



Evaluation of Squalastatine I as an Enzyme Inhibitor for Lowering Cholesterol

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Abstract

The objective of this project is to determine the feasibility of manufacturing and commercialization of a novel enzyme inhibitor of cholesterol synthesis. The goal is to propose a drug capable of lowering at least 50% of the total cholesterol level in patients dealing with high serum levels with the highest efficacy. This was done by analyzing the FDA and manufacturing processes, equipment pricing, manufacturing prices and determining highest demand for the drug, therefore, determining the best price for the drug.

The suggested drug inhibits an enzyme in biosynthesis of cholesterol but is differentiated from statin drugs by its higher efficacy and its area of operation. By working only as a squalene synthase inhibitor, squalostatin 1 (SQ1) does not decrease the production of coenzyme Q₁₀ (ubiquinone). Research has shown that this drug will lower serum cholesterol level by 50% using 10-20 mg/day dosage.

The success of this enterprise will mainly repose on the likelihood of its approval by the FDA and its marketing strategy. FDA process will be subdivided in four different phases with a specific goal at each step. Calculations evaluate the chances of SQ1 being endorsed by the FDA on its first attempt to reach 69%. Its overall duration is estimated at 10 years for a total cost of \$69.9 million.

To determine the best price for a unit of SQ1, four different prices were chosen; first, with \$1.33, second with \$1.7, third with \$4.8 and fourth with \$5.0 per unit. Best price for the drug was calculated using pricing analysis and demand model. The price was chosen based on the trends observed on the demand graphs. These graphs showed that lower prices give higher demand for the drug. The best price was determined to be \$1.33 per unit. This is lower than the generic brand of statin drugs in the market but based on the demand model and NPV graphs the demand will increase over years.

SQ1 is the product of a multi-stage process starting from the 48 hr fermentation of a fungus (*Phoma* sp.) and passing through series of separation systems such as column chromatography, centrifuge and packed bed column. Duration of the project is approximately 20 years and it takes into account the FDA approval process. TCI and FCI for this production are \$76 and \$77 million dollars with a manufacturing cost of \$271 million. Also, observed trends in NPV and ROI of 2% show that the project will be acceptable.

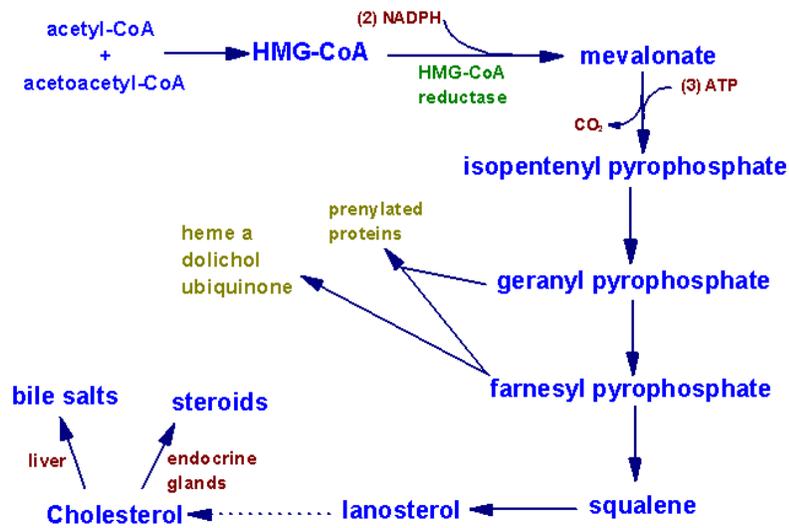
Introduction and Background

Cholesterol

According to the center for disease control, (CDC) heart diseases and strokes are the first and third leading causes of death in the United States. A study performed in 2002 revealed that 29% percent of the mortality in America was related to heart diseases. The study projected that heart disease related costs for 2006 were estimated to be more than \$258 billion in America. The American Heart Association attributed to \$57 billion the costs directly or indirectly related to strokes in America for the year 2005. The studies also showed that the major risk factors for those diseases are: high blood pressure, high cholesterol, diabetes, smoking, physical inactivity, and obesity. The following report will mainly focus on the eradication of these diseases by using a new enzyme to lower the cholesterol level in humans.

Cholesterol is a biological molecule found in all mammalian cells' membrane. This molecule is necessary for the cell survival and is an obligatory precursor in the synthesis of steroid hormones, lipoproteins and bile acids. Cholesterol is also essential for the transport of blood constituents such as lipids and to maintain the cellular membrane structural and functional integrity.

Cells fulfill their needs in cholesterol from two principal sources. The first source is performed endogenously in the cytoplasm and microsomes by synthesis from acetyl-coenzyme-A. Acetyl-coenzyme A is converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) which is converted in to mevalonate (rate limiting step) by HMG-CoA reductase. The mevalonate then become isopentenyl pyrophosphate (IPP) which becomes squalene from which the cholesterol is obtained in the endoplasmic reticulum. Figure 1 gives a visual representation of the cholesterol biosynthesis.



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Figure 1: Endogenous Cholesterol Synthesis

The second source is performed exogenously via Low Density Lipoprotein (LDL) receptors pathway. This is the way of acquiring cholesterol from animal meat consumption. Due to its hydrophobic characteristic, cholesterol is not transferable from liver or intestine to cell tissue through blood. The molecule is then packaged in small lipoprotein droplets to facilitate their transport.

The two forms of cholesterol carriers found in the organism are: Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and triglycerides. The HDL or “good” cholesterol is responsible for carrying the excess cholesterol from the cells back to the liver for excretion. A high level of HDL significantly reduces the risks of heart diseases (40 mg/dl or higher). LDL or “bad” cholesterol on the other hand carries the cholesterol toward the cells through the arteries. During its transport, cholesterol is accumulated on the arteries wall by arterial proteoglycans by forming plaques (Figure 2) which are partly responsible for atherosclerosis. Atherosclerosis is a precursor for heart attacks and strokes specially when occurring in coronary and cerebral blood vessels. Maintaining the level of LDL in the organism under 100 mg/dl will considerably reduce the formation of plaques.

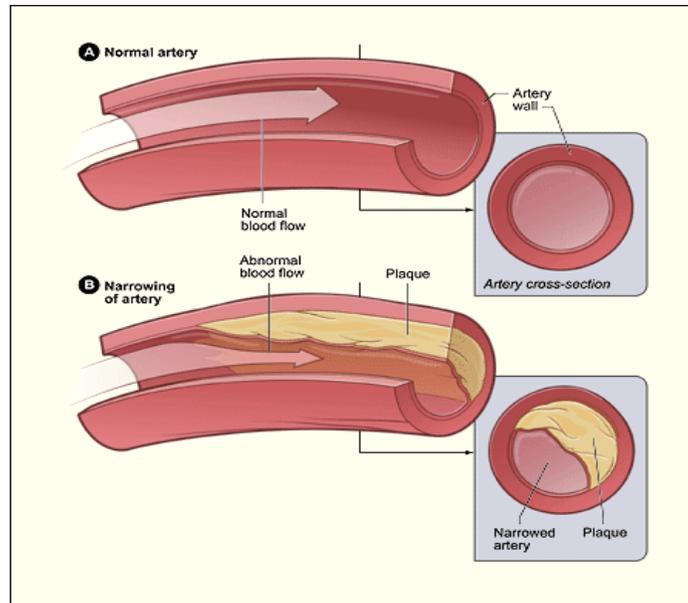


Figure 2: Plaque Formation in Arteries

Methods for Reducing Cholesterol Level

Statins are used to lower bad cholesterol in human blood. They are the top selling drugs worldwide with \$35 billion in annual sale. These drugs are mostly used in high dosage in familial hypercholesterolemia (FH) patients. FH patients have deficiency of receptors for plasma LDL. Statin drugs reduce the risk of cardiovascular disease by acting as a competitive inhibitor on HMG-CoA reductase. This enzyme contributes to the rate limiting step of more than 50% of the cholesterol synthesis in the organism (reduction HMG-CoA to mevalonate). By competing with HMG-CoA reductase, these drugs participate in the reduction of cholesterol level in plasma.

Most of statins have the same common side effect; some less than others. For example, Zetia's most common side effect is head pain but Zocor's most common side effects are dizziness, rash, head pain, nausea, etc. These drugs have to be taken as an alternative to lowering bad cholesterol and LDL level in blood because of the side effects they can cause.

There are many different statin drugs prescribed to patients today. Vitortyn, Zocor, Zetia, Mevinolin (Lovastatin), Lipitor, Pravachol-ORAL are a few highly used statin drugs. Vitortyn cuts cholesterol but it does not reduce plaque in the arteries. It is a combination of two other statin drugs Zetia and Zocor. Zocor or known as Simvastatin-ORAL is another statin drug used to lower cholesterol in patients with high LDL levels or FH. Zocor has the capacity to dissolve in fat and reach barriers into the brain which can be the cause of insomnia in some patients. This drug can be used by children 10 and up as well as adults and it takes up to 4 weeks for the results to show. Table below gives a representation of the percentage a drug, available in the market, will lower LDL and serum cholesterol level. Most statin drugs show the same efficacy.

Table 1: Comparison between Different Statin Drugs in the Market

Drug	Dosage (mg/day)	Percent Reduced
Lipitor	10 to 20	30%-45%
Mevacor	40	30%-45%
Pravachol	40	30%-45%
Crestor	10	30%-45%
Zocor	20 to 40	30%-45%

Zetia or Ezetimibe-ORAL is another cholesterol lowering drug. Zetia lowers the amount of cholesterol absorbed from diet. But unlike Zocor, it takes two weeks for Zetia to become effective. Another drug prescribed to patients is Pravachol ORAL which has an enzyme blocker. The effects of this drug are observed in 4 weeks. Lipitor or atorvastatin is the leading statin drug in the market. Lipitor is a lipid lowering agent and it has been proven to reduce the risk of stroke and myocardial infarction.

Mevinolin (Lovastatin) which is the first cholesterol lowering drugs discovered. Mevinolin increases receptors for LDL and decreases LDL concentration. This drug can reduce cholesterol by 23% and LDL cholesterol by 24%. Lovastatin was commercialized under lovastatin (Mevacor) in 1987 (Figure 3). Most of the statin drugs like Mevinolin are obtained from a multi stage fermentation process of a fungus named *Aspergillus terreus* (Figure 3).

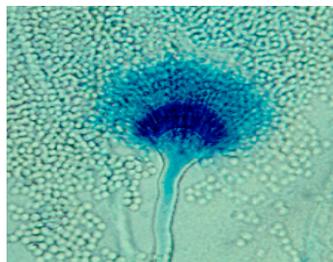
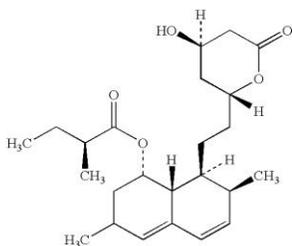


Figure 3: (Right) Mevinolin Structure, (Left) A. Terreus

The Drug Model

Problem with Statin Drugs

Statin drugs are successful in reducing cholesterol levels and in high doses they can reduce the risk of stroke and heart attack. But the problem with statin drugs and many other drugs are due to the side effects and the high cost of the medication. Some drugs like Lipitor cause the breakdown of skeletal muscles which lead to kidney failure. Another problem with statin drugs are that they interfere with the biosynthesis of Coenzyme Q₁₀. CoQ₁₀ is a vitamin like, fat-soluble antioxidant found in high concentrations in vital organs in a human body like heart. The concentration of CoQ₁₀ reduces by age. By 80, the concentration is cut in half. It is believed now that CoQ₁₀ is required for the production of 95% of the energy needed for human body. To overcome this deficiency 300 mg CoQ₁₀ has be taken daily.

