of outsourcing API production to Anthem scores 96 in total. The scoring system is from 1 to 3\textsuperscript{10}, so 96 stands at a low percentile roughly about 0.1%, which means the project is relatively controllable in terms of risks and costs. However, the supply assurance issue is a major red flag that may need lots of attention from the senior management before initiating the project as it can lead to project delays and loss of expensive products. If no effective solutions to mitigate the risk were available at the time when we needed to make the decision, Thermalin should not proceed with the option of outsourcing the API production because it doesn’t provide Thermalin a significant cost saving and also the red flag may cause
bigger problems during the project execution.

6 Conclusion
As I have explored the outsourcing risks in the pharmaceutical industry and specifically for Thermalin above, it is certain that outsourcing any activity has various types of risk\textsuperscript{387}. Some risks are caused internally by poor planning and managing, some are caused by outside vendors, and some are operational and due to the complexity of processes outsourced\textsuperscript{388}. Regardless of the type of risk, in order to reduce that risk, it is clear that Thermalin must understand how to make the correct outsourcing decision. As Thermalin is marching forward on its product development and is constantly expanding, Thermalin needs to create a culture in the organization that can reinforce the importance of outsourcing. Integrating the outsourcing decision-making process with strategic planning is also beneficial for Thermalin. The decision matrix, risk assessment model, and management and mitigation plans discussed above should be able to guide Thermalin make the “what to outsource and what not to outsource” decision.

7 Discussion
As a small pharmaceutical company, Thermalin is experiencing and will continue to experience many changes due to its growth and also from other aspects in the next five years. Thermalin is currently dealing with a moderate amount of outsourcing activities to satisfy its operational needs. This thesis was mainly based on the extensive vendor experience that I have had while
trying to establish a solid vendor network for GMP manufacturing. Therefore, much of the analysis is a snapshot of Thermalin’s current progress. It would be interesting to investigate further when Thermalin needs more capacity in outsourcing. Moreover, the scoring system in Section 5.3 could be further refined by adding a weighing factor to each single risk category based on its criticality and impact on Thermalin’s overall performance. By doing so, the scoring system can be more powerful in the way that it captures the risk impact individually, which improves the specificity of this scoring system. Nevertheless, I still believe that what is discussed in this paper will still apply, but more unseen risks may show themselves when the scale is significantly larger.
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