Passi (2003) explains his findings on the effects of three different statin drugs on cholesterol and plasma. Findings in this study by examining hypercholesterolemia patients (HPC) showed that statins lower cholesterol, plasma and also the non-sterol ubiquinone (CoAQ₁₀) and possibly dolichols which is a derivative from the same biosynthesis. This study examined 42 HPC patients for a period of three months and the results show that the reduction in CoAQ₁₀ can lead to reduction of antioxidant capacity in lymphocytes and LDL.

Another paper by Tavintharan (2007) shows results from affect of simvastatin on HepG2 cells. The results of this study show that mitochondrial CoAQ₁₀ decreased as this drug was consumed by cells. Also, higher dosage of this drug resulted in higher cell death, increased DNA oxidative damage and reduction in ATP synthesis. But at the end, supplying CoAQ₁₀, reduced these effects.

It has been shown that CoAQ₁₀ deficiency in statin users causes cognitive and muscular deficiencies. It has been shown that statin drugs block the enzyme that produces cholesterol and CoQ₁₀. Some countries like Canada have warning labels on the statin drugs sold about the cause of CoQ₁₀ deficiency.

Squalestatin 1

Many studies have shown that lowering cholesterol serum level will lower the risk of coronary-related deaths. It has been shown that elevated serum cholesterol levels is a major risk factor for heart attack which is the leading cause of death in the U.S. Appropriate cholesterol level in the body is close to 199-200 mg/mL but in 2005-2006, 16% of American adults had serum cholesterol levels of 240 mg/ML (Shcober 2006). Mean cholesterol level is significantly higher in women aged 60 and over compared to men in this age range. But it was the same for men and women ages 20-59 years. Many other drugs like Lovastatin inhibit the HMG CoA reductase enzyme but more selective inhibition of cholesterol synthesis can take place. This is done via squalestatin compounds like squalestatin 1 (SQ1) (Figure 4).

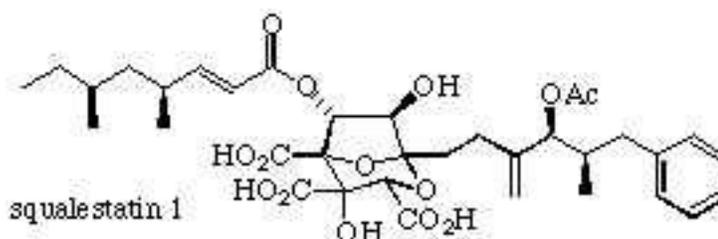


Figure 4: Squalestatin Formula; www.chem.ox.ac.uk/researchguide/dmhodgson.html

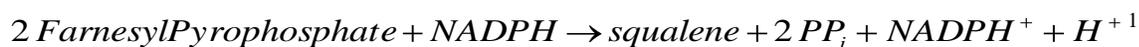
Squalestatin 1 (Fitzgerald 1992) is a potent, selective inhibitor of squalene synthase. Squalene synthase is a key enzyme in cholesterol biosynthesis from squalene to cholesterol. Studies have shown that squalestatin 1 lowered cholesterol by 75% in marmosets which have lipoprotein profiles like humans. This could be a new method of therapy for lowering the serum cholesterol level in humans.

Enzyme squalene synthase is rate limiting in the process of making cholesterol because it is regulated to control flux *in vivo* and *in vitro* (Shcober 2006). A type of fungal has been found that works well *in vivo* in comparison to other compounds. This is used to produce the squalestatin compounds, *Phoma sp.*

In this model, SQ1 is being studied for production as a new potent inhibitor of cholesterol. Studies of this compound have shown to control the flux of cholesterol biosynthesis and that this compound can lower serum cholesterol levels *in vivo*. This inhibitor will have minimal effect on non-sterol products in the pathway of mevanolate-cholesterol biosynthesis step.

Cholesterol biosynthesis was lowered by 50% *in vivo* using 0.1 mg/kg dosage. Testing of squalestatin 1 on marmosets shows a decrease in the serum cholesterol level by 75% at a dose of 100 mg/kg/day and significant effect with a dose of 10 mg/kg/day. The lowering of cholesterol was shown in 24 hours. This was maintained for 8 weeks and decrease in cholesterol levels was consistent. Overall, serum cholesterol was lowered by $51 \pm 4\%$ with 4.6 ± 0.5 mM.

As explained above, production of cholesterol in body starts with acetyl CoA. The next major step is the *squalene*. Squalene is a C₃₀ hydrocarbon and an intermediate in production of cholesterol. Squalene itself is synthesized from isopentyl pyrophosphate by conversion to farnesyl pyrophosphate. The reaction below shows how this occurs:



At the final stage of the production of cholesterol, cyclization of the squalene occurs. This stage requires molecular oxygen called squalene epoxide. This is because cholesterol is in need of oxygen for biosynthesis. After the squalene cycle, cholesterol is produced.

Drug Model

One solution that has been investigated for reducing cholesterol in a way that reduces the side effects caused by statins and also doesn't cut the biosynthesis of CoQ₁₀ is the use of a drug in which inhibits a different enzyme in the cholesterol biosynthesis. Squalostatins have been researched and proven to lower cholesterol serum level by inhibiting an enzyme in a later stage of production of cholesterol. For this, it can be assumed that this drug will not have the same side effects as statin drugs. Also, since squalostatins don't inhibit HMG-CoA which is the leading enzyme in cholesterol production, it can be said that this drug will not inhibit the production of CoQ₁₀.

SQ1 is effective in lower dosages and because it has not produced serious side effects like other statin drugs it can be produced in higher dosages, 10-80 mM, to lower cholesterol faster. This drug can perform better than the statin drugs produced so far. One reason is because of its ability to lower serum cholesterol level in higher rates and in low doses. Statin drugs have 20-60% ability to lower cholesterol but in high doses which can cause numerous side effects. This drug does not deal with the ATP (important in the transfer of energy into cells) when inhibiting the squalene synthase therefore it doesn't have extreme effects on the human body.

The price has to be competitive in respect to other drugs. Statin drugs can cost up to \$144/month because few generic brands are available. The main group of buyers will be women over 60 and anyone between 20-59 years. But since older women have a higher risk of heart attack due to higher serum cholesterol level, this group would be the main focus.

Market for cholesterol lowering drugs is open and expanding. The reason is that despite the medical treatments, public health campaigns to have low cholesterol intake, and increase in physical activity, high cholesterol level remains the most important health problem in the U.S.

Dosage

The required dose of daily squalostatin will be estimated by appreciating the overall cholesterol synthesis inhibition mechanism at the molecular level. Different tests have been performed by researchers at Pfizer in 1994 (Lindsey and Harwood). These tests calculated the rate and effectiveness of the inhibition under various conditions such as an increasing

concentration of both squalene synthase (targeted enzyme) and squalostatatin. The results of these experiments show an increase of the squalene synthase inhibition activity with both its own and the SQ1 increase in concentrations. The researchers concluded that SQ1 inhibited the enzyme activity therefore cholesterol synthesis by binding to the enzyme to form a complex that will be excreted out of the body.

In other words for each molecule of enzyme that will be inhibited, there should be one molecule of SQ1. Knowing the average daily production of squalene synthase in hypercholesteremic patients (13.4 $\mu\text{mole/day}$) the dose should then be dependent of the fraction to be inhibited. For a 40 and 60 % inhibition, using mole balance and molecular weights, the SQ1 daily doses should 10 and 20 mg respectively.

Pharmacokinetics

This section will analyze the SQ1 overall metabolism in the human organism from its ingestion to its excretion. SQ1 will be orally ingested and will follow the path taken by nutrients in the digestive tract. SQ1 will be absorbed in the blood stream through the small intestines microvilli. The drug will then be directed toward the hepatic cells where cholesterol inhibition will occur. After inhibition, hemoglobin cells will recognize the complex formed by SQ1 and squalene synthase as a foreign substance and will be eliminated by both the liver and the kidneys.

SQ1 will mostly be eliminated at the kidneys because of its hydrophilic and hydro soluble properties. The drug will undergo passive diffusion through the kidneys glomerulus and will be collected in the bladder and excreted in the form of urine. The rate of elimination of SQ1 is determined using fick's law (equation 1)- since this is a passive diffusion with concentration gradients. This rate is dependent on the molecular size of the drug and its concentration in the organism. The initial plasma concentration is obtained using the daily dose (10mg) and the total blood volume (3 liters). Average value will be taken to estimate the glomerulus filtration area (516 cm^2) and the blood flow rate through the kidneys.

$$flux = -p \times A \times (C_{Plasma} - C_{kidneys})$$

Equation 1

From this equation, the change in plasma drug concentration will be calculated over a 24 hour period and will be plotted in the following graph.

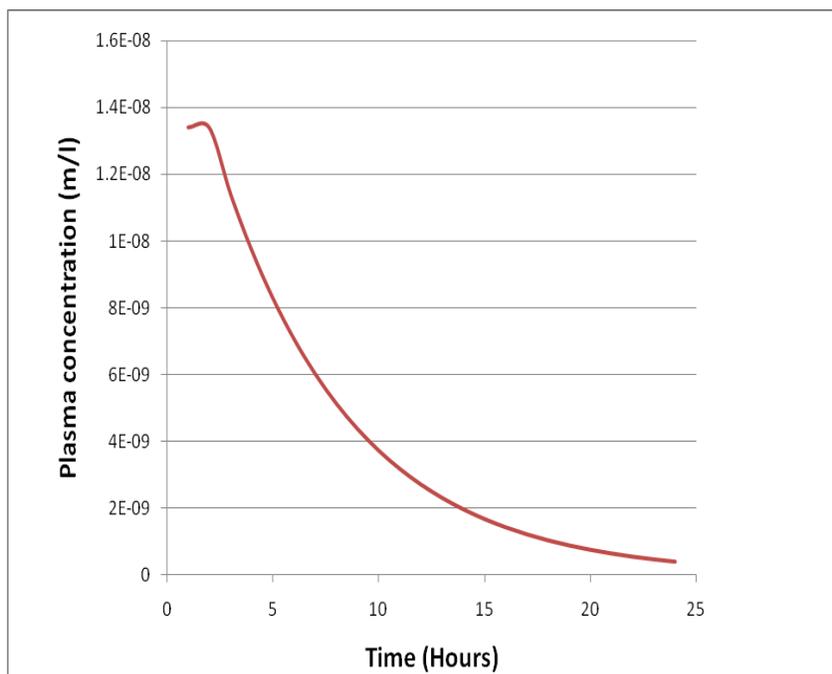


Figure 5 plasma concentration Vs time

This graph shows that a decrease of the drug concentration in the plasma over time. The rate of elimination of the drug also decreases with time. Most importantly the amount of drug left in the plasma after 24 hours is insignificant (less than 1-% of the initial concentration). The graph finally allows to determine a half life of approximately 8 hours which is very good compared to other statin drugs.

Manufacturing Squalestatin 1

Process overview

The squalestatin synthesis procedure will be obtained from the volume 47 of The Journal of antibiotics by William M. Blows and Graham Foster. The overall procedure will be summarized as followed. The fungus is introduced in a seed fermenter with water and a medium of glycerol, soybean, oil and cotton seed flour. The medium constituents will provide nutrients necessary for the fungus metabolism. This mixture will be ventilated and agitated at 500 rpm for

48 hours. The resulting broth is submitted to a packed bed column, two filtrations, a centrifugation and two high performance liquid chromatography (HPLC). The complete process is illustrated in the following figure.

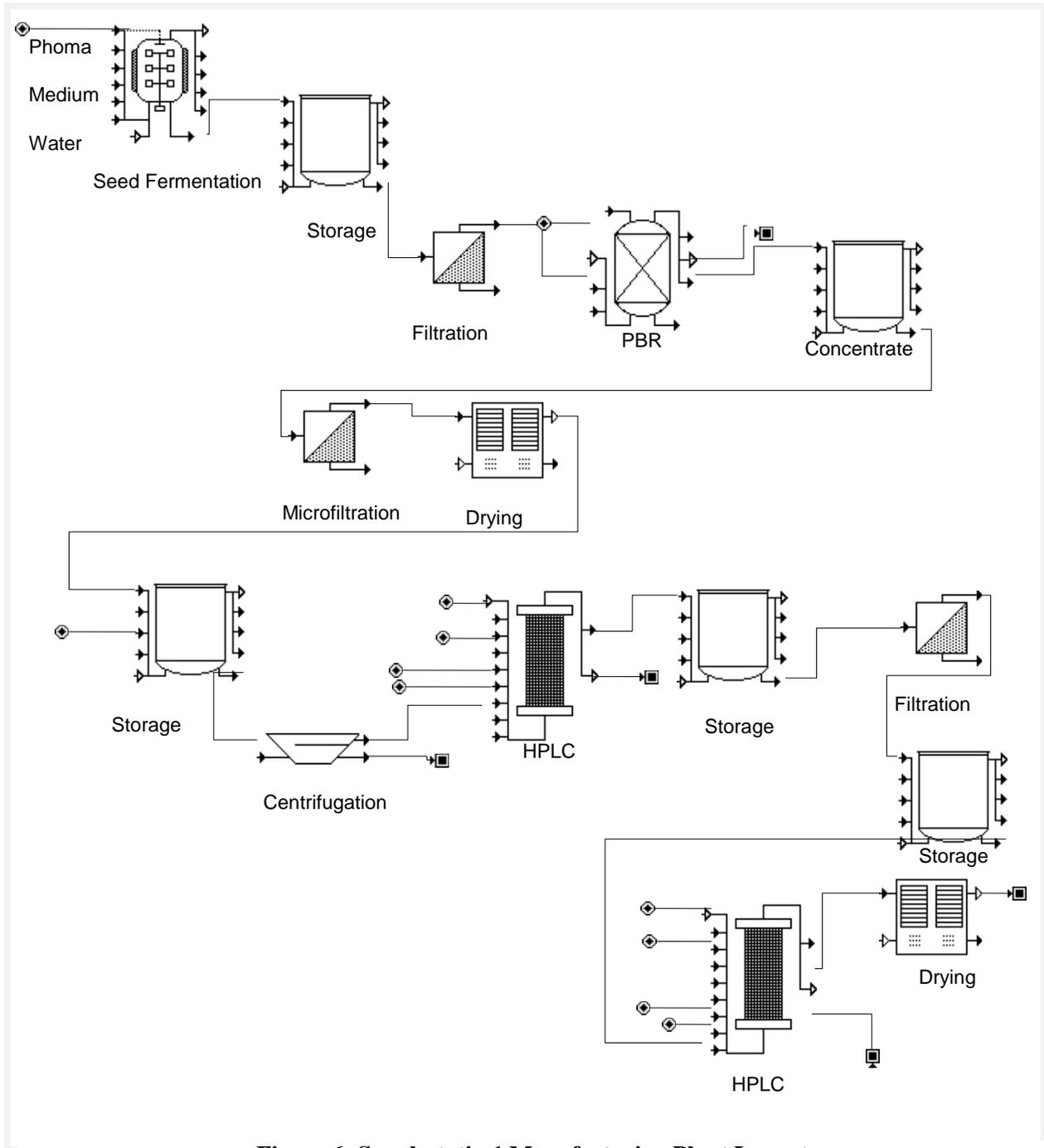


Figure 6: Squalstatin 1 Manufacturing Plant Layout

Scale up

The manufacturing process will be sized to satisfy the demand throughout the life of the operation. Equipments having the largest impact on the scaling process are the fermenter and column chromatography. These items are the most delicate and expensive and will dictate the economic viability of this operation.

Fermenters

The elements considered when scaling the fermenter are:

- The height over diameter ratio (H/D)
- The impeller velocity
- The volumetric oxygen transfer coefficient (K_{la})
- The power requirements

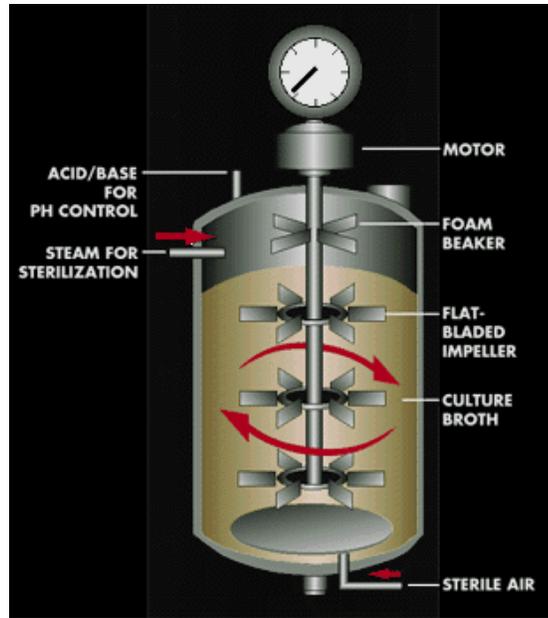


Figure 7: Sample Air Impelled Fermenter

The H/D ratio chosen for all the fermenters in this plant will have a value of 3. This will give greater pressure at the bottom of the vessel and will give the oxygen molecules a longer residence time. Other parameters will be dependent on the flow rate of air entering the container. For this reason, all the fermenters in this plant will be air impelled. The remaining containers parameters will be set using equation 1. This equation relates the experimental vessels volumes and flow rates to the scaled vessels volumes and flow rates

$$\frac{Q1}{V1} = \frac{Q2}{V2} \quad \text{Equation (2)}$$

Q1, V1 are the experimental flow rate and volume. Q2, V2 are the scaled flow rate and volume.

This equation will be used to determine the charge at each container, and the yearly total amount of raw materials. The equipment sizes and raw material quantities are necessary to determine their prices and estimate the total capital investment (Table 6). These calculations are performed considering that this process will be an extension to an already existing plant.

Phase I-Pre-FDA

The prospective of using squalastatin as a method of treatment for hypercholesterolemia makes it fulfill the characteristics of a drug. It is therefore imperative that before its commercialization, squalastatin receives the approval of the Food and Drug Administration (FDA). This long and costly process (FDA approval), not only represents a determining step in the success or failure of squalastatin, but will also be used to validate its safety and efficiency. Before its introduction to the market, squalastatin will undergo four different stages, one stage of Pre-FDA and the three routines phases of the FDA approval process. The cost and length of each phase will be determined by the quantity and category of experiments to be performed and also by the personnel and equipments required. The costs of the facilities and utility used for the approval process will not be included in this section. These will be taken into account when determining the total capital investment for the entire company. This is done because most of the plants built for the Pre-FDA process will later on be used for research and development.

A successful execution of this phase will significantly reduce the duration and increase the chances of squalastatin through the FDA. It is therefore necessary that a large number of experiments are conducted very thoroughly during this stage as to provide the FDA with the product presenting the less amount of risk. On the other hand conducting too many experiments is more time and funds consuming than efficient. It is therefore necessary to determine the best combination through a decision tree. During this phase, experiments will be conducted both in vitro and in vivo. In vitro experiments will be used to prove squalastatin cholesterol lowering effect. Theses set of tests will be conducted in test-tubes and under the supervision of at least one highly qualified scientist (PhD level). Different amount of Squalastatin will be added to some extra of rats' liver in test-tubes and the cholesterol biosynthesis will be analyzed. If the biosynthesis process is proven to have been slow down by the addition of squalastatin, the investigations will then move to the in vivo stage. The first part of the in vivo phase will focus on analyzing the effect of squalastatin on mammalian metabolism. The following will be evaluated: the different variation of LDL, HDL and total cholesterol levels, all noticeable side effects will be recorded. The different amount of hormone and steroid secretion will also be recorded to

ensure that squalastatin does not interfere with cholesterol necessary body functions. During this phase, about 200 rats will be used and tested everyday. Rats were chosen because of the similarities between rodents and human for cholesterol metabolism. The next and last phase of the pre-FDA process will be conducted on 100 dogs with familial hypercholesterolemia. These will be chosen because of their size (larger than rats) also the main human users of squalastatin will have familial hypercholesterolemia. The dogs will be submitted to different dosage of squalastatin (0 to 100 mg, 10mg intervals) daily. Some of the dogs will also be submitted to Simvastatin (one of the statins available on the market today) at its most effective dosage 60 mg daily. The same tests and recordings conducted on rats will be performed here. Liver samples will also be collected to evaluate the impact of squalastatin on the LDL receptor production. Lastly squalastatin safety and efficiency will be compared to those of simvastatin.

Cost and Duration

To evaluate the cost and duration of the pre-FDA phase, different parameters will be considered. As previously stated, the cost of equipment, facility and utilities will not be considered in this section because they will be used for future research even after squalastatin is approved. The major factor impacting the cost and duration will then be the amount and qualification of personnel used. Three different possibilities will be considered: the first one use a minimum number of technicians and scientists for a minimum yearly total salary (1 PHD, 8 technicians \$ 300,000), the second increases the number of technician to 12. This particular possibility will considerably reduce the time spent on the second phase of the pre-FDA process. During this stage most of the measurement s such as side effects recordings are really basic operations and can be performed by technicians. Lastly the number of scientist will be double while the number of technicians is maintained to 8. This possibility will mainly impact the first and third stages. During these phases complicated measurements such as the percent increase of LDL receptors production on the liver surface will be made. Also 2 sets of number experiments will be considered for the three possibilities. These are clarified in the table below (table 2).

Table 2: Different Sets of Experiments

Stages	In Test Tubes	On Rats	On FH Dogs
Option A	250 tests	2000 tests	500 tests
Option B	250 tests	1500 tests	800 tests

Calculations were performed considering that each scientist will be able to performed at least 10 experiments daily on stages 1 and 3 (test tubes and FH dogs) while each technician will be in charge of 4 experiments daily on stage2 (rats experiments). The salary of a scientist will be evaluated to \$100,000 and that of a technician at \$25,000 yearly. All the results are then tabulated in the following diagram.

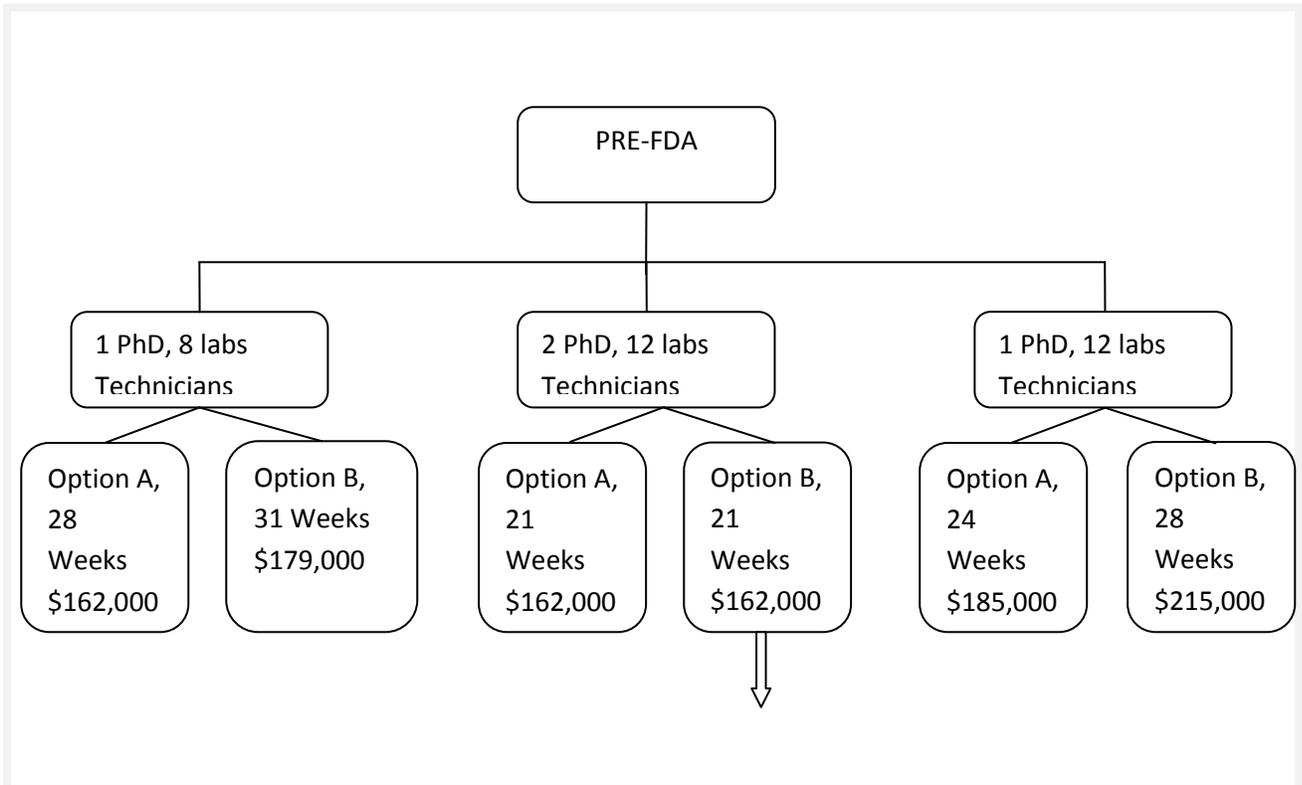


Figure 8: Pre-FDA Decision Tree

Pre-FDA summary

The pre-FDA process will consist in conducting around 2550 experiments in 21 weeks for a total salary cost of \$162,000. If the expected results are obtained during these tests, squalestatin will more likely receive FDA approval on the first trial. It also important to note that any observed serious or unexpected side effects during the conduction of these experiments will require further research by our team of scientists to either eliminate the condition or at least minimize it. Another important measure will consist on having some of the FDA scientists inspect the entire Pre-FDA process to ensure its authenticity before squalestatin is tested on humans.

FDA

The division of the FDA responsible for squalestatin approval is called the Center for Drug Evaluation and Research (CDER). Just like all the other drugs, squalestatin will undergo the three main phases of the FDA approval process.

Phase I

This section mainly focuses on establishing the drug toxicity, its metabolism and its mode of excretion by humans. The goal is to offer squalestatin to a small group of subjects not presenting a specific health conditions. The subjects will then be observed and analyzed for acute side effects. In this particular case, 70 volunteers will be administered squalestatin and all the tests will be performed for a year under the supervision of 2 medical doctors and 7 healthcare technicians. The drug will move to the next phase if it only presents mild and acceptable side effects.

Phase II

The second phase of the FDA approval process will accentuate on determining the drug effectiveness. Thus it is necessary for the new drug to be at least as effective as the ones already commercialized for it to be approved. This section will require more subjects than the previous phase and this time the subjects need to be familial hypercholesterolemic. This is the specific condition presented by most cholesterol lowering drugs patients. The subjects will be administered different dosages of squalestatin. Blood and urine sample will be taken and analyzed. The different cholesterol and steroids levels will be recorded and compare to the ones for subjects using the competitor's drug (atorvastatin) and placebo. Side effects will also be documented in order to gather further safety information. In this case, 200 volunteers will be required under the supervision of 3 medical doctors and 20 health care technicians for 2 years. For the drug to move to the next phase, it has to be established safe and effective by the second phase.

Phase III

The last phase of the FDA approval process will involve even more subjects than the previous two phases. The accent will be on identifying any form of unexpected side effects that could compromise the safety of the drug. Subjects will be selected from a wider range of ethnicity, and age group. The subjects also need to present a variety of specific health conditions such as high blood pressure, diabetes or pregnancy. This will determine whether specific contraindications need to be mentioned for the usage of squalestatin. During the 6 years that the phase III will last, 900 patients will be needed for 10 medical doctors and 70 health care technicians. A successful completion of phase III will mark the end of the clinical trials for the approval process.

FDA Costs

The entire FDA application process costs will be related to the amount of staffing, subjects and the length of each phase. During the entire process, each patient will be health insured for an average amount of \$5000 per subjects per year. The medical doctors and PHDs hired will be remunerated at an average of \$200,000 per scientist per year. Finally each healthcare technician will receive around \$40,000 per year. These initial salaries will be submitted to a 2% inflation each year. The cost of the equipments required to perform the tests (syringe, test tubes etc...) and power supply will be estimated to \$200,000 per year.

Toxicity and Efficacy Estimation

Squalestatin toxicity was estimated using results of FDA clinical trials for another statin drug (atorvastatin). This was done due to the unavailability of squalestatin clinical results. In general statin drugs present similar side effects so it is expected that squalestatin be at least as safe as its counterparts. Due to their sites of action, all the other statin inhibits the HmG CoA reductase while squalestatin inhibits squalene synthetase it is then expected that squalestatin present less side effects. By inhibiting HmG CoA reductase, those statins considerably decrease the amount of Coenzyme Q10 in the organism which is not the case for squalestatin. From Atorvastatin clinical results, side effects were selected on the basis of their severity and regularity of occurrence. These were added up and divided by the total possible number of appearances and classify as severe, mild or unexpected side effects.

The mild and minor side effects were mostly related to the digestive tract dysfunction such as diarrhea and vomiting. These are simply the result of the decrease in cholesterol level. Cholesterol mainly responsible for the production of bile acids in the organism, a reduction of its production should also impact the digestive system therefore generate in some patients the side effects mentioned above. These conditions had an occurrence rate of about 10.5 % in clinical trials. Similar to other drugs, squalestatin will generate allergic reactions in some patients. These reactions however are not expected to present serious problems to the patients' health because of the nature of the drug as an organic compound. The drug present consists of a very simple

formula made of elements such as carbon, hydrogen, oxygen and becomes a very weak acid (zaragozic acid) once inserted in the body. This is similar to the other statins which present 0.5% occurrence of allergic reaction throughout clinical trials.

The analysis of the severe side effects of the other statins drugs revealed that 43% of occurrence were related to their impact on the ubiquinone or energy synthesis pathway. Myalgia only was responsible for 24% of severe side effects occurrences. This condition is characterized by the inability of muscle to appropriately function resulting in them aching and gradually shrinking. Physiologically, muscle fibers operate using ATP (energy) to bind calcium. The absence of energy due to the inhibition of the ATP synthesis will cause the muscles fibers to degenerate. The calcium will be accumulated around the articulations of the patients leading to a condition called athralgia (figure 9). This disease accounts for 19% of the severe side effects encountered by statin users and would lead to an even harsher side effects such as arthritis. By switching to SQ1, patients will decrease by almost 50% the chance of acquiring those conditions. Reducing these aches will also improve SQ1 customer satisfactory rate which will eventually positively impact its demand.

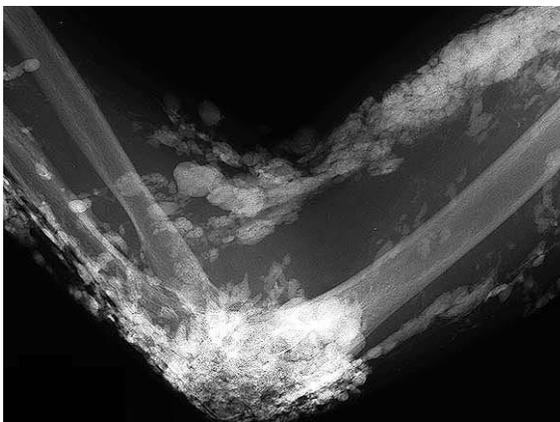


Figure 9 Athralgia

The remainder severe side effects of statins that could be share by SQ1 would account for 1.1% of total side effect occurrence.

The efficacy was estimated by using results of trials performed on rodents. Squalestatin was determined to be efficient for total cholesterol decline above 40%. This is the value observed with most commercially available statins. The total number of efficient cases was then divided

by the total number subjects. Also tests comparing SQ1 efficacy to other highly efficient statins showed that the new drug was at least as competent as its counterparts more than 90% of the time. This lead to account for the possibility of inefficiency estimated at approximately 10%

The entire FDA process with all the necessary costs and percentages is summarized and illustrated in the following diagram.

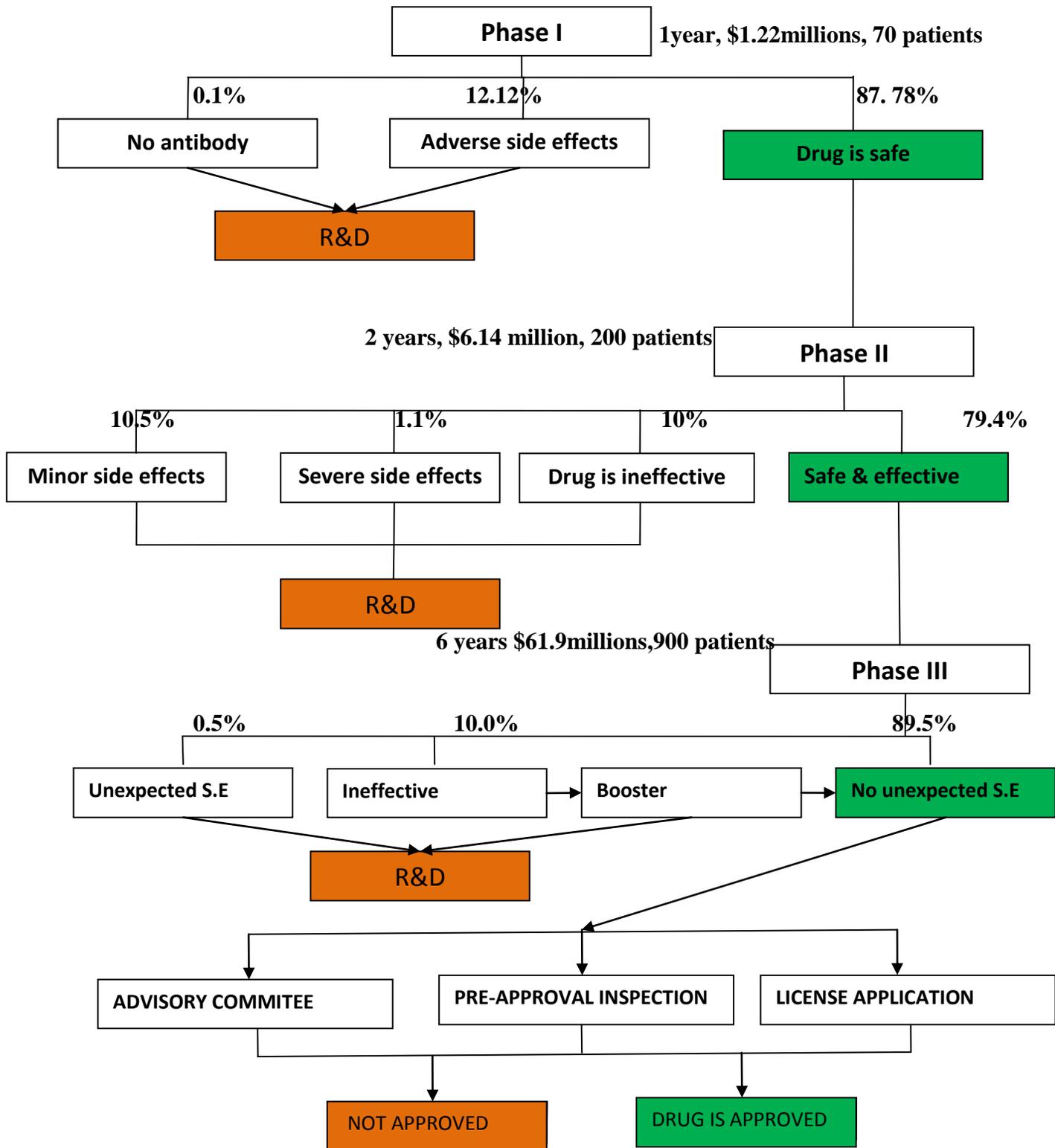


Figure 10: FDA Process Diagram

The overall FDA process will be evaluated to \$69.91 million for duration of 10 years. The overall chances of squalastatin passing the FDA on the first trial are estimated by the product of the probability of passing each specific phase. For this calculation, the drug effectiveness will only be accounted for once unlike in the diagram. The result of this computation is found to be of 69%. The diagram also indicates a possibility of failure of FDA approval estimated at 31%. At this point of the development of the drug the inability to pass the FDA will lead to total loss of \$138 millions. This cost not only accounts for the prices involved in performing the tests but also the cost of the facilities built to produce the drug used during the clinical trials.

Price Analysis

Pricing a new drug could be a monopoly, or a perfect competition with a bargaining power. Different scenarios can exist when a new product is produced. Three of these scenarios are explained here. The first scenario deals with monopoly in a market. Monopoly occurs when a company or an individual has a significant and sufficient control over a product because of lack of competition. For monopoly, price of a specific drug can be set as high as the pharmaceutical company desires. Relating to the current study, monopoly would occur if the new drug with a higher degree of efficacy than any other type of treatment enters the market where it can control the market. In monopoly, the demand for the specific drug will be kept constant until competition rises.

In a hypothetical market, the new drug is under patent which means the price of this drug can be as high as the pharmaceutical company dictates. Because of the elasticity of demand for the case of this drug, price can be set significantly higher than usual. In this case, HMOs and insurance companies will have inelastic demand. Elasticity and inelasticity of demand are the measures of the degree of the relationship between changes in demand and changes in price.

The second scenario entails the case of SQ1 where monopoly is not a factor since there are many other treatments available for lowering high cholesterol levels. In this case, competition becomes an important factor. If two brand name drugs exist with the same goal, perfect competition exists. Here, both drugs are used for curing the same disease or condition but

both have differences which can set their demands. The difference could be due to the coverage that the insurance company provides for the prescription or doctor's preference for prescribing a specific drug. In this scenario, pharmaceutical companies can use their bargaining power with HMOs and insurance companies and they can use it with doctors whom would prescribe to the patients. In this scenario, drug companies try to serve any type of patient so that maximum sales are met.

The last scenario is when the patent of a specific prescription drug has expired. In this case, that drug can't compete with the generic brand therefore demand will decrease. In these cases, changes have to be made within drug companies. In many cases, it is likely that the price of a brand name drug increases as the generics emerge into the market. Automatic loss in demand is observed when this scenario occurs and bargaining power with HMOs and insurance companies have to increase to prevent a dramatic change in sales of the brand name drug.

Price Model

Determining a price for a new drug is an important task and insurance companies and HMOs have enormous power in determining what type of drug a patient can be prescribed. In this section an explanation is made on how insurance companies work in determining the demand for a drug.

Many different types of insurance companies with different coverage plans exist. Some have "good" coverage and some have "medium" coverage. "Good" coverage will cover most of the payment of a prescription drug. "Medium" insurance will only cover a specified amount and a specific drug. Another group of individuals exist who have no insurance coverage and pay for a prescription drugs without dealing with the third party.

From the congressional budget office (CBO) 1998 analysis, 21-31 million American are uninsured. CBO explains that based on historical trends it is un-likely that this figure will change in consecutive years. These three categories can be studied and researched to determine a good and reasonable price for a new drug entering the market.

Three scenarios for pricing the drugs can be explained. First, if it is assumed that the drug is set as a lower price compared to the drugs available in the market then it is highly likely that all insurances will cover the payment for that drug. Second, for medium price drugs, only good insurances will cover the payment and medium insurances will either recommend other brands or won't cover the price.

For this scenario, since good insurance companies will have different coverage plans in different states, price analysis involving insurance companies has to be concentrated on one or two sections of the United States. For example; Blue Cross Blue Shields of Oklahoma covers statins, Crestor and Lipitor. If a doctor prescribes Zocor to a patient using this insurance company then the doctor is required to change the prescription. An important factor here is that at the beginning the choice is with the doctor and the insurance company but when the patient is purchasing the drug, the choice lies with him.

In this case study, Lipitor is more expensive than Zocor therefore the patient will not be happy with this choice. When insurance companies have limitations on the type of drug they will cover, this may hurt many pharmaceutical companies and it will result in low demands. In these situations, bargaining power comes into play. The pharmaceutical companies can make deals with insurance companies for covering their drug. Other factor that can help with a high demand for the specific drug is if the drug has higher efficacy than other drugs and is set at a lower price than the highest selling drug in the existing market. This can lead to a higher demand by doctors, patients and eventually insurance companies and HMOs.

The third scenario discusses people with no insurance. In this case, the doctor has to make the choice of prescribing a drug that will be lower in price and relatively higher efficacy compared to the competition. One problem that exists with this scenario is that if the new drug is highly effective compared to other drugs in the market, the patient has to choose efficacy over price. The reason is that efficacy is a first priority for a doctor when prescribing medication. This can fall in to the case of monopoly where the patient and insurance companies have no choice but to follow doctor's orders.

Demand for a drug is highly dependent on patients and doctors. For example, according to New York Times (1996), Health Insurance Plan of Greater New York told its 850,000

members that they would not pay for Merck's expensive products; this led to loss of many customers for Merck. In regard of this loss, in order for Merck to gain its customers back they used different advertising strategies and free concessions. To prevent cases such as these, appropriate prices have to be determined for a drug entering the market.

To determine the best price for a new drug that results in higher efficacy, three factors have to be considered. One, it has to be low enough for the insurance companies to cover it. Two, doctors have to prefer this drug over other type of medication and prescribe it to most of their patients. Three, patients have to be satisfied with the price and efficacy of the drug. If these factors are met, demand for the drug will increase.

To determine the best selling price for a new drug, a pricing model is used by considering important product properties associated with the drug. This model is derived from a simple microeconomics model. This model describes two products, P_1 (new) and P_2 (old) with specific demands, d_1 and d_2 . Based on this model, the consumer maximizes satisfaction by having constraints on the amount spent on the drug. For this analysis, consumers are doctors and patients.

The demand model used to determine the demand of the new drug is derived from Equation (3):

$$P_1d_1 + P_2d_2 \leq Y \quad \text{Equation (3)}$$

Where P_1 and P_2 are prices of new and old drug, Y is the total consumer budget and d is the demand for the new and old drug.

From Equation (3), the demand model was derived:

$$d_1 = \left[\frac{\alpha P_2}{\beta P_1} \left(\frac{Y}{P_2} - \frac{P_1}{P_2} d_1 \right)^{1-\beta} \right]^{1/(1-\alpha)} \quad \text{Equation (4)}$$

Here, α and β are the awareness function and ratio of the consumer satisfaction of the old drug to the new drug. β equation is shown below:

$$\beta = \frac{H_2}{H_1} \quad \text{Equation (5)}$$

Here, H_1 and H_2 are the happiness factor of the new and old drug. This factor is dependent on many factors but in the case of SQ1, it is dependent on efficacy and side effects produced by using the drug. H is calculated as follows:

$$H_i = \sum_i w_{i,j} y_{i,j} \quad \text{Equation (6)}$$

Where w and y are the weight of the corresponding parameter and y is the value of the parameter relating to the satisfaction of the customer. These parameters are explained in more detail in the following sections.

Alpha factor

Alpha or the awareness function is a time dependant parameter which depends on the awareness of customers towards a new drug. In the case of SQ1, doctors and patients are the customers. As the doctors and patients become familiar with the new drug and its high efficacy, sales become higher because prescription will increase significantly. Figure 9 shows the relationship between time and alpha. To determine the demand from doctors, alpha was kept constant at 0.9. To determine demand from patients, change in alpha was assumed therefore figure 9 was used.

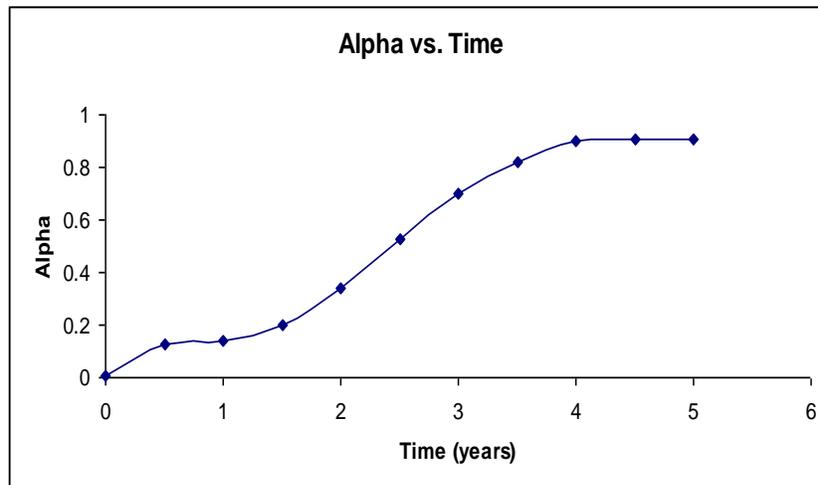


Figure 10: Relationship between Alpha and Time (Harl-Martin 2006)

Beta Factor

To determine beta factor, two factors which are usually included when prescribing a drug to patients have been discussed; side effects and efficacy. Side effects are undesirable effects that can occur by taking prescription drugs. For SQ1, no side effects have been reported because no clinical trials have been done thus far. When compared to other statin drugs, it can be assumed that SQ1 and statins have the same y factor. This assumption was made because efficacy dominates side effects in many life threatening situations. Since having high cholesterol serum level can increase the possibility of heart disease and heart attack, it can be assumed that efficacy has a higher importance than side effects.

Most statins have the same side effects when higher dosage of the drug is consumed. It can be assumed that 50% of the prescriptions written by doctors are for the 10 mg/day dosage (lowest dosage) therefore no or low side effects will be observed at this amount. As dosage increase, possibility of side effects increases but since lower dosage can provide the same efficacy only in a longer period of time, it can be assumed that low dosage will be prescribed more frequently than high.

On the other hand, efficacy is the major factor that is discussed between a patient and the doctor. Efficacy is the measure of the effectiveness of the drug in reducing the life threatening condition a patient is suffering from. In comparison to other drugs in the market, the new drug has to be “therapeutically acceptable.” For SQ1, weight of importance of side effect has been assumed to be 5% and weight for efficacy is 95%. Table below gives the values for y , w and beta using Equations 3 and 4.

Table 3: Beta Calculation

<i>Beta</i>			
	Weight	Y_1	Y_2
Efficacy	0.95	1.26	0.74
Side effects	0.05	0.5	0.5
$H = \sum (\text{weight} * y)$		1.22	0.73
β	0.6		

Effectiveness

To determine the beta factor for the SQ1, efficacy of the drug was taken into account. Figure 10 shows the relationship between percent level of cholesterol serum in animals and the dosage given to rats in a period of one week. As shown in Figure 7, percent cholesterol level lowers as the dosage increases. Highest dose (100 mg/day) of this drug lowers percent cholesterol by about 80%. These data were used to determine the efficacy of SQ1.

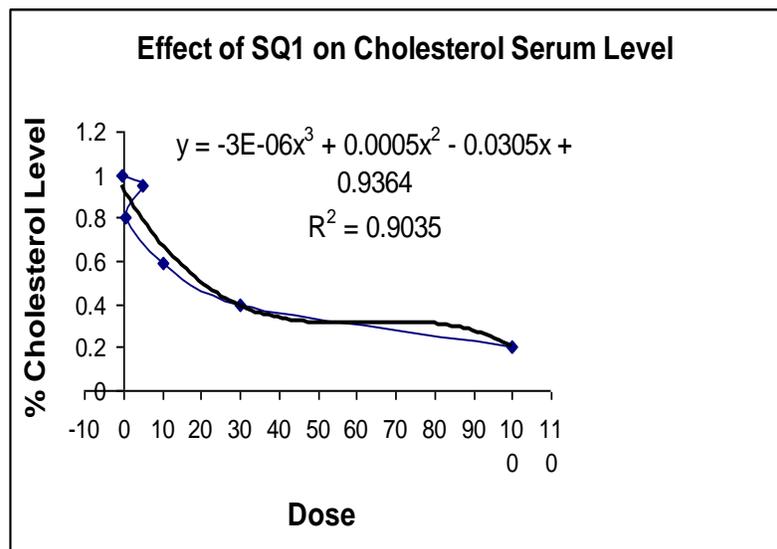


Figure 12: Percent Cholesterol Level versus Dosage in Marmosets for a Period of 1 Week

Figure 11 shows the relationship between satisfaction of the customer and doctors when serum cholesterol level decreases. According to these data, decrease in percent serum cholesterol level results in increase in satisfaction. This drug reduces cholesterol level in body by more than 50% using lower dosage compared to statin drugs. This study is a proof that SQ1 provides higher efficacy by using lower dosage in a shorter period of time.

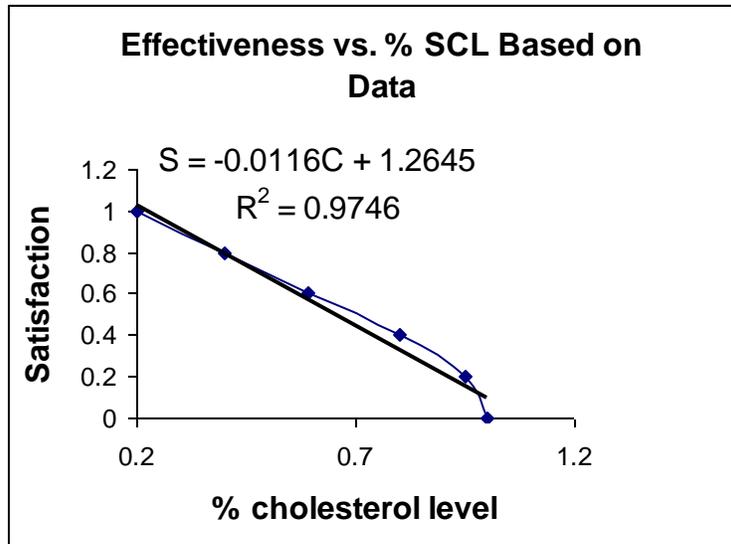


Figure 13: Satisfaction versus Percent Cholesterol Level

Equation below was used to determine y in the happiness function:

$$S = -0.0116C + 1.2645 \qquad \text{Equation (7)}$$

S is consumer satisfaction ranging from 0-1, and C is the percent cholesterol. As figure 11 shows, satisfaction is highest when the percent level of serum cholesterol is 0.2% and the lowest satisfaction is when percent level cholesterol is at 1%. C value for calculating the demand was 0.2% in both doctor and patient scenarios since the importance of efficacy is equal for both patient and doctor.

Demand Model Results

Equation 3 was used to determine the demand for the new drug in two cases; doctor and patient demand. The demand for the new drug was established using the statistics provided by U.S Census Bureau and FDA webpage. Based on these values and percentages, figure 12 was generated. For this analysis, a market of 0.8-1 million patients was assumed. This number was

based on the amount of people using the cheapest and the highest selling drug in today's market, Lovastatin and Lipitor.

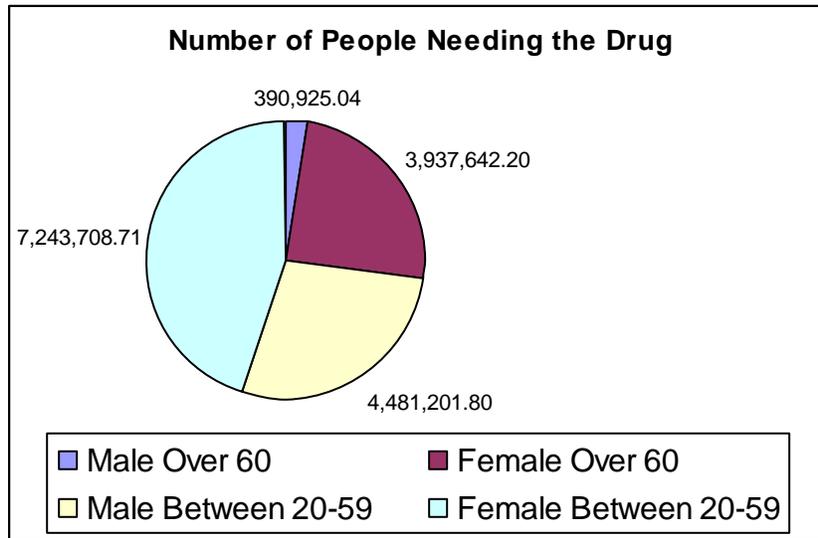


Figure 11: Number of People Suffering from High Serum Cholesterol Levels in the U.S

By using the demand model and excel program, demands for the new drug at three different statin drug prices were determined. Possible prices of the new drug were varied from high to low. These prices were determined based on the current market of statin drugs. Figure 13 was established using the new demand over a range of new prices. These values were varied from \$1.33-\$5 per unit. As seen in the figure, demand increases as the price of new drug decreases. When the drug is below or close to the generic brand drug (\$1.33 and \$1.77 per unit), demand is higher. Demand calculated using the model for this price range was about 0.7 to 0.8 million which were close to the estimated demand from statistics.

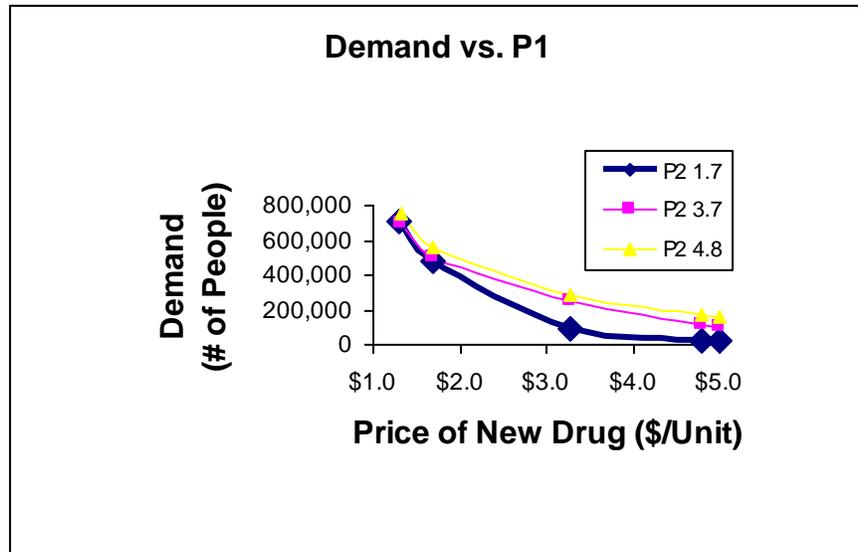


Figure 15: Demand versus Price of New Drug

The trend in figure 13 is expected since patients with insurance would rather pay less co-payment which is connected with a lower priced prescription drug. Generic drugs have the lowest co-payments and therefore prescribed more often. This is also true for patients with no insurance since they would prefer to pay less for a highly effective drug. In the case of insurance covered prescription, usually a \$10, \$15, and \$20 co-payment is required by the insurance companies.

As mentioned before, consumer in this scenario is the doctor and insurance companies. But this analysis was done with the patient being the primary consumer. The drug has to be prescribed and approved by the doctor and insurance company before it is purchased. A patient will possibly be prescribed a generic brand since the co-payment is much lower than a brand name drug. If the insurance company accepts this drug and they cover the price then the patient will purchase the drug. If the insurance company doesn't cover the specified drug then the patient will request a cheaper drug from the physician. This drug could be either generic, or brand name.

Figure 14 gives a representation of which drug price would give the highest demand. To determine this, alpha was varied and the demand equation was solved for a range of P_1 , P_2 was a

fixed price at \$3.27 per unit. Results show that over a period of eleven years demand for \$1.33 per unit drug would be much higher than any other price. This price is lower than the generic brand in the market today (\$1.70 per unit). Although \$1.33 line starts with a lower demand, by the end of fifth year, demand increases drastically.

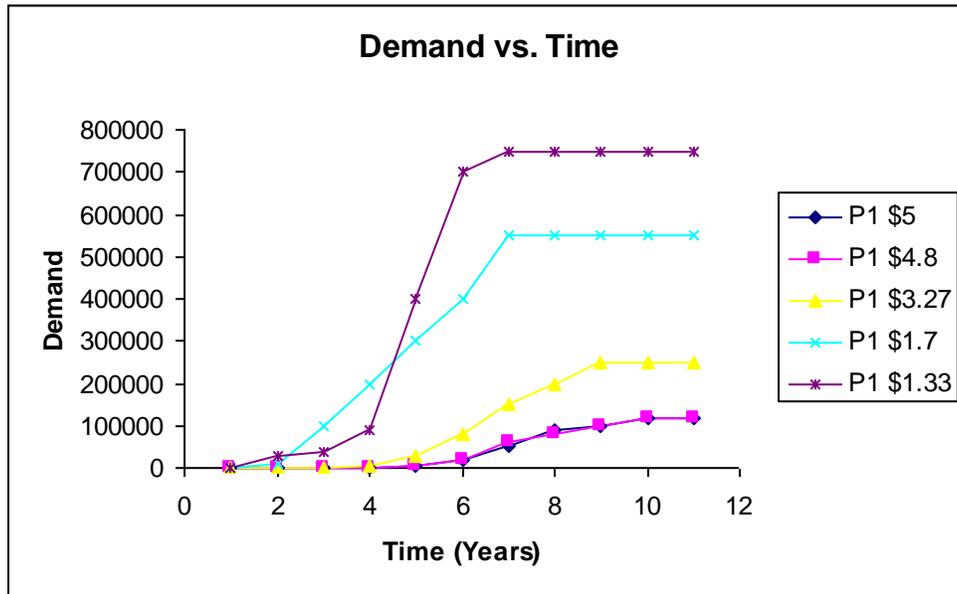


Figure 16: Demand versus Time with Different P1

Figure 17 represents the two high demand drugs (\$1.33 and \$1.7 per unit). This figure shows that \$1.7 per unit can be a starting price for the drug since demand increases faster than the \$1.33 per unit. But by the middle of 4th year, the price has to drop to \$1.33 per unit for an increase in demand.

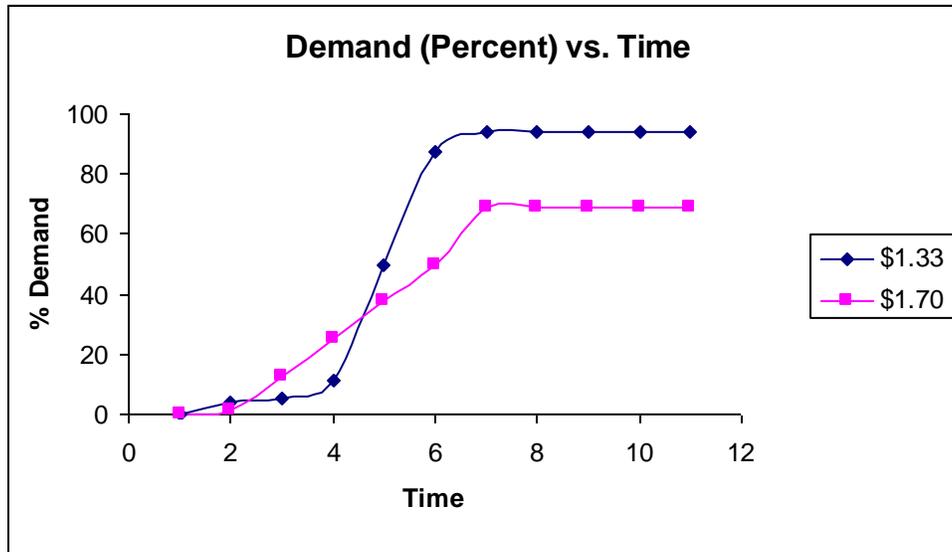


Figure17: Percent Demand versus Time

Price analysis helps determine the best price for a new prescription drug in a competitive market. In this case, best prices with the highest demand based on a patient preference were \$1.33 and \$1.7 per unit. Either of these drugs would have a high demand over an 11 year period. Other analysis has to be done to determine the demand doctors would have for a drug. But as explained before, efficacy is the main concern for a doctor when prescribing drugs and not price. But it is understood from the laboratory experiments on SQ1 that promising results will be observed by using this drug and high efficacy can be predicted for patients. Based on this, it can be said that demand for this drug would be high among doctors as well.

Business Economics

If SQ1 passes the FDA process, next step would be to manufacture this drug in a large scale to accommodate rising demand for the drug. Economic analysis was done on the drug where TCI and FCI for four scenarios were determined. 1 and 2 scenarios entail the cheapest possible price that can be put on the drug, \$1.33 and \$1.77 per unit. Scenarios 3 and 4 entail prices for the medium to highest price of the new drug, \$4.8 and \$5 per unit. Since the amount produced each year for each set of prices were close, same equipment costs were used for scenarios 1 and 2. Same was done for scenarios 3 and 4. Amount to be produced each year for scenario 1 or 2 would be close to 6,000,000 Kg/year and if scenarios 3 or 4 are chosen, amount produced would be 200,000 Kg/year. This is expected since demand for scenarios 1 and 2 are higher than scenarios 3 and 4. Amount to be produced was determined based on the demand for the drug. More detailed calculations and values are shown in the attached material.

Table 4 gives the manufacturing cost for the cheapest drug, \$1.33 per unit. Suggested factors were kept constant for each case. Total product cost for this scenario is \$271 million dollars. Total product cost for scenarios 2, 3 and 4 are \$248, \$230 and \$224 million.

Table 4: Product Cost Price List for \$1.33 per Unit Scenario

	Suggested Factor	Amount Per Year	Price Per year
<i>Operating Labor</i>	25.58\$/h		\$181,618
<i>Operating Supervision</i>	0.15		\$27,243
<i>Electricity</i>	0.045\$/kWh		\$18,696
<i>Fuel</i>	1.26\$/GJ		
<i>Steam</i>	4.2\$/1000kg	424 Kg	\$2
<i>Maintenance</i>	0.07		\$4,691,327
<i>Operating Supplies</i>	0.15		\$703,699
<i>Laboratory Charges</i>	0.15		\$105,055
Utilities			\$5,594,778
Manufacturing Costs			\$121,107,449
<i>Taxes</i>	0.02		\$1,340,379
<i>Financing</i>	0		
<i>Insurance</i>	0.01		\$670,190
<i>Rent</i>	0		
<i>Depreciation</i>			\$3,015,853
Fixed Charges w/o Depreciation			\$5,026,422
<i>Plant Overhead Costs</i>	0.6		\$144,907,909
<i>Administrative Costs</i>			Included Above
<i>Distribution and Marketing</i>			Included Above
<i>Research and Development</i>			Included Above
<i>General Expenses</i>			\$144,907,909
Total Product Cost w/o depreciation			\$271,041,780

Table 5 represents the cost of raw material for the first scenario with \$1.33 per unit. Total cost of feed is \$115 million dollars. Major cost is corresponded to the Phoma, Calcium acetate and Aceto-nitrile. This is due to the high use of these products. Prices for other scenarios can be found in attached material.

Table 5: Feed Product Cost for \$1.33 per Unit Scenario

1	<i>Suggested Factor</i>	<i>Quantity Per year</i>	<i>Cost Per Unit</i>	<i>Value (\$/year)</i>
Water (Process)	\$/Kg	70,339,560	0.53/1000	\$37,280
Glycerol	Kg	28,136	0.6	\$16,881
Cotton Seed Flour	Kg	2,432	1	\$2,432
Soybean Oil	Kg	84,407	2.5	\$211,019
Acetonitrile	Kg	17,993,088	1.39	\$25,010,392
Sulfuric acid	Kg	71,962	0.07	\$5,037
Ammonium sulfate	Kg	450,944	0.08	\$36,037
Resin	liters	236	200	\$47,124
Calcium acetate	Kg	172,486	179	\$30,875,010
Phoma sp.	Kg	270,037	219	\$59,138,059
			Total	\$115,379,310

Table 6 gives a breakdown of the calculating FCI, TCI and working capital for scenarios 1, 2 and 3, 4. FDA was taken into account in these calculations as a constant and onetime cost for all scenarios. TCI for scenarios 1 and 2 are \$68 million and FCI is \$67 million. TCI for both processes are the same because of the high cost of FDA process for all scenarios. If FDA is not taken into account, TCI for scenarios 3 and 4 would be much lower than scenarios 1 and 2.

Table 6: FCI and TCI Estimations for Scenarios 1, 2 and 3, 4

<i>Direct Cost</i>	Percent for 2008	Price for 1 and 2	Price for 3 and 4
Equipment	1.04	\$1,341,000	\$506,700
Equipment Installation	0.49	\$654,546	\$247,322
Instrumentations and Control	0.37	\$501,354	\$189,438
Piping	0.71	\$947,002	\$357,827
Electrical Systems	0.11	\$153,192	\$57,884
Building	0.19	\$250,677	\$94,719
Yard Improvement	0.10	\$139,265	\$52,622
Service Facility	0.73	\$974,855	\$368,351
Total Direct Plant Cost	3.74	\$5,013,541	\$1,894,378
<i>Indirect Cost</i>			
Engineering and Supervision	0.34	\$459,575	\$173,651
Construction Expenses	0.43	\$570,987	\$215,749
Legal Expenses	0.04	\$55,706	\$21,049
Contractor's Fee	0.23	\$306,383	\$115,768
Contingency	0.46	\$612,766	\$231,535
Total Indirect Plant Cost	1.50	\$2,005,416	\$757,751
FDA (Fixed Cost)		\$60,000,000	\$69,000,000
Fixed Capital Investment	5.23	\$67,018,956	\$76,018,956
Working Capital	0.92	\$1,239,459	\$1,239,458
Total Capital Investment	6.16	\$68,258,415	\$77,258,415

Figure 18 gives a representation of the amount of equipment used in each set of scenarios. Because of the high demand in scenarios 1 and 2, higher equipment cost is expected for these scenarios. For scenarios 1 and 2, microfilter is the major equipment of the process. For scenarios 3 and 4, amount of microfilters, fermenter, and chromatography columns are distributed equally. The most expensive equipments are microfilter and chromatography columns. For a complete list of equipment and price breakdown refer to the attached material.

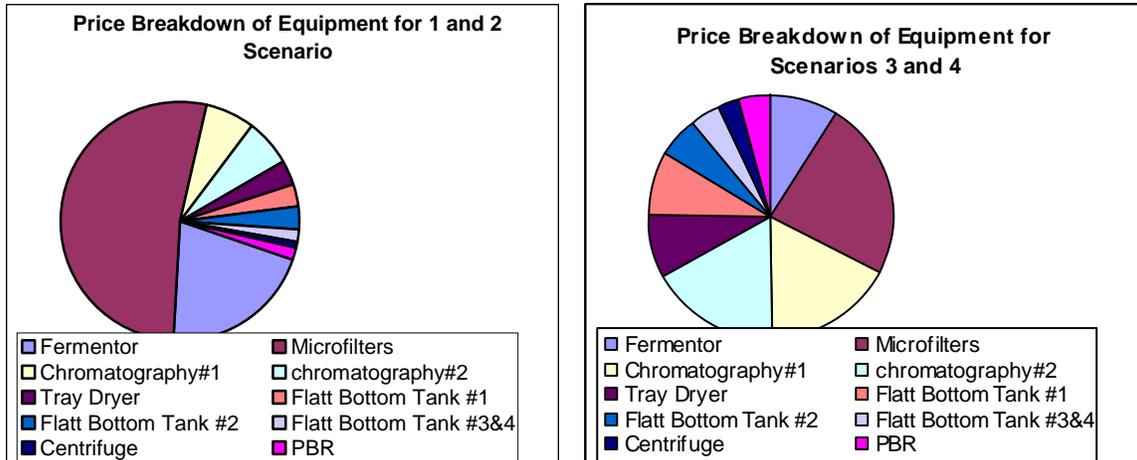


Figure 18: Equipment Prices for Scenarios 1, 2 and 3, 4

NPV Analysis

Best price scenarios have to be determined by using the demand for the product and net present value (NPV) of the project. Net present value is the measure of financial assessment for a long term project. Basically NPV is a measure of present value of net cash flows. Equation (8) was used to calculate cash flow for a 20 year long project.

$$NPV = C_0 + \sum_{t=1}^N \frac{C_t}{(1+r)^t} \quad \text{Equation (8)}$$

Here, C is the cash flow, t is time, N is the length of the project, and r is the discount rate which was kept constant at 8%.

NPV accounts for both demand and cost and the trend is shown in the following graphs. Figure 17 represents the NPV for four scenarios. Scenarios 1 and 2 show the best NPV over a 20 year project. Scenarios 3 and 4 have negative NPV's which explains that the scenario should be rejected.

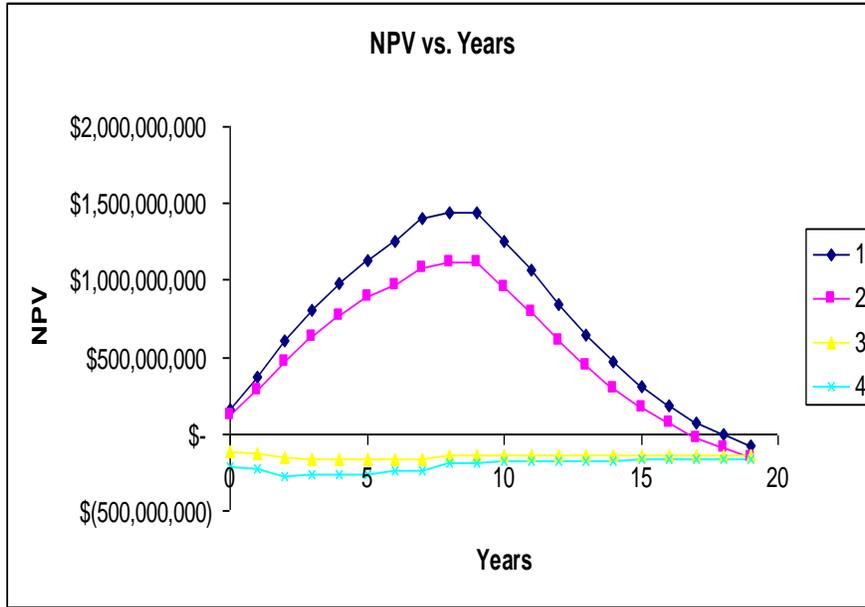


Figure 19: NPV versus Years of Project Including FDA Process

Figure 20 shows the NPV over a range of new product prices. As shown here, best scenarios are 1 and 2 with maximums at about \$1.33 and \$1.77 per unit of drug. Other scenarios can be ignored because of the trend they present. From this graph and the graph above, best price for the drug was determined.

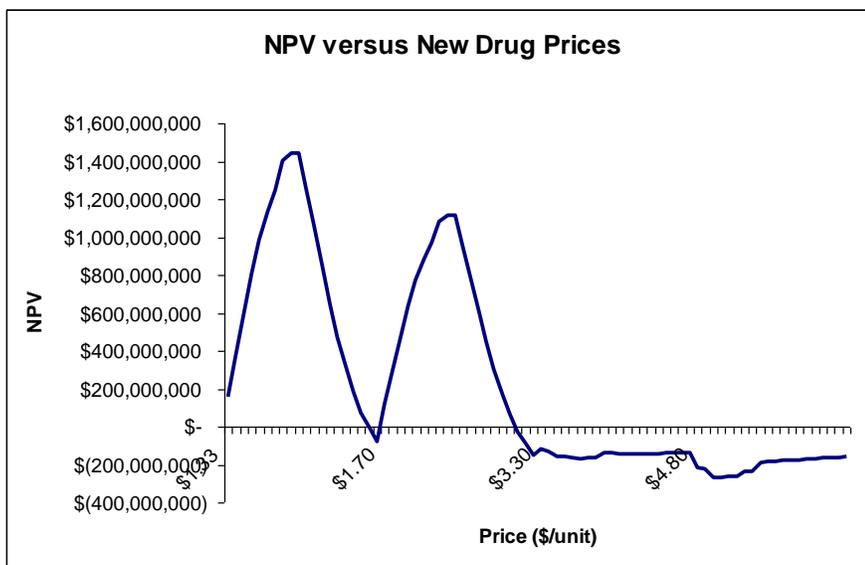


Figure 20: NPV versus Different Price of New Drug

Return on investment (ROI) which is the ratio of net profit to total capital investment was determined for all four scenarios, for the first scenario ROI of 2% and for the second scenario an ROI of 1% were calculated. Other two scenarios gave negative ROIs. Based on these calculations the highest ROI was observed with the first scenario. (-See Attached Material)

Risk Analysis

High risk in a decision is directly related to its profit. As shown in figure 19, the risk for this project may not be too high because of the assumed probabilities for each scenario. For the middle years of the project profitability is much higher compared to other times of the project. These risk curves were generated for the first scenario. Probabilities were determined based on figures 17, and 14. Based on these values and figures, the highest demand and NPV will be lying on years 4th through the 14th therefore it was assumed that the project will have a high probability over this time.

Before and after years 4-14th, low NPV and profit are observed. This is expected since the project is in its early years and high revenues are not expected. It is also shown from the demand model that demand for the drug would be low compared to later years. Revenue and NPV increase after a certain point and then a decrease is observed.

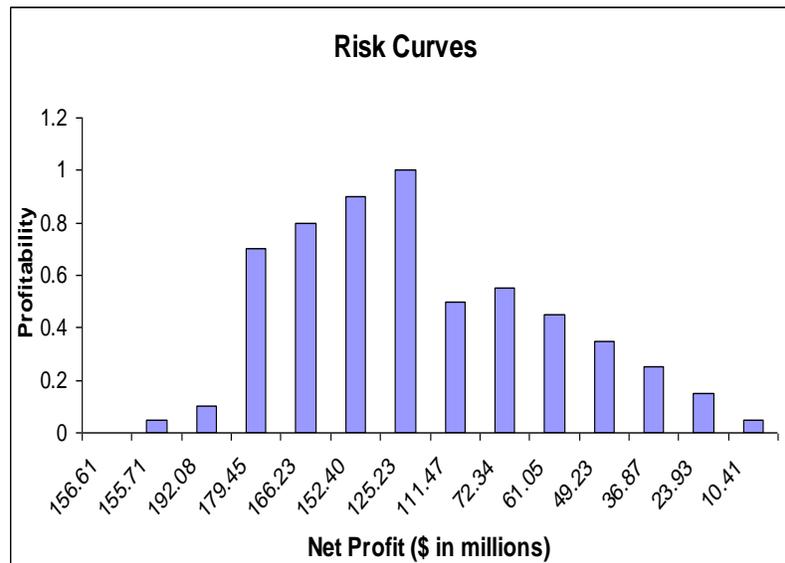


Figure 21: Risk Curve based on Net Profit

Since demand from consumer and doctors will stay constant after the 8th year of the project, the project will have a low chance of losing its customers. Figure 20 shows a risk curve

for scenario 1 based on NPV. Low risk is observed with this graph. The NPV at highest probability is \$1,200 million.

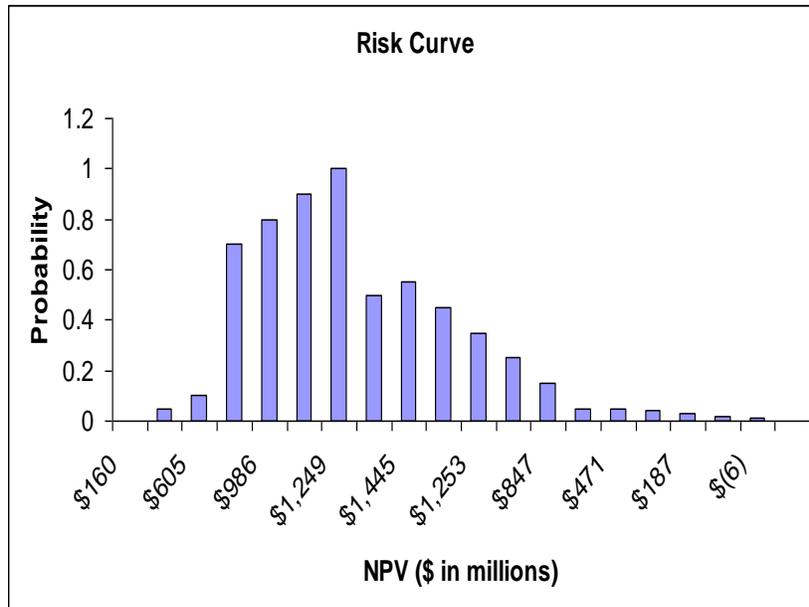


Figure22: Risk Curve based on NPV

One explanation for the low risk scenario one would be that since the drug has higher efficacy than other treatments, lower risk is associated with it. Another reason is related to the high demand which takes into account efficacy and price of the drug. Since this drug is at the lowest price and has a good chance of dominating the market in short amount of time, risk associated with this drug is low.

Conclusions

SQ1 is a new enzyme inhibitor for lowering cholesterol. This drug will lower cholesterol by inhibiting enzyme squalene synthase and lowering the production of cholesterol. Research has shown that this drug will lower cholesterol by 50% using lower dosages compared to statin drugs. Probability of the drug passing the FDA is good since the process of lowering the cholesterol is different than statins and is more effective in lowering cholesterol. Best price for SQ1 was determined to be \$1.33 per unit. TCI and FCI to manufacture SQ1 are \$76 and \$77 million including the FDA prices.

Demand model was used to determine the best price for this drug. It was discussed that since most of the decisions made when prescribing a drug are made based on the insurance coverage, this can have a major affect on the demand. If an insurance company doesn't cover the drug then the demand for that drug will drop. It is likely that this drug will be covered by insurance companies because of the low price it has and its high efficacy. NPV and ROI of the project gave a positive value which explains an acceptable and profitable project.

